# BLOOD BRAIN BARRIER

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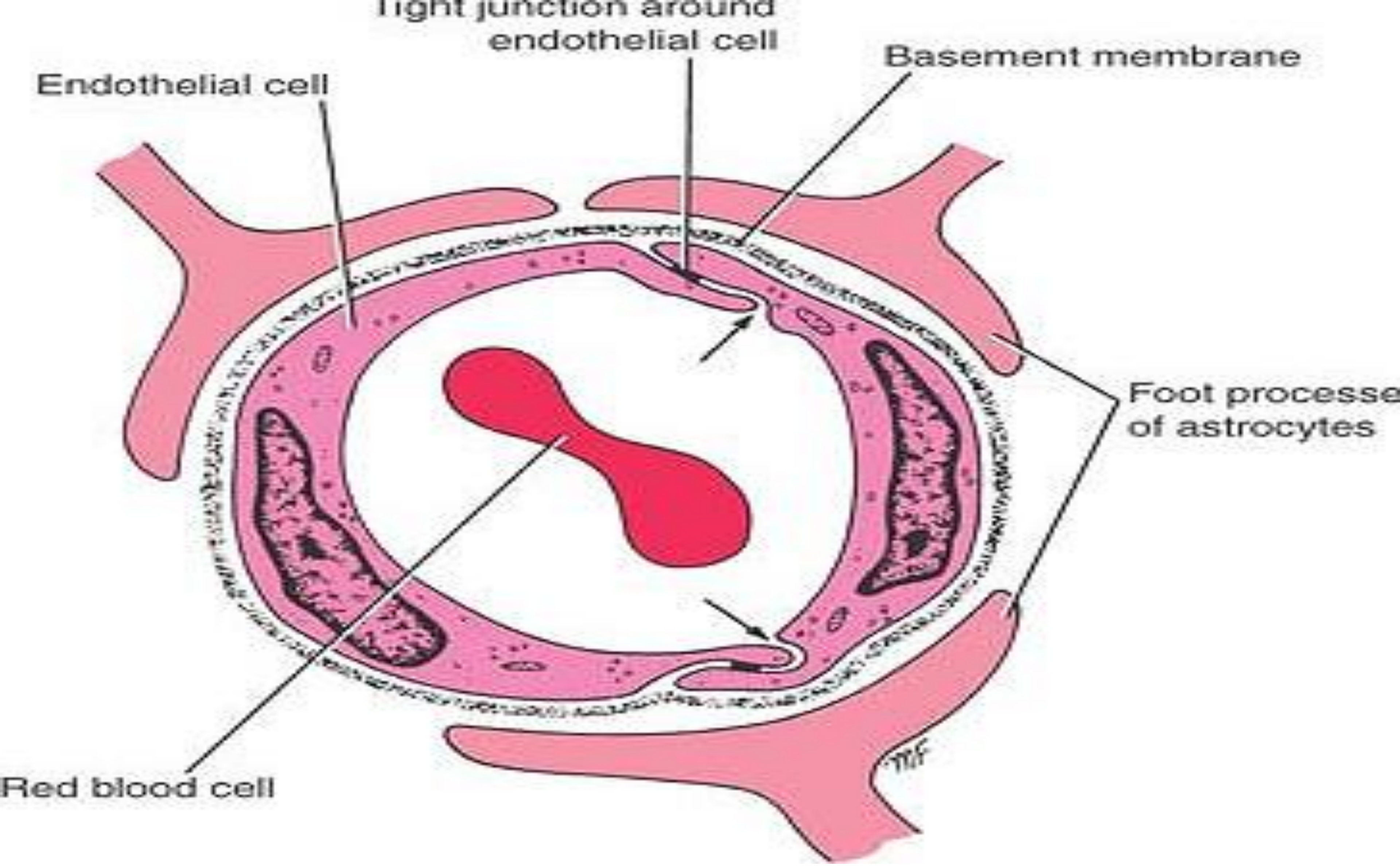
# CONCEPT OF BLOOD-BRAIN BARRIER

