CHAPTER - I

GENERAL INTRODUCTION
1.1 **INTRODUCTION:**

Body tissues derive their nourishment from the blood in the direct or indirect manner for their survival. There are continuous solute exchanges between the blood vessels and the tissues while in the latter some tissue-fluids are introduced from the blood by some physiological phenomena and this fluid supplies nutritional elements to the tissues. Body tissues receive their nutrients from the fluid environment. Similarly, the metabolic products or metabolites and catabolic products released by the tissues or organisms are excreted by circulation of the fluid which continuously bathes the tissues. There are continuous solute exchanges between blood, tissues and the fluid environment. These solute exchange processes are essential for life and normality of the body tissues.

The interaction between tissues and the fluid environment depends on various factors — mechanical physiological, biochemical and neural factors — which control and regulate the solute exchanges between blood tissues and body cavities. Production of the tissue-fluids which provide a medium to supply nutritional substances to the tissues and contribute in the disposal of metabolites is dependent on various factors. Actually, all these factors are responsible for regulating the transport of solutes and water between the blood vessels, the
tissue spaces and or cavities of an organ. Solute transport processes are necessary and essential for life and normal functions of the tissues. The solute exchange processes are also dependent on the chemical composition of the fluids bathing the tissues.

All the blood-borne nutrients and other substances circulating in the fluid system are not required by a particular tissue or organism. Some may be detrimental to the tissues. There must exist a mechanism by which tissue components are protected from circulating harmful substances. Also there is great body of evidence obtained from tracer studies in the different organs of human body that different blood-borne nutrients and other substances have different rates of transport. Some substances or ions move slowly in one direction as compared to that in the opposite direction. The above nature of the interaction between blood tissues and fluid environment suggests a selective transport mechanism and provides the physiological concept of the barrier which are situated on the boundary or surface separating the two systems.

Recently, new concepts of solute transport processes through barriers have been developed in literature. Physiological transport processes across the cell membrane are responsible for solute exchanges between the blood and the tissue space or cavities of an organ, avascular tissues and the fluid. A number of mechanisms are involved in such
types of transport phenomena. Some of the mechanisms involved in transport phenomenon are:

i) Diffusion

ii) Convective diffusion of fluids or carrier transport

iii) Filtration or ultrafiltration

iv) Dialysis

v) Vesicular transport

vi) Active transport.

Barrier is not a physiological concept. Its morphological existence has been confirmed in different organs of the body. For example, blood-retina and blood-aqueous barriers in eye and blood-brain, blood-cerebrospinal fluid and cerebrospinal fluid-brain barriers in brain have been morphologically confirmed. Barrier may be defined as a constant level of various substances which is established and maintained in the blood of an experimental animal. The rate at which their extracellular fluid concentrations approach the plasma concentration varies among different regions of the body. When the rate is very low, physiologists postulate the existence of a barrier which prevents free diffusion of solutes from the blood into tissue spaces or cavities of an organ.

Usually, barriers are localized in an epithelium or a vascular endothelium i.e. in a layer of cells that separates two different compartments of the body. In addition, the tissue distribution of the blood-borne molecules is influenced
by local factors which include the geometry of the vascular
tree and the spatial distribution of permeable and imper-
meable vessels. These factors acquire special significance
in the instances in which the barrier is limited to a spe-
cific compartment of an organ such as the testes [Dym and
Fawett (1971)] and thymus [Raviola and Karnovsky (1972)]

Passage of substances through an epithelium or an
endothelium can occur both across cell (transcellular route)
and between the cells (paracellular route). The trans-
cellular route is mediated by two types of mechanisms:
facilitated transport, and movement of plasmalemmal
vesicles. Facilitated transport is highly selective,
limited to relatively small molecules and may be controlled
by cell-activity. On the other hand, plasmalemmal vesicles
seem to be capable of indiscriminately ferrying various types
of molecules [Karnovsky (1967); Bruns and Palade (1968);
Simionescu and Palade (1971) Simionescu, Simionescu and
Polade (1974)]. They appear to move randomly in the cyto-
plasma [Karnovsky and Shea (1970)], but their formation is
likely to be energy-dependent. Passage along the paracellular
routes is passive and is limited by the size of the inter-
cellular clefts.

Thus, the presence of a barrier to a circulating
substances across an epithelium or an endothelium implies
(i) that this substance is not actively transporated by
the epithelial or endothelium cells; (ii) transcellular
movement of plasmalemmal vesicles is negligible; and
(iii) the intercellular clefts are sealed by impermeable
junctions.

Exchanges of solutes and water between plasma
(blood), intra-ocular fluids and ocular tissues in eye,
and between blood-plasma, cerebrospinal fluid and cerebral
tissues in brain are important physiological transport
phenomena occurring in the body. These transport processes
are regulated through the barrier systems. The barrier is
at the interface of either blood and fluid or fluid and
tissue or blood and tissue. These barriers are mainly
responsible for maintaining homeostasis of the system,
which is essential for the life and normality of organisms/
tissues through the nourishment and disposal of metabolites.

Blood-aqueous and blood-retina barriers and blood-
cerebrospinal fluid and blood-brain barriers are the well
recognized barriers in eye and brain respectively. The
interaction between either blood and fluid environment or
tissues and fluid environment is dependent on the transport
mechanism and the permeability characteristics of the barrier.
Under normal conditions, the chemical equilibrium is main-
tained by the barrier which is essential for the nourishment
of the avascular tissues and normal functions of the organ.
Malfunctioning of the barrier causes dramatic changes in
its permeability characteristics resulting in a pathological
state which may be fatal to life.
A mathematical analysis of these physiological solute transport phenomena in eye and brain can give a better understanding of the transport mechanisms and provide an insight in the formation of aqueous humour and cerebrospinal fluid. Physiological functions and the transport processes in eye and brain can contribute in a better understanding of secretion of aqueous humour and cerebrospinal fluid which are a matter of speculation to physiologists as well as physicians till date and in a clear understanding of nutritional transport phenomena in these organs. The present studies can identify certain areas in which more advanced studies should be conducted in future. We now briefly describe the two organs mentioned above.

1.2 THE EYE

The eye, prime one of the five sense organs, is a nearly spherical fluid-filled elastic shell with an anterior bulge whose properties are constantly changing, so sensitive that they will show even a diurnal variation [Kollner (1916), Davis and de Venecia (1963), Drance and Carr (1961)]. Its properties are changing with change in age [Levene (1961), Boles-Carenini and Cabiaggi (1960), Boles-Carenini and Nevi (1961)]. The outer wall of the globe is composed of a dense, imperfectly supported elastic membrane filled with three incompressible fluids: aqueous humour, vitreous-humour and blood.
The shape of the posterior half of human eye ball is close to spherical (Figure 1.1) and the anterior to the equator the curvature of the eye ball decreases gradually and then increases sharply to form a dome-like anterior projection.

In human eyes, the external diameter of the eye globe is 24 mm, giving an external volume of about 7,000 µl. The thickness of the eye's covering the cornea in front and the sclera behind—varies between 0.3 and 1.3 mm, so that the internal volume of the is approximated 6,000 µl. Table 1.1 gives approximate comparative information for human, cat and rabbit eyes.

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Cat</th>
<th>Rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye diameter</td>
<td>24 mm</td>
<td>21 mm</td>
<td>16 mm</td>
</tr>
<tr>
<td>Eye volume (external)</td>
<td>7,000µl</td>
<td>5,000µl</td>
<td>2,000µl</td>
</tr>
<tr>
<td>Eye volume (internal)</td>
<td>6,000µl</td>
<td>4,000µl</td>
<td>1,500µl</td>
</tr>
<tr>
<td>Anterior chamber volume</td>
<td>180-280µl</td>
<td>300-690µl</td>
<td>57µl</td>
</tr>
<tr>
<td>Posterior chamber volume</td>
<td>60µl</td>
<td></td>
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</tbody>
</table>
Fig. 1.1 Vertical cross-section of the Eye
1.2.1 INTRAOCULAR FLUIDS:

a) Blood:

In humans, blood-reaches the eye through the ophthalmic artery, a branch of internal carotid artery, whereas in cats and rabbits, the principal experimental animals, the blood supply originates in both the internal and external carotid arteries [Adler (1965), Bill (1970)]. Human eye comprises two separate circulatory systems: retinal and uveal. Both of these emanate from the ophthalmic artery. The retinal system supplies the inner layers of the retina and is almost perfectly autoregulatory [Bill (1975)]. The uveal (or choroidal) system consisting of the anterior and posterior ciliary arteries, supplies the outer layers of the retina and the outer coats of the eye.

b) Aqueous Humour:

It is clear watery fluid occupying both the anterior and posterior chambers of the eye. It is known as the only secretary product of epithelium covering the ciliary body and iris. It is not stagnant fluid but continuously secretes and passes over the lens through the pupil into the anterior chamber and drains into the vascular system - the anterior ciliary veins. The specific gravity, viscosity and referective index are 1.002 - 1.004, 1.029 and 1.34 respectively.
c) **Vitreous Humour:**

It is gelly like material covered by a homogeneous membrane, the hyaloid membrane, and occupying the posterior compartment of the eye known as vitreous chamber. The transparent fluid content of this gel is the vitreous humour. The gel structure is produced by a combination of collagen fibres and mucopolysaccharide. Piri (1969) estimated the water content to be about 99% by weight. The liquid component of the vitreous body has the same composition as the aqueous humour [Davson (1969)]. It enters through the retrozonular and retrolental spaces.

1.2.2 **SUB-SYSTEMS:**

Anatomically, the eye comprises three coats and three chambers:

a) **Outer Coat:**

The outer coat consists of relatively tough fibrous tissues shaped as segments of two spheres:

1. **The Sclera:**

The sclera is a dense, fibrous relatively avascular structure that comprises the posterior five sixths of the eye ball with a radius of curvature of about 33 mm. Three ill-defined layers of the sclera are described, (i) the episclera, (ii) the sclera proper and (iii) the lamina fusca.
2. **Cornea:**

The cornea is a transparent anterior one sixth of the eye ball. It is approximately circular in shape and fits, as a watch glass into the beveled edge of the sclera with a radius of curvature of about $7.5\,\text{mm}$. The cornea is avascular. It derives the metabolites and oxygen either by diffusion from the pericorneal capillaries or from the aqueous humour and tears.

The junction of the cornea and the sclera (corneo-scleral limbus) is an important functional and anatomic area. This area is clinically important because it encompasses the trabecular meshwork and canal of Schlemm, which form the drainage system.

3. **Trabecular Meshwork:**

Surrounding the entire circumference of the anterior chamber is the trabecular meshwork, a pore like structure through which aqueous humour percolates to the canal of Schlemm. It is usual to divide the meshwork into two distinct regions - the uveal meshwork, constituting the layer next to the ciliary body and roots of the iris, and the corneo-scleral meshwork which is the outer portion connected with the scleral spur and is in contact of Schlemm's canal.
4. **Canal of Schlemm:**

The canal of Schlemm is an endothelium-lined channel, approximately oval in cross section and surrounds the entire circumference of the anterior chamber. On its inner surface, it is communicated with anterior chamber through the trabecular meshwork. The endothelium contains numerous pores through which the aqueous humour percolates. The canal of Schlemm connect with the venous system through a system of 25 to 35 collector channels that anastomose to form a deep intrascleral plexus.

b) **Middle Coat:**

The middle or uveal coat of the eye ball consists of the choroid; the ciliary body and the iris

1. **The Choroid:**

Choroid structure of the uveal tract lies between the retina and the sclera, composed of vessels which are bounded by the Bruch's membrane internally and lamina suprachoroidal externally.

2. **Ciliary Body:**

The ciliary body is a ring of tissue about 6 mm wide, extending from the base of the iris to the choroid. In cross section the ciliary forms approximately a right angle attached to the sclera spur and faces the anterior chamber and insertion of the iris. The hypotenuse faces the vitreous
and posterior chambers, and the intermediate side is adjacent to the sclera.

3. **Iris and Pupil**:

The iris is a delicate diaphragm lying in front of the lens and the ciliary body and separating the anterior and posterior chambers. Located slightly to its nasal side is a circular aperture, the pupil, which reflexly controls the amount of light admitted to the eye. The iris inserts into the scleral spur by means of its connection to the middle of the anterior surface of the ciliary body. The pupillary border rests upon the lens. When the lens is absent, the iris is tremulous and flat.

c) **Inner Coat of the Eye (The Retina)**:

The third innermost coat of the eye ball or the retina has a complex structure and contains elements sensitive to light, nerve cells and supporting structures. It is about 0.5 mm thick. The vertical cross-section of the retina of the human eye shows that retina has ten layers (Fig. 1.2).

1. Bruch's membrane
2. Outer nuclear layer
3. Pigment epithelium
4. External limiting membrane
5. Outer molecular layer
6. Inner nuclear layer
7. Inner molecular layer
Fig. 1.2 Layers of the Retina.
8. Ganglion cell layer  
9. Nerve fiber layer  
10. Internal limiting membrane  

1.2.3 CHAMBERS OF THE EYE:

a) Anterior Chamber:  
The anterior chamber is bounded by the posterior surface of the cornea, tiny portion of the inner surface of the sclera, a variable portion of the anterior surface of the ciliary body, the entire anterior surface of the iris and the intra-pupillary portion of the anterior surface of the crystalline lens filled with a transparent fluid aqueous humour.  
The shape of the anterior chamber resembles that of spherical surface of the cornea, with the roughly conical surface of the iris. The dimension of the spherical segment and particularly its axial depth are subjected to wide variations from the normal human eye with age and disease [Heim (1941), Rosengren (1950)].  

b) The Posterior Chamber:  
The term posterior chamber denotes the space bounded by the posterior surface of the iris, the equatorial portion of the lens, the anterior surface of the ciliary body. Its volume in adults is about 0.06 ml filled with aqueous humour, secreted by the ciliary body, flowing through the pupil into the anterior chamber.
c) **The Vitreous Chamber:**

The vitreous body occupies the greater part of the interior of the eye, lying behind the lens and its suspensory ligament. It is a colourless, highly transparent, gel-like mass which in the normal, mature eye contains only a small number of living cells, but no blood vessels or nerve fibres. The function of these cells are probably related to the formation and maintenance of the gel [Hamburg (1959)]. Because of its great delicacy, and because of the profound alterations produced by fixatives, the anatomical approach to the structures of the vitreous body has been less revealing than the chemical approach. Its volume is 4.5 ml.

The vitreous body is a transparent gel having the shape of a sphere with a segment removed anteriorly to provide hollowed out space for lens. In health, the vitreous body is in contact with the retina throughout. It has firm attachment to the ciliary body and the retina in the region of the ora serrata and to the margin of the optic disc.

1.2.4 **Production and Circulation of Ocular Fluids:**

a) **Blood:**

The arteries of the eyeball are all branches of the ophthalmic artery, and the important veins all empty into the cavernous sinus. Before entering the eyeball, the vessels divide into two distinct systems - retinal and ciliary which, except for capillary anastomoses, remain separate
through their intracellular and part of their extracellular courses.

In the retinal system, the circulation is dual mediated by the central artery and veins of retina, entering and leaving the globe in the optic nerve and supplying the inner layers of the retina directly; and a uveal circulation, mediated by a system of ciliary arteries that penetrate the globe independently of the optic nerve and run in the middle coat of the eye - the uvea. It is with the uveal circulation that we are primarily concerned here [Davson (1969)], since the ciliary body and iris are supplied entirely by it, but in so far as the aqueous humour and vitreous humour related chemically and dynamically and retinal circulation cannot be ignored.

b) Aqueous Humour:

1) Production:

Aqueous humour is produced continuously from all blood vessels within the eye, but the density of these vessels is greatest at the posterior surface of iris and in the ciliary body [Green and Pederson (1973)]. The formation process is not well understood, but it is thought to involve transport across the capillary walls. But most of the fluid is produced by the blood vessels of the ciliary body and is accumulated into the posterior chamber. The aqueous humour escapes from the posterior chamber into the
anterior chamber. Therefore, its composition differs considerably in the anterior and posterior chambers of the eye.

Four mechanisms have been proposed for the formation of aqueous humour: ultrafiltration; dialysis; secretion; and secretion-diffusion [Adler (1965)]. The osmotic pressure is not high enough for dialysis to account for the observed rates although can control the chemical composition concentration gradients. Thus, some investigators support the hypothesis that aqueous humour is formed both by secretion within the cells of the ciliary epithelium (Figure 1.3) and the ultrafiltration [Green and Pederson (1973)].

2) Circulation:

The transparent fluid aqueous humour is produced by the ciliary body into the posterior chamber. The aqueous humour leaves the posterior chamber through three accessory exits [Pederson and Green (1973)].