- The experiments of Paul Ehrlich in 1882 showed that living animals injected intravascularly with vital dyes, such as trypan blue, demonstrated staining of all the tissues of the body except the brain and spinal cord.
- Later, it was demonstrated that although most of the brain is not stained after the intravenous injection of trypan blue ,the following areas do in fact become stained: the pineal gland, the posterior lobe of the pituitary, the tuber cinereum, the wall of the optic recess, and the vascular area postrema1 at the lower end of the fourth ventricle.
- These observations led to the concept of a blood-brain barrier.




**Cross section of a blood capillary of the central nervous system in the area where the blood-brain barrier exists.**

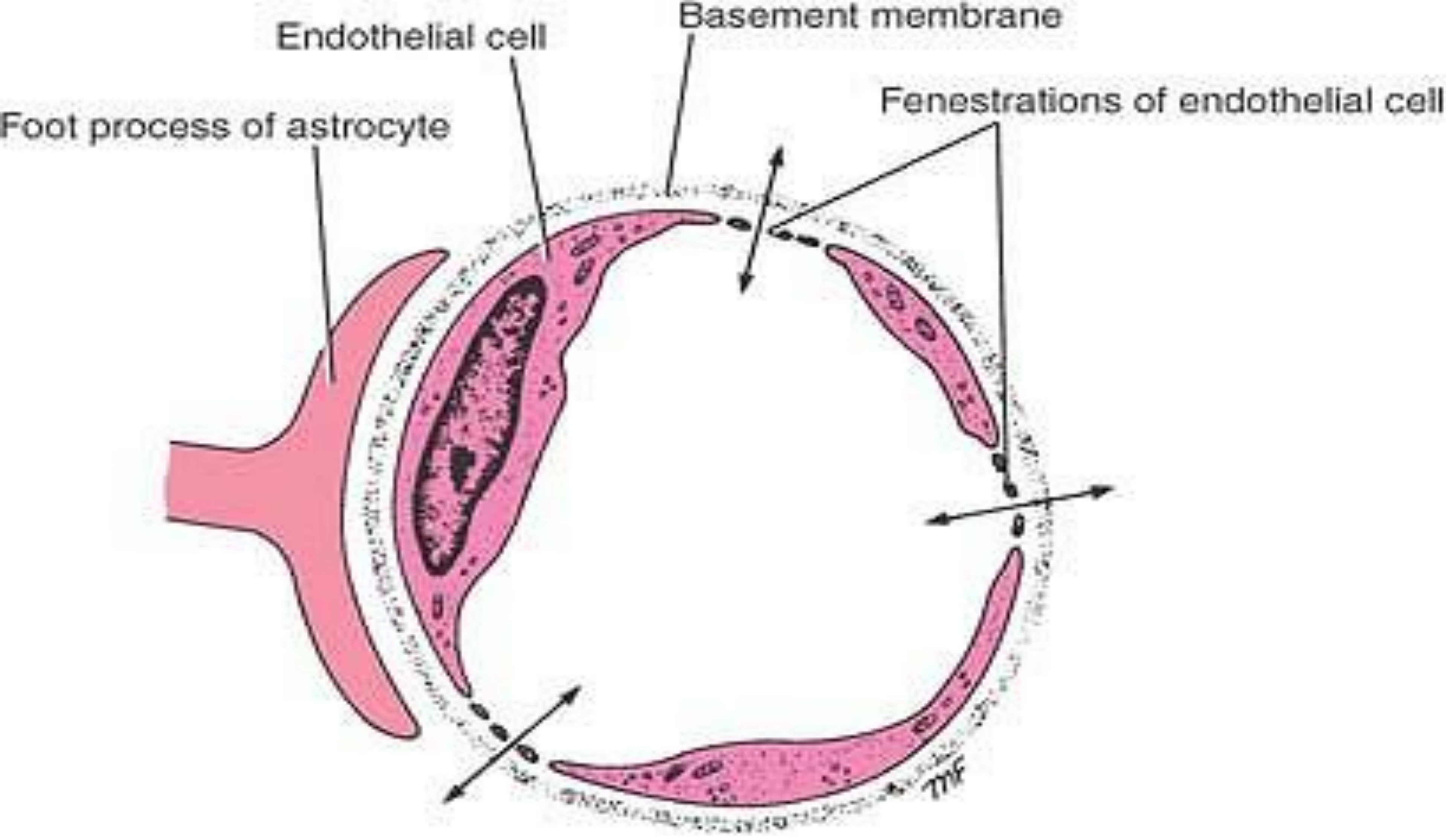
- The permeability of the blood-brain barrier is inversely related to the size of the molecules and directly related to their lipid solubility.
- Gases and water pass readily through the barrier, whereas glucose and electrolytes pass more slowly.
- The barrier is almost impermeable to plasma proteins and other large organic molecules.
- Compounds with molecular weights of about 60,000 and higher remain within the blood circulatory system.
- This would explain why in the early experiments with trypan blue, which quickly binds to the plasma protein albumin, the dye did not pass into the neural tissue in the greater part of the brain.