The first accessory exit leaves the posterior chamber through the pupillary aperture into the anterior chamber and escapes the anterior chamber by transudating into the canal of Schlemm through the trabecular meshwork at the filtration angle and thence into the recipient veins carrying blood [McEwan (1958), Ruskell (1961)] [Fig.1.3].
Fig. 1.3 Circulation of aqueous humour and blood
There is second accessory exit [Bill (1970,1975)] (the uveal scleral outflow) through the ciliary body into the choroid and suprachoroid and thence into the episcleral tissue; although a minor means of exit, this pathway may sometimes be of importance.

1% of the total fluid of aqueous humour in the posterior chamber, leaves the posterior chamber through the vitreous body.

3) Vitreous Humour:

1% of total fluid of aqueous humour in the posterior chamber, enters the vitreous chamber through the retrolental space and retrozonular space and it escapes the vitreous chamber through the hyloid canal and then out of the eye.

b) Composition of Aqueous Humour:

The aqueous humour appears as a transparent colourless liquid of low viscosity containing 98.6% water and 1.31% solid; it differs from the blood plasma mainly by the virtue of low concentration of protein - about 15 to 16 mg/100 ml in man and 50 mg/100 ml in rabbit, compared with some 6000 to 7000 mg/100 ml in the plasma [Francois et al (1958)]. Further details, as compared to plasma are as follows: the diffusible, non-ionisable substances, colloids and ehoroides.
**Table - 1.2**

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<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Aqueous Humour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>151.50</td>
<td>143.50</td>
</tr>
<tr>
<td>K</td>
<td>5.25</td>
<td>5.50</td>
</tr>
<tr>
<td>Ca</td>
<td>1.70</td>
<td>2.60</td>
</tr>
<tr>
<td>Mg</td>
<td>0.78</td>
<td>1.00</td>
</tr>
<tr>
<td>Cl</td>
<td>109.50</td>
<td>108.00</td>
</tr>
<tr>
<td>HCO₃</td>
<td>33.60</td>
<td>27.40</td>
</tr>
<tr>
<td>Lactate</td>
<td>7.40</td>
<td>4.33</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>0.66</td>
<td>0.22</td>
</tr>
<tr>
<td>Ascorbate</td>
<td>0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>Urea</td>
<td>7.00</td>
<td>9.10</td>
</tr>
</tbody>
</table>
The crystalloidal composition of the aqueous humour is similar to that of plasma. But the concentrations of ascorbate, pyruvate and lactate are much higher than those in plasma, whilst those of urea and glucose are much less. The comparison of different substances in aqueous humour to that in plasma are given in the Table - 1.2.

1.2.5 INTRA-OCULAR PRESSURE AND FUNCTIONS OF AQUEOUS HUMOUR:

On insertion of a cannula into the anterior chamber of the eye, the aqueous humour flows out, and the pressure required to prevent this loss of fluid may be defined as intra-ocular pressure. There have been several studies on the normal intra-ocular pressure distribution in human eyes. But the most extensive study is probably that of Leydhecker (1959) who obtained 95.5% of all healthy eyes have an intra-ocular pressure lying within the range 10.5 to 20.5 mmHg. This range has been supported by many investigators [Becker (1958), Becker and Drews (1967), Linner (1959, 1966), Schmidt and Goldmann (1957a)]. Also, the intra-ocular pressure changes with age and in various deceased states.

The prime function of the aqueous humour is to maintain a constant level of intra-ocular pressure and to supply the blood-borne nutrients to avascular tissues e.g. the lens and the cornea.
The intra-ocular pressure in the eye is chiefly maintained by regulation of aqueous humour. The two rates, however, closely linked and the regulation of intra-ocular pressure relates essentially to the inflow and outflow of aqueous humour. The intraocular pressure remains steady if the netflow (inflow minus outflow) of ocular fluids is balanced by a corresponding variation in the volume enclosed by the corneascleral envelope. If prolonged changes occur in outflow and inflow of aqueous humour, eye develops the pathological state "Glaucoma".

1.2.6 BLOOD-OCULAR BARRIERS

There are two main barrier systems in the eye Fig. 1.4:

One regulating changes between the blood and the intra-ocular fluid and involving the variety of structures relating to the ciliary body and is called the blood-aqueous barrier.

The inward movements from the blood into the eye predominate [Davson (1956)]. The diffusional solute exchanges take place between the aqueous humour and the surrounding tissues the posterior chamber and vitreous compartment [Adler (1965), Bito (1977), Cunha-Vaz and Maurice (1967), Kay, Sibley and Hoefle (1973), Kinsey and Palm (1955)].

The outer barrier, particularly tight, where outward movement from the eye into the blood appears to predominate and where the penetration into the eye of only a few metabolic products is responsible for homeostasis of the neuroretina. In the posterior segment, the concept of blood-vitreous barrier
Fig. 1.4 Diagram of blood-ocular barriers.
RET-retina; PC-posterior chamber; AC-anterior chamber
is vague, has no morphological basis, and is, on the whole, untenable. Such a barrier is entirely absent in the anterior region of the vitreous where free diffusion is present between the anterior and posterior segment of the eye. There are, therefore, no significant diffusional barriers to molecular markers between the vitreous and the posterior chambers. The vitreous humour, thus, appears to be located between two barriers – the blood-aqueous barrier anteriorly, and the blood-retina barrier posteriorly.

a) **Blood-Aqueous Barrier:**

The ciliary epithelium consists of two cell layers, the *non*-pigmented and pigmented epithelium. The bases of the *non*-pigmented cells line the posterior chamber whereas the bases of the pigmented cells rest on the ciliary body stroma. The apices of the pigmented and *non*-pigmented cells are in contact with one another. The pigmented layer is continuous posteriorly with the pigmented epithelium of the iris. The *non*-pigmented layer is continuous with the neutral retina at the ora serrata and anteriorly merges with the posterior epithelium of the iris.

A number of investigators have shown that circulating horseradish peroxidase, after escaping through the walls of the vessels of the ciliary body stroma, penetrates the intercellular clefts of the pigmented layer of the ciliary epithelium and is finally blocked by *non*-pigmented layer of the ciliary
epithelium and is finally blocked by non-pigmented layer of the ciliary epithelium [Raviola (1971)]. The tight junctions of the non-pigmented ciliary epithelium must, therefore, represent the principal site of blood-aqueous barrier to circulating macromolecules [Raviola (1974), Shiose (1970), Smith (1971) and Smith and Rudt (1975)].

If the aqueous is formed by a process of secretion by the ciliary epithelium, we may imagine this process to consist of first, a filtration of the plasma from the capillaries of the ciliary body into the extracellular space of the processes; subsequently, the constituents of this filtrate would be absorbed by the cells of the ciliary processes and transferred into the posterior chamber as a secreted fluid, the various constituents being transferred in the plasma-filtrate. Alternatively, the filtrate might pass between the cells of the ciliary epithelium and on its way through the cells, it might add certain substances such as ascorbic acid, sodium chloride and bicarbonate, and substrate certain others, such as urea, whilst other substances might be allowed to remain with their concentrations unaltered e.g. amino acids and glucose their low concentration in the aqueous humour being ultimately due to consumption by the metabolizing tissues within the eye [Raviola (1974), Smith and Rudt (1975), Faviola (1976, 1977), Cole (1977)]. Unfortunately, so little is known about the fundamental mechanisms of secretion that it would be painless at present to attempt to decide
between these two, or any of several other possible mechanisms [Vegge (1971 a,b), Loties and Rapoport (1976)]. Tentatively let us elect the second hypothesis as the basis on which to explain the main phenomena concerned with exchanges between blood and aqueous humour, exchanges which are included under the term-blood aqueous barrier.

b) **Blood-Retina Barrier:**

The blood-retina barrier is located at two levels, forming an outer blood-retina barrier and the inner blood-retina barrier. The main structures involved appear to be, the retinal pigment epithelium and the endothelium membrane of the retinal vessels respectively. The knowledge on diffusion and transport mechanisms of the blood-retina barrier refers generally to both the outer and inner barriers, because there is yet no clear information on difference in permeability rates between the outer and inner parts of the blood-retina barrier and the physiological distance between these barriers is a few micrometer. It takes, therefore, a single barrier.

The retinal cells are separated from the blood stream by the blood-retina barrier system. This barrier permits only the passage of biologically important substances, i.e. glucose and certain aminoacids while all other water soluble substances are retained. Thus, the blood-retina barrier is of the greatest importance for the maintenance of retinal homeostasis and thus for the normal visual functions.
1.3 THE BRAIN:

Like the intraocular fluid, aqueous humour, cerebrospinal fluid is a special body fluid of the central nervous system and is unique in its function being mainly responsible for the homeostasis of chemical environment within the central nervous system and for providing mechanical cushion to the brain tissue which protects the brain from external injuries. In addition to its nutritive and excretory functions, it also acts as a link in the transport of a number of hormones and as a vehicle in the intracerebral transport. The main fluid involved in the process is cerebrospinal fluid.

1.3.1 THE CEREBROSPINAL FLUID SYSTEM:

The entire cavity enclosing the brain and spinal cord has a volume of approximately 1650 ml and about 150 ml of this volume is occupied by cerebrospinal fluid. The brain and spinal cord remain covered by three membranes known as the dura matter. The cerebrospinal fluid is found in cisterns around the brain and spinal cord. The interior of the nervous system is hollowed out by four cavities (ventricles) in brain and two canals; all filled with cerebrospinal fluid. One cavity is present in each cerebral hemisphere called the lateral ventricle. They open into a common central cavity - The third ventricle, through an opening on each side - The foramen of monro (intraventricular foramen). The third ventricle is continued down through
the midbrain as the aqueduct of sylvius (cerebral aqueduct). The aqueduct opens into another dilatation in the medulla—the fourth ventricle, which again is continued downwards as the central canal of the spinal cord. The roof of the fourth ventricle has three perforations called the foramina. Through these foramina, the cerebrospinal fluid enters the subarachnoid space. Thus, the cerebrospinal fluid surrounds the whole central nervous system being both inside and outside it. The ventricles and canals are lined by a ciliated cubical epithelium called the ependyma.

1.3.2 PRODUCTION OF CEREBROSPINAL FLUID:

There are two possible sources for the production of cerebrospinal fluid within the ventricles; the choroidal source and extrachoroidal source:

a) The Choroidal Source:

From strictly morphological considerations, the choroidal plexuses have long been implicated as a major source of cerebrospinal fluid production [Miner and Reed (1972), Welch (1963), Hiratsuka, Tabata et al (1982)]. The choroidal plexuses are supplied with blood by anterior and posterior arteries which arise from the internal carotid and posterior cerebral arteries. During the last two decades
anatomical speculation concerning the plexus's role in cerebrospinal fluid production has been confirmed. Although, estimates of total production of cerebrospinal fluid by choroid plexuses are difficult, Welch (1963) and Davson and Segal (1970) have argued that the plexuses form some-what 70-80% of total secretion of the cerebrospinal fluid. Results from the isolated choroid plexus preparation indicate that 80% or more cerebrospinal fluid production is from the choroidal sources alone. Welch and Sadler (1966), Miner and Reed (1972), Sahar (1972), Segal and Pollay (1977), Cutler and Spertell (1982), Milhorat (1975) suggested that undoubtedly the choroid plexuses are the site of the bulk of cerebrospinal fluid formation. It was suggested by McComb (1983), McComb, Hyman and Weiss (1983) that normally about 80% to 90% of cerebrospinal fluid secretion is derived from the choroid plexuses. Thus, most of the cerebrospinal fluid is formed in the ventricular system from the choroid plexuses.

b) Extrachoroidal Source:

Possible sites of the extrachoroidal source for the production of cerebrospinal fluid are ependyma and the parenchyma. The choroid plexuses comprises 60% of the internal surface area of the brain, with the ependyma accounting for the rest [Voetmann (1949), Wood (1982)]. Separate functions of the ependyma from that of the remainder of the parenchyma are not known. The role of
the ependyma in bulk cerebrospinal fluid formation is not known [Bradbury and Stulcova (1979), Bering and Sato (1963), Milhorat (1975)]. Although, from the morphological considerations, its contribution is likely to be insignificant. Brightman (1968), Brightman and Reese (1969), Rall (1968) and Welch (1975) suggested that parenchyma may be the main source of nonchoroidal cerebrospinal fluid formation. Support for the brain substances as the principal source of extrachoroidal cerebrospinal fluid amounting to possibly 10% to 20% of the total cerebrospinal fluid production, has been shown in several studies [Rosenberg, Kyner and Estrada (1980), Csern, Cooperpn and Milhorat (1977) and Csern, Cooper and Suri (1971)]. Thus, it appears that normally about 80% to 90% of cerebrospinal fluid secretion is derived from the choroid plexus, with the remaining portion most likely originating from the parenchyma.

Thus, the choroid plexuses are principal source of the cerebrospinal fluid. In the secretion of cerebrospinal fluid certain solutes coupled with water are transported from the blood into the ventricles across the choroid plexuses. In order to accomplish a theoretical analysis of the solute transport coupled with water, a knowledge of the morphology of the choroid plexus is required.
1) **Choroid Plexus:**

The choroid plexuses are delicate frond like gel structures which float in the cerebrospinal fluid. Morphologically, as the other familiar fluid transporting epithelia (gall bladder, renal tubule, ciliary process) [Wright (1972), Davson (1967), Cserr (1971), Segal and Pollay (1971)], the choroid plexuses are characterised by a rich capillary bed closely opposed to a single layer of epithelial cells folding into numerous villi, each with monolayered cuboidal epithelium which is a modified ependyma covering a stromal core derived from a double layer of pia. There are numerous microvilli and a few cilia on the apical or ventricular surfaces of the epithelial cells and complex infoldings of the basal cell membrane [Stewart and Willy (1981) Cserr Mangnus and Budgaard (1984), Segal and Burgess (1974)]. Tight junctions are present at the apical side of the cells. The cells lie on a basement membrane beneath which is a stromal space containing collagen, fibroblasts and nerve fibres. A blood-cerebrospinal fluid barrier results from the presence of tight junctions at the apical end of the choroid epithelium [Brightman (1968)]. This is in contradistinction to the capillaries of the parenchyma where tight junctions between the endothelial cells constitute the blood-brain barrier. The choroidal epithelium has the histological features characteristic of epithelia specialized for the transcellular transport of solutes and solvent [Davson (1967), Dohrmann (1971)]. Ultrastructural modifications of
the choroid ependymal cell membrane into infoldings and apical microvilli are also characteristic of epithelia that transport fluid [Cserr, Cooper and Milhorat (1977), Cserr (1981)].

d) **Composition of Cerebrospinal Fluid:**

Cerebrospinal fluid is a clear colourless fluid and specific gravity is 1.004 - 1.006. Chemical composition of cerebrospinal fluid is shown in Table-1.3.

Table 1.3

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Cerebrospinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>6300 - 8500</td>
<td>16 - 38</td>
</tr>
<tr>
<td>Amino acids</td>
<td>4.5 - 9</td>
<td>1.5 - 3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7 - 2.0</td>
<td>0.45 - 2.20</td>
</tr>
<tr>
<td>Uric acid</td>
<td>2.9 - 6.9</td>
<td>0.5 - 2.8</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>100 - 150</td>
<td>0.06 - 0.22</td>
</tr>
<tr>
<td>Urea</td>
<td>20 - 42</td>
<td>5 - 39</td>
</tr>
<tr>
<td>Sugar</td>
<td>70 - 120</td>
<td>45 - 80</td>
</tr>
<tr>
<td>Chloride</td>
<td>560 - 630</td>
<td>720 - 750</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>2-5</td>
<td>1.25 - 2.0</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>40 - 60</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Hydrogen ions (PH)</td>
<td>7.35 - 7.40</td>
<td>7.35 - 7.40</td>
</tr>
<tr>
<td>Sodium</td>
<td>325</td>
<td>335</td>
</tr>
<tr>
<td>Potassium</td>
<td>20</td>
<td>12-17</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.4 - 1.3</td>
<td>3-3.6</td>
</tr>
<tr>
<td>Calcium</td>
<td>9 - 11.5</td>
<td>4-7</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>10 - 32</td>
<td>8 - 27</td>
</tr>
</tbody>
</table>
1.3.3 CEREBROSPINAL FLUID PRESSURE:

The cerebrospinal fluid pressure is regulated by the product of the rate of fluid formation and the resistance to absorption through the arachnoidal villi. When either of these is increased, the pressure rises; when either is decreased, the pressure falls.