# Structure of Blood Brain Barrier

- Electron-microscopic examination of a villus of a choroid plexus shows that the lumen of a blood capillary is separated from the lumen of the ventricle by the following structures:
- (1) the endothelial cells, which are fenestrated and have very thin walls (the fenestrations are not true perforations but are filled by a thin diaphragm)
- (2) a continuous basement membrane surrounding the capillary outside the endothelial cells
- (3) scattered pale cells with flattened processesd
- (4) a continuous basement membrane, on which rest (5) the choroidal epithelial cells .

- The use of electron-dense markers such as lanthanum and horseradish peroxidase (Brightman and Reese, 1969) has shown that these substances do not penetrate between the endothelial cells of the capillaries because of the presence of tight junctions that form belts around the cells. When the dense markers are introduced into the extracellular spaces of the neuropil, they pass between the perivascular foot processes of the astrocytes as far as the endothelial lining of the capillary.
- On the basis of this evidence, it is now known that the tight junctions between the endothelial cells of the blood capillaries are responsible for the blood-brain barrier
- In molecular terms, the blood-brain barrier is thus a continuous lipid bilayer that encircles the endothelial cells and isolates the brain tissue from the blood.
- This explains how lipophilic molecules can readily diffuse through the barrier, whereas hydrophilic molecules are excluded.