The normal pressure in the cerebrospinal fluid system when one is lying in a horizontal position averages 130 mm water (10 mmHg), though this may be as low as 70 mm water or as high as 180 mm water even in the normal person. These values are considerably greater than the 6.3 mmHg pressure in the interstitial spaces elsewhere in the body.

1.3.4 CIRCULATION OF CEREBROSPINAL FLUID:

The main channel of fluid flow from the choroid plexuses and then through the cerebrospinal fluid system has been shown in Fig. 1.5. The fluid secreted in the lateral ventricles passes into the third ventricle, and then passes along the aqueduct of sylvius into the fourth ventricle where a small amount of additional fluid is added. It then passes out of the fourth ventricle through three small openings [Gomez and Potts (1981)] for lateral formina of luschka and a mid line foramen of magendie, entering the cisterna magna, a large fluid space that lies behind the medula and beneath the cerebellum. The cisterna magna is continuous with the subarachnoid space that surrounds the entire brain.
Fig. 1.5 The circulation of the cerebrospinal fluid
and spinal cord, and the cerebrospinal fluid flows upward through his space towards the cerebrum; but before it can reach the cerebrum it must flow through the small tentorial opening around the mesencephalon where the flow is sometimes impeded. From the cerebral subarachnoid spaces, the fluid flows into the arachnoid villi that project mainly into the large sagittal venous sinus. Finally, the fluid empties into the venous blood through the surface of these villi.

1.3.5 ABSORPTION OF CEREBROSPINAL FLUID:

Cerebrospinal fluid is absorbed mainly into the venous system through the arachnoid villi, investigations of the subarachnoid space into the large venous sinuses of the cranium [Gramez and Potts (1977, 81), Gomes, Potts, Deonarine et al (1973), Shabo and Maxwell (1971), Mam, Butler, Johnson et al (1979), Alksne and Lovings (1972), Levine, Poulishock and Becker (1982)] . The arachnoid villi contain a labyrinth of cells separating cerebrospinal fluid and blood. When the subarachnoid pressure is lower that in the sinus, reflex of blood is prevented by collapse of the vacuoles. It is likely that a rise in cerebrospinal fluid pressure is sufficient to operate this mechanism which occurs at each arterial pulse.

Some cerebrospinal fluid must be absorbed elsewhere because in chronic obstructive hydrocephalus the
increase in brain size per day is only 2 percent of the amount of fluid formed per day Bradbury, Cserr and Westrop (1981), [Zervas, Liszczak, Mayberg et al (1982)]. Also, some cerebrospinal fluid into the blood is favoured by the colloid osmotic pressure of the plasma protein, since cerebrospinal fluid normally contains very little protein.

1.3.6 FUNCTION OF CEREBROSPINAL FLUID:

A major function of the cerebrospinal fluid is to cushion the brain within the soft and delicate brain substances and the rigid cranium. Any change of pressure is equally distributed and thus mechanical injury is prevented. If intracranium pressure tends to fall, more cerebrospinal fluid is retained. Fortunately, the brain and cerebrospinal fluid have approximately the same specific gravity. Therefore a blow on the head moves the entire brain simultaneously, causing no one portion of the blow.

1.3.7 BRAIN BARRIERS:

The selective membranes of the blood brain interface are illustrated schematically in Fig. 1.6. Many large molecular substances hardly pass at all from the blood into the cerebrospinal fluid or into the interstitial fluids of the brain even though these substances pass readily into the usual interstitial fluids.
(a) The blood-brain barrier

(b) The blood-cerebrospinal fluid barrier

Fig. 1.6 The blood-brain-cerebrospinal fluid system
of the body [Manery and Bale (1941), Katzmann and Leidermann (1953), Davson and Spaziani (1959), Crone (1965)]. Therefore, it is said that barriers called the blood-cerebrospinal fluid barrier, cerebrospinal fluid-brain barrier [Fishmann (1964)] and blood-brain barrier [Davson and Spaziani (1959)], exist between the blood and cerebrospinal fluid, cerebrospinal fluid and blood and blood and the brain fluid, respectively. These barriers exist in the choroid plexus and in essentially all areas of the brain parenchyma except the hypothalamus where substances diffuses easily into the tissue spaces. This ease of diffusion is very important because the hypothalamus responds to many different changes in the body fluids such as changes in osmolality, glucose concentration, and so forth, these responses provide the signals for feedback regulation of each of the factors. In general, these barriers are highly permeable to water, carbon dioxide, oxygen and most liquid-soluble substances such as alcohol and most anesthetics [Bohlowing, Hertz and Halnjen (1977), Bohlowing and Lassin (1975)]; slightly permeable to the electrolytes, such as sodium, chloride and potassium; and almost totally impermeable to substances like arsenic, sulfur and gold.
a) **Cerebrospinal Fluid-Brain Barrier:**

The cerebrospinal fluid-brain barrier is located in the layer of glial fibres lining the outer surface of the brain or in ependyma that lies the ventricles [Mayer, Maickel and Brodie (1959)]. Between the cerebrospinal fluid and brain the exchange rate is faster than its exchange across the cerebral capillaries of choroid plexus. But water soluble materials of large molecular weight cannot pass easily cerebrospinal fluid-brain barrier.

b) **Blood-Cerebrospinal Fluid Barrier:**

The transfer of materials from the blood into the cerebrospinal fluid takes place very slowly because there is a blood-cerebrospinal fluid barrier [Fishmann (1961), Feinsteinacher (1975)]. A lepoid soluble substances may pass from the blood to the cerebrospinal fluid than a less lepoid soluble material and ions, active compounds and drugs pass from the blood to the cerebrospinal fluid after passing from the brain-cerebrospinal fluid barrier. Epinephrine and calcium decreases the permeability of the above barrier. Theophyline on the other hand, increases the permeability of blood-cerebrospinal fluid barrier.

The blood-cerebrospinal fluid barrier is associated mainly with the endothelia of the choroid plexus and also in part with those of the meaningeal capillaries of the pia.
c) **The Blood-Brain Barrier:**

The blood-brain barrier is a controlling mechanism existing hypothetically as membrane barrier system which allows selectively some substances from the capillary blood to enter the brain [Dobbing (1961), Davson (1964), Crone (1976), Hansen, Lund-Andersencrone (1975), Paulson, Hertz, Bolowing and Lassen (1977)]. Its exact anatomical entity has not been clear, but it can be easily demonstrated to exist by administering certain dyes (trypan blue) into blood which will stain most of the blood tissues except the nerve tissue of the brain and spinal cord. Endothelium of the vessels with its basal membrane and astroglia are presumably involved in functioning the blood–brain barrier.

Morphologically, the blood–brain barrier is composed of endothelial cells of brain capillaries which are without vesicles and fenestrate ions and are bound together with tight junctions [Brightman and Reese (1969), Millgaard and Saunders (1975), Henrik Lund-Andsen (1979), Reese and Karnovsky (1967)]. Since, the endothelium constitutes a single layered epithelium Crone (1976). Lateral zonulae occludentes of the capillary endothelium forces solutes to pass through the cytoplasm of astrocyte which restrains the passage of molecule through its plasma membrane.
1.3.7 PHYSIOLOGICAL IMPORTANCE OF THE COMPOSITION OF CEREBROSPINAL FLUID AND BLOOD-BRAIN AND CEREBROSPINAL FLUID BARRIERS:

One of the most important results of this special brain fluid control system is the low concentration of potassium ions in the brain interstitial fluid. Experiments have shown that even when the circulating blood potassium rises to values almost two times normal, the potassium concentration of the cerebrospinal fluid still remains at its normal low value. Thus, the barrier system, along with its carrier-mediated transport of potassium, not only maintains a low potassium concentration but also keeps this concentration very constant, allowing the neurons to generate very high electrical potential that do not change with time vagaries of the test of the body.

The neurons of the brain require controlled environment, or else their function becomes abnormal and so also does the function of the entire brain. The blood-brain barrier protects the core brain tissue from determined substances in the blood and the transport processes of the choroid plexuses and the brain capillary endothelium help to provide the appropriate fluid environment for the brain.

The blood-brain barrier also prevents such substances as acetylcholine, norepinephrine, dopamine and glycine from entering the brain from the blood even though their concentration might become quite high in the circulating blood.
This is exceedingly important, because all these are very powerful synaptic transmitter substances and could have devastating effect on brain function.

1.4 DIFFUSION IN EYE AND BRAIN:

Diffusion is a transport process of physical quantities due to a concentration gradient. For a unit area to the transfer direction, the relationship between the flux and the gradient of concentration, C in the gap dy between the fluid layers can be stated in form of a constitutive equation

\[ \vec{F} = - D \frac{dC}{dy} \]  

(1.1)

This relation is called the first Fick's law of diffusion. The negative sign in equation (1.1) indicates that the flow takes place in the direction of decreasing concentration. D is a function of space coordinate and is called diffusion coefficient. If it is constant called diffusion constant. Its value for some common biological solutes in water lies between $0.05 \times 10^{-6}$ and $10 \times 10^{-6}$ cm$^2$/sec.

The diffusion processes are accompanied by mass flow, the total flux of the quantity transporated, F, with respect to a fixed coordinate system, is the summation of the two processes. Thus, for the case of diffusion of any species, from one place to another, the mass flux is given by

\[ \vec{F} = - D \nabla \vec{C} + \vec{C} \nabla \vec{F} \]  

(1.2)
where the first term of the right hand side is the vectorial generalization of equation (1.1) called the passive solute flux. The second term represents the carrier mediated flux under the action of velocity fluid $\vec{v}$, called the convective flux.

The equation of conservation of mass for the species is stating that the net flux of mass through an infinitesimal reference volume, plus the rate of production $P$ inside the volume $V$ equals the rate of mass accumulation inside the volume

$$\frac{\partial C}{\partial t} + \nabla \cdot \vec{F} = P \quad (1.3)$$

where $P$ is, in general, a function of concentration, tissue and location. From Equation (1.2), Equation (1.3) can be written as

$$\frac{\partial C}{\partial t} + \nabla \cdot (\vec{v} C) = D \nabla^2 C + (\nabla C) (\nabla D) + P \quad (1.4)$$

For incompressible, homogeneous fluid and dilute solute ($D = \text{constant}$), the equation (1.4) can be written as

$$\frac{\partial C}{\partial t} + \vec{v} \cdot \nabla C = D \nabla^2 C + P \quad (1.5)$$

If there is no source or sink inside the volume, the rate of change of the amount of the solute is equal to the amount of the solute which comes out of the surface per
unit time is given by

$$\frac{\partial C}{\partial t} = - \text{div} (F)$$  \hspace{1cm} (1.6)

This equation is known as second Fick's law of diffusion.

From Equation (1.2), Equation (1.6) can be written as

$$\frac{\partial C}{\partial t} = - \nabla (-D \nabla C + \nabla C)$$

or

$$\frac{\partial C}{\partial t} + \nabla \cdot (\nabla C) = \nabla \cdot (D \nabla C)$$  \hspace{1cm} (1.7)

For incompressible and homogeneous fluid with dilute solution, Equation (1.7) is written as follows:

$$\frac{\partial C}{\partial t} + \nabla \nabla C = D \nabla^2 C$$  \hspace{1cm} (1.8)

1.5 FLOW THROUGH POROUS MEDIA:

The velocity, $\vec{v}$ of fluid in porous medium is obtained by the Darcy's law for small Reynold number and Brinkman's equation for small permeability.

a) Darcy's Law:

Darcy's law is generally accepted as a macroscopic equation of motion for Newtonian fluid in porous media at small Reynold numbers, established empirically by Darcy (1856).
According to this law, the mean filter velocity \( v \), is proportional to the sum of gradient of the pressure and the gravitational force, i.e.

\[
\vec{v} = \frac{K}{\mu} (-\nabla P + \rho g)
\]  

Later Musket (1937) has proved that the \( K \) in equation (1.9) should be related to the permeability of the porous material and Equation (1.9) takes the form

\[
\vec{v} = - \frac{K}{\mu} \nabla P
\]  

where \( K \) is the permeability of the porous medium and has the dimension of length squared.

Many investigators have studied the effect of porosity of many physiological system e.g. trabecular meshwork and vitreous body in human eye [Tandon et al (1986, 1987), Weinbaum (1965), Fatt (1965), Jakson et al (1982)] by using Darcy's law.

b) **Brinkman's Equation:**

Equation (1.10) is of the potential flow form and is valid when \( K \) is very large. However, in many practical problems the permeability is small near the boundary, i.e. particles are loosely packed such that there exists a boundary layer thickness very near to the surface. The existence of this boundary layer thickness very near to the surface. The existence of this boundary layer thickness is experimentally demonstrated by Beavers and Joseph (1967). For this
purpose, instead of the potential nature of flow Equation (1.10), we need the boundary layer type equation of the form:

$$\nabla P = \rho g - \frac{\mu}{K} u + u \nabla^2 u$$  \hspace{1cm} (1.11)

This boundary layer type equation for flow through porous media was originally postulated by Brinkman (1941) and a rigorous theoretical proof using the ensemble averages and point-force approximations was given by Latter by Tam (1969).

1.6 TRANSPORT THROUGH EPITHELIA:

(a) Passive Transport:

Let us consider the case of a membrane which hinders the movement of solvent. If the membrane separates two solutions of the same solute which are initially at different concentrations, solute moves from more concentrated to the less concentrated solution and solvent moves in the opposite direction. Then,

$$\text{Diffusional flow} = J_D = L_D \Delta \pi$$ \hspace{1cm} (1.13)

where $\Delta \pi$ is osmotic pressure difference and $L_D$ is constant which is determined by the diffusivity of the solute and solvent within the membrane and

$$\text{Osmotic flow} = J_V = J_{PD} \Delta \pi$$ \hspace{1cm} (1.14)
where \( L_{PD} \) is constant and is determined by the relative conductivity of the membrane for solute and solvent.

Let us consider the membrane, which resists solute transport more than solvent flow, separating the two dilute, equi-molar solutions of the same solute. If a pressure gradient, \( \Delta P \), is applied across the membrane. Thus,

\[
\text{Volume flow} = J_V = L_P \Delta P
\]  

(1.15)

where \( L_P \) is determined by the conductivity of the membrane for the solvent and

\[
\text{Flow of solute relative to that of solvent} = J_D = L_{DP} \Delta P
\]  

(1.16)

where \( L_{DP} \) is constant, which is determined by the relative conductivities of the membrane for solute and solvent.

Therefore, from Equations (1.13) and (1.16) we obtained for a membranes separating solutions of different osmotic and hydrostatic pressure.

\[
\text{Volume flow} = J_V = L_P \Delta P + L_{PD} \Delta \pi
\]  

(1.17)

\[
\text{Diffusional flow} = J_D = L_{DP} \Delta P + L_D \Delta \pi
\]  

(1.18)

Onsager (1931 a,b) suggested that

\[
L_{PD} = L_{DP}
\]

The coefficient \( L_P \) is also known as hydraulic conductivity or filtration coefficient and

\[
L_P = \frac{1}{f_{wm}}
\]  

(1.19)
Also,

\[
\text{Measured osmotic pressure } = P = - \frac{L_{PD}}{L_P} 
\]  
(1.20)

in which \(-\frac{L_{PD}}{L_P}\) is called reflection coefficient and is denoted by \(\sigma\):

\[
\sigma = - \frac{L_{PD}}{L_p} = \frac{V_w - V_s}{V_w} = 1 - \frac{V_s}{V_w} 
\]  
(1.21)

Therefore equation (1.17) becomes

\[
J_V = L_P (\Delta P - \Delta \pi) 
\]  
(1.22)

In most practical situations, we are concerned with the total mass flow of solute across a membrane rather than its volume flow relative to solvent. This total flow, \(J_s\), may be readily calculated from (1.18) and (1.22) if the mean concentration of solute within the membrane (\(\bar{c}_s\)) is known, since:

\[
J_s = (J_V + J_D) \bar{c}_s 
\]  
(1.23)

Substituting for \(J_V\) and \(J_D\)

\[
J_s = \{L_P(\Delta P - \Delta \pi) + (L_{PD} \Delta P + L_D \Delta \pi)\} - \bar{c}_s 
\]  
(1.24)

From Eq. (1.31)

\[
\Delta P = \frac{J_V}{L_P} + \sigma \Delta \pi 
\]  
(1.25)

and remembering

\[
\frac{L_{PD}}{L_P} = - \sigma 
\]  
(1.26)
\[ J_s = \{J_V + L_p \alpha \Delta \pi - L_p \alpha \Delta \pi - \sigma J_V + L_{PD} \alpha \Delta \pi + L_p \Delta \pi \} \bar{C}_s \]  

(1.27)

\[ = J_V (1 - \sigma) \bar{C}_s + \Delta \pi (L_{PD} + L_D) \bar{C}_s \]  

(1.28)

when

\[ J_V = 0 \]

\[ \frac{J_s}{\Delta \pi} = (L_{PD} - L_D) \bar{C}_s = \omega \]  

(1.29)

where, \( J_s/\Delta \pi \) (when \( J_V = 0 \)) represents the permeability of the membrane to solute and is, for this reason, given the separate symbol, \( \omega \), (1.28) may then be rewritten in more compact form as

\[ J_s = J_V (1 - \sigma) \bar{C}_s + \omega \Delta \pi \]  

(1.30)

in which

\[ J_V = L_p (\Delta P - \sigma \Delta \pi) \]  

(1.31)

\[ J_s = L_p (\Delta P - \sigma \Delta \pi) (1 - \sigma) \bar{C}_s + \omega \Delta \pi \]  

(1.41)

(b) Active Transport:

Active transport occurs from the lower concentration zones to the higher concentration zones, which over-rides the passive diffusion processes (e.g. leakage of Na\(^+\) into the cell). In this case, however, transport is truly against often large concentration gradients, and
therefore biochemical cellular energy is required to fuel the process.

Very little is known about active transport. Enzymes are believed to catalyze the chemical reactions between solutes and carrier. The carriers, probably proteins or lipoproteins, may work in three possible ways, as discussed earlier. Besides the usual diffusive motion type of mechanism, the carrier might (if long enough) simply pick up the solute, rotate 180 degrees, and release it at the other side. Or, the carrier (again, if long enough) may shuttle the solute along a series of active sites of some sort.

Active transport is often limited to certain areas or organs of the body, such as the eye, brain, kidneys, intestines and liver however facilitated transport, when it occurs, appears to be general for nearly all cells in the body. Hormones have a particularly great influence on active transport processes, especially amino acid transport.

(c) Facilitated Transport:

Some substances, quite insoluble in lipids, are larger than the membrane pores, and yet still transfer through cell membranes quite well sugars (e.g. glucose) are typical solutes of this kind.

The rate of this facilitated carrier transport depends on (a) the concentration difference of solute across the membrane (b) the amount of carrier present
(c) the rate of combination and splitting reactions and (d) the diffusion coefficient of the carrier, solute combination. The nature of the carrier is not yet known.

1.7 Survey Related to the Work Reported in the Thesis:

So far we have concentrated ourselves in giving a brief introduction of anatomical and physiological background of the systems - the eye and the brain (cerebrospinal fluid). For the proposed investigations in two systems for this thesis relating to diffusion and fluid transport across and through the biological tissues and membranes, we present below a brief survey of the recent research work pertaining to this thesis so that contributions of this thesis may be placed in their proper perspective.

Transport of various ions between blood vessels of the eye and intraocular fluids take place across membranes which offer varying degrees of resistance to the diffusion of different ions and substances. The main region of such resistances are: ciliary epithelium, capillary wall and epithelium of the iris. The transport of various ions across the ciliary epithelium accompanied by osmotic movement of water from the ciliary body stroma into the posterior chamber constitute the prime mover in the formation of aqueous humour. The production of aqueous humour is essential for the stability and regulation of intra-ocular pressure which
is necessary for the nourishment of avascular tissues and visual functions of the eye. It is, therefore, a subject of special interest to the physiologists and clinicians alike. In the aqueous humour formation principal ions and substances which are transported across the ciliary epithelium are sodium, potassium, chloride, bicarbonate, thiocyanate, bromide glucose, amino-acids, ascorbic-acids. The sodium ion is the predominant one transported across the ciliary epithelium from the ciliary body stroma into the posterior chamber [Davson (1969)].

The ciliary epithelium is unique in its organization, because it consists of two layers of cuboidal cells joined at their apices and sandwiched between the two basal laminae. The layer closest to highly vascularized stroma is pigmented layer. The inner layer next to posterior chamber consists of non-pigmented cells characterized by numerous and extensive cell infoldings. The non-pigmented cells, pigmented cells and both layers are connected by various types of leaky intercellular junctions.

Due to complicated structure of the ciliary epithelium, the mechanism of transport through it has not been duly elucidated. Various theories have been proposed to treat epithelial transport. One of them is "Local Osmotic Gradient" transport model proposed by Diamond and Bossert that can be employed to describe the transport of solute coupled with water across the ciliary epithelium. In their original model,
the intercellular space was closed at one end by a tight function which allowed no flow of water or solute. Water flow within the extracellular space was generated by an osmotic gradient set up by active transport of solute across the cell wall. A non-dimensional treatment of Diamond and Bossert model was given by Segal (1970) introducing the concept of "isotonic convection approximation".

The original Diamond and Bossert model has been extended by several workers since 1970. Using the concept of Diamond and Bossert's "local osmotic gradient" theory, Weinbaum and Goldgraben (1972) presented a non-dimensional model for the transport of solute coupled with water across the ciliary epithelium. A generalization to different boundary conditions has been given by Sackin and Boulpaep (1975), while the case of two solutes has been considered by Andrietti et al (1979). Also, if the original Diamond and Bossert's non-linear model is not suitable to analytical solutions, some considerations on the qualitative behaviour of the solutions, their existence and uniqueness have been given by Sackin and Boulpaep (1975) and Garner and Kellogg (1980).

Therefore, Segal's approximation has been used by many authors interested in the analysis of water and solute transport in epithelia [Hill (1975), King-Hele (1977), Weinslein and Stephenson (1981), Andrietti (1986), Andretti and Pezzotta (1982), Andretti et al (1979)].
Weinbaum and Goldgraben (1972) in their model for the ciliary epithelium, assumed that the solute is actively transported into the extracellular channel of the ciliary epithelium from the adjacent cells and the water movement is passive. They finally concluded that the formation of the aqueous humour is pressure dependent mechanism associated with an active transport.

Based on the literature studied, Chapter II presents a qualitative two-dimensional theoretical model for the ion-transport from the ciliary body stroma to the posterior chamber of the eye by extending Diamond and Bossert's "Local Osmotic Gradient" theory for epithelial transport. In this model, it is assumed that the solute is actively transported into the extracellular channels of the ciliary epithelium from the adjacent cells and the water is transported passively. Thus, the chapter is devoted to the study of the transport phenomenon through leaky ciliary epithelium under the influence of three driving forces: transmembrane osmotic pressure between inner and outer bathing solutions, hydrodynamical pressure difference and local osmotic pressure due to ion pump (active transport).

Avascular ocular tissues such as cornea and lens derive their nutrients from the aqueous humour occupying the ocular chambers. For the nourishment purposes homeostasis of the aqueous humour concentration in the
posterior and anterior chambers is essential. Any disturbance in the homeostasis interrupts the nutritional supply to the ocular tissues. The nutritional substances penetrate into the aqueous humour from the blood vessels of ciliary processes and iris. A knowledge of the accumulation of various ions and substances into the posterior chambers and factors influencing the transport of them is essential in understanding of the homeostasis of concentration of the anterior chamber and posterior chamber aqueous humour. A theoretical study can contribute in the knowledge pertaining to the ions accumulation in the anterior and posterior chambers. The accumulation of ions into the ocular chambers depends upon the penetrating quantity of ions into the chambers and quantity of ions leaving the chamber which, in turn, depends upon transfer coefficients of the membranes and potential difference across the membranes known as blood aqueous barrier separating the blood and the aqueous humour. Most of experimental studies of solute transfer in the anterior and posterior chambers have been concerned with the estimation of the quantity of ions which enter and leave the posterior and anterior aqueous by passive diffusion and unidirectional flow. Therefore, it is appropriate to accomplish a mathematical analysis of the ion accumulation in the posterior and anterior aqueous humour considering the quantity of ions entering and leaving the ocular chamber's aqueous.
Chapter III is devoted to a mathematical analysis of transient accumulation of ions from the plasma into the ocular chamber's aqueous humour following a continuous administration of ions in the plasma. It is assumed that the penetration of ions Na\(^+\) and Cl\(^-\) occurs across the ciliary processes due to passive unidirectional flow to posterior chamber and potential difference across the ciliary epithelium. The movement of ions across the iris–anterior chamber interface occurs due to passive diffusion. It is concluded from the results that the concentration in the posterior aqueous is large initially and in the later stage of the process, this concentration becomes the lower than that in the anterior aqueous humour. Also, the effect of various physiological parameters is discussed.

The movement of substances into and out of the vitreous body plays a very vital role in the understanding of the homeostosis mechanism of the blood–retina barrier. A substance that diffuses across the vitreous–posterior chamber interface into the vitreous body from the posterior aqueous humour, secreted by the ciliary processes crosses the blood–retina barrier. Also, blood–borne substances penetrate the blood–retina barrier to enter the vitreous body. A knowledge of the mechanism of movement of a substance within the vitreous body which may interact with the surrounding media, i.e. blood–retina barrier is essential as a basis for further studies pertaining the blood–retina barrier.
In 1975, Fatt presented a mathematical model for simultaneous liquid flow and diffusion in the vitreous body, treating it as a spherical cavity. From this study he concluded that the velocity of the carrier fluid obtained from estimated flow of liquid through the vitreous body is uniform [Hedbyes and Fatt]. Jakson (1982) suggested that the flow of liquid through the vitreous body can be described by D'Ary's law.

Chapter IV deals with the liquid flow and transient diffusion of fluorescein simultaneously through the vitreous body of the eye. The vitreous chamber is modelled as a spherical cavity with an internal concentric cavity of very small radius. It is assumed that there is a continuous production of liquid in the internal cavity. The bulk velocity is described by Darcy's law as suggested by Jakson et al (1982). The differential equation governing the concentration in the vitreous body is solved by using Laplace transform and Residual Galerkin technique. From the analysis, we conclude that the convection plays an important role in the diffusion of tracers in the vitreous body and the ratio of diffusion to convective flux depends on permeability and the viscosity of vitreous fluid. Delayed diffusion of fluorescein as observed in case of diabetic subjects may be attributed to the higher viscosity of vitreous fluid in diabetic patients.
Most of the surface of vitreous body is bounded by the retina - a structure that allows the passage of certain substances across it. A substance which diffuses through the vitreous body crosses the blood-retina barrier to leave the eye. Thus, the concentration of tracer at the external surface of the vitreous body is not constant. Also, the mechanism of movement of a substances within the vitreous will be influenced by the characteristics of the barrier. Thus, the boundary condition at the external surface of the vitreous chamber can be improved by introducing the condition at the barrier

\[ D \frac{\partial C}{\partial r} = P (C - C_p) \]

where \( C_p \) is the blood plasma concentration, \( P \) the permeability of the barrier and \( D \) the diffusion coefficient of the tracer.

Therefore, Chapter V is concerned with the bulk diffusion of intravitreally injected fluorescein in the vitreous body and the subsequent transport across the blood-retina barrier in the transient state. The flow of liquid in the vitreous body is described by the Brinkman's equation and resultant equation is solved by the Galerkin technique using Laplace transformation. The effect of the permeability coefficient characterising the function of blood-retina barrier on the tracer distribution is discussed.
The blood-retina barrier which is constituted by the endothelial lining of the retinal vasculature and the pigment epithelium separates the retinal cells from the blood stream. In normal subjects, the blood retina barrier is tight and it allows the passage of only a few metabolically important substances from the blood stream into the vitreous body while all other substances are retained. Certain substances from the aqueous humour which are required for the retina for its nutritional purpose pass through the vitreous body and subsequently, the blood-retina barrier permits their passage. Thus, blood-retina barrier has twin mechanism of solute transport.

A number of experimental investigators have established that the rate of disappearance of intravitreally injected fluorescein out of the eye is greater than that of intraperitoneally administered fluorescein into the vitreous body across the barrier [Cunha-Vaz and Maurice (1967)].

One of the characteristics of the blood-retina barrier responsible for the solute transport across it is the permeability. The permeability of the barrier is the most suitable parameter for analysis of the transport characteristics of the barrier.

An exact determination of the permeability may provide a deeper and more viable understanding of pathophysiology of the disease which is associated with barrier breakdown. Also, the permeability may be a sensitive parameter for the
assessment of certain diseases and their intensity. The permeability of the blood-retina barrier is suitable for the mathematical analysis. Thus the permeability of the barrier is the most suitable parameter for identification and location of the various diseases and may prove useful for the clinical purposes.

In order to investigate the permeability properties of the blood-retina barrier for intravitreally as well as intraperitoneally injected fluorescein and its determination requires a knowledge of the fluorescein concentration in the vitreous body.

Therefore, Chapter VI deals with the diffusion of fluorescein in the vitreous body and its transient transport across the blood-retina barrier in the eye for both intravitreally and intraperitoneally administration of the tracer. In the analysis the permeability coefficient - a parameter characterising the function of blood-retina barrier and diffusion coefficient are determined. The inward and outward permeability of the barrier are discussed. In order to explain outward disappearance, the problem analyzed, incorporates an extrusion mechanism in outward transport of the tracer as suggested by Blair et al (1983).

Most of the cerebrospinal fluid is produced by the choroid plexuses in the lateral ventricles. According to Welch (1963) and Davson and Segal (1970) the plexuses produce about 70-80% of the cerebrospinal fluid. In 1983, McComb
suggested that normally 80 to 90% of the total cerebrospinal fluid secretion is derived from the choroid plexuses.

Morphologically, the choroid plexuses are characterized by a rich capillary bed closely opposed to a single layer of endothelial cells folded into numerous small villi. The tight junctions are attached at the apical sides of the cells and present blood cerebrospinal fluid barrier.

The formation of cerebrospinal fluid in the ventricular cavities derives from the transport of certain solutes and solvents across the choroid plexuses. Na\(^+\) is the principal one of the solutes that are transported coupled with water from the blood to the ventricles across the choroid plexuses. Thus, a theoretical study of the Na\(^+\) ion transport coupled with water can be helpful in enhancing our understanding regarding the mechanism of cerebrospinal fluid secretion.

Chapter VII is primarily concerned with a theoretical study of Na\(^+\) transport coupled with water across the blood-cerebrospinal fluid barrier. The model for Na\(^+\) ion transport across the choroid plexuses has been developed by using an extended form of Diamond and Bossert's "Osmotic Gradient Theory" for transepithelial transport of solutes along with the water. The flow system is assumed as a channel consisting of two sections representing the intracellular space and tight junction. Fluid movement occurs under the influence of solute transport of Na\(^+\) concentration and pressure differences.
Analytical solutions are obtained using Segal's "isotonic convection approximation". Theoretical results have been presented through the graphs and the effects of group parameters on the flow variables have been brought out through graphs.

Glucose is the brain's most important substrate for energy metabolism [McElwain (1966), Siesjo (1978)]. The brain is dependent on a constant supply of glucose from blood stream to the brain tissue from which adequate amounts of glucose are transported to the nerve and glial cell metabolic system. These processes involve transport through the blood-brain barrier, diffusion through the brain's extracellular space, transport through the nerve and glial cell system and transport over the choroid plexus. Thus, the transport of glucose in blood-brain-cerebrospinal fluid system has attracted the attention of a number of the physiologists and other investigators working in this area.

The transport of glucose across the blood-brain and blood-cerebrospinal fluid barriers is subtle to mathematical analysis because the mechanism of glucose transport in the blood-brain-cerebrospinal fluid system has not been quite clear despite of a large number of investigators. It has been established that the tight junctions between the endothelial cells of the brain capillaries represent the blood-brain barrier while the tight junctions between the epithelial cells of the choroid plexuses constitute the
blood-cerebrospinal fluid barrier.

A theoretical analysis of the glucose transport in the blood-brain-cerebrospinal fluid system and its distribution in the brain extracellular space as well as in cerebrospinal fluid can provide a better understanding of physiology of the barriers. The Chapter VIII is primarily devoted to a theoretical study of the penetration of intravenously or intraventricularly injected glucose in the brain's extracellular space and cerebrospinal fluid. Also, a study of the relation between the average concentrations in blood-plasma, brains extracellular space and in cerebrospinal fluid has been conducted and the effects of the different model parameters on the penetration of glucose in the brains extracellular space and cerebrospinal fluid have been analysed.

The model assumes the brain to be a shell round the centre occupied by the ventricular space and covered on the outside by cerebral subarachonoid space. The transport of glucose from blood into the brain tissue and from cerebrospinal fluid into the blood occurs due to the facilitated diffusion. Glucose diffuses freely in the extracellular brain tissue and cerebrospinal fluid. The bulk flow of cerebrospinal fluid also contributes to the glucose transport. Also, glucose is metabolized in extracellular space of the brain. Analytical solution has been obtained using a approximate method introduced by Rashevsky (1960).