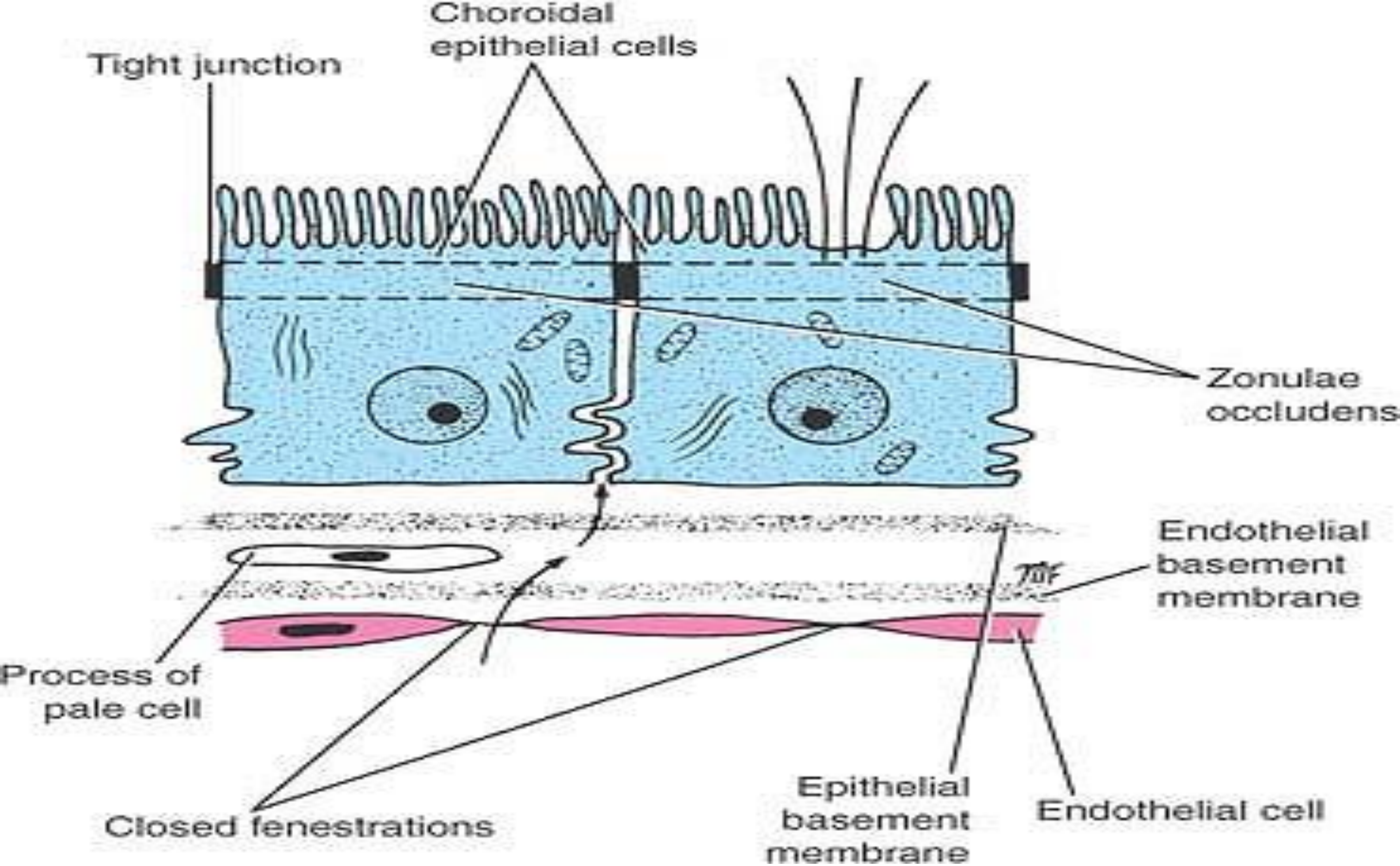
- Although the blood-brain barrier exists in the newborn, there is evidence that it is more  barrier exists in the newborn, there is evidence that it is more permeable to certain substances than it is in the adult.
- The structure of the blood-brain barrier is not identical in all regions of the central nervous system. In fact, in those areas where the blood-brain barrier appears to be absent, the capillary endothelium contains fenestrations across which proteins and small organic molecules may pass from the blood to the nervous tissue.
- It has been suggested that areas such as the area postrema of the floor of the fourth ventricle and the hypothalamus may serve as sites at which neuronal receptors may sample the chemical content of the plasma directly.
- The hypothalamus, which is involved in the regulation of the metabolic activity of the body, might bring about appropriate modifications of activity, thereby protecting the nervous tissue.




**Cross section of a blood capillary of the central nervous system where the blood-brain barrier appears to be absent.**
**Note the presence of fenestrations in the endothelial cells.**

# *Blood Cerebrospinal Fluid Barrier*

- There is free passage of water, gases, and lipid-soluble substances from the blood to the cerebrospinal fluid.
- Macromolecules such as proteins and most hexoses other than glucose are unable to enter the cerebrospinal fluid.
- It has been suggested that a barrier similar to the blood-brain barrier exists in the choroid plexuses.




**Section of villus of choroid plexus.**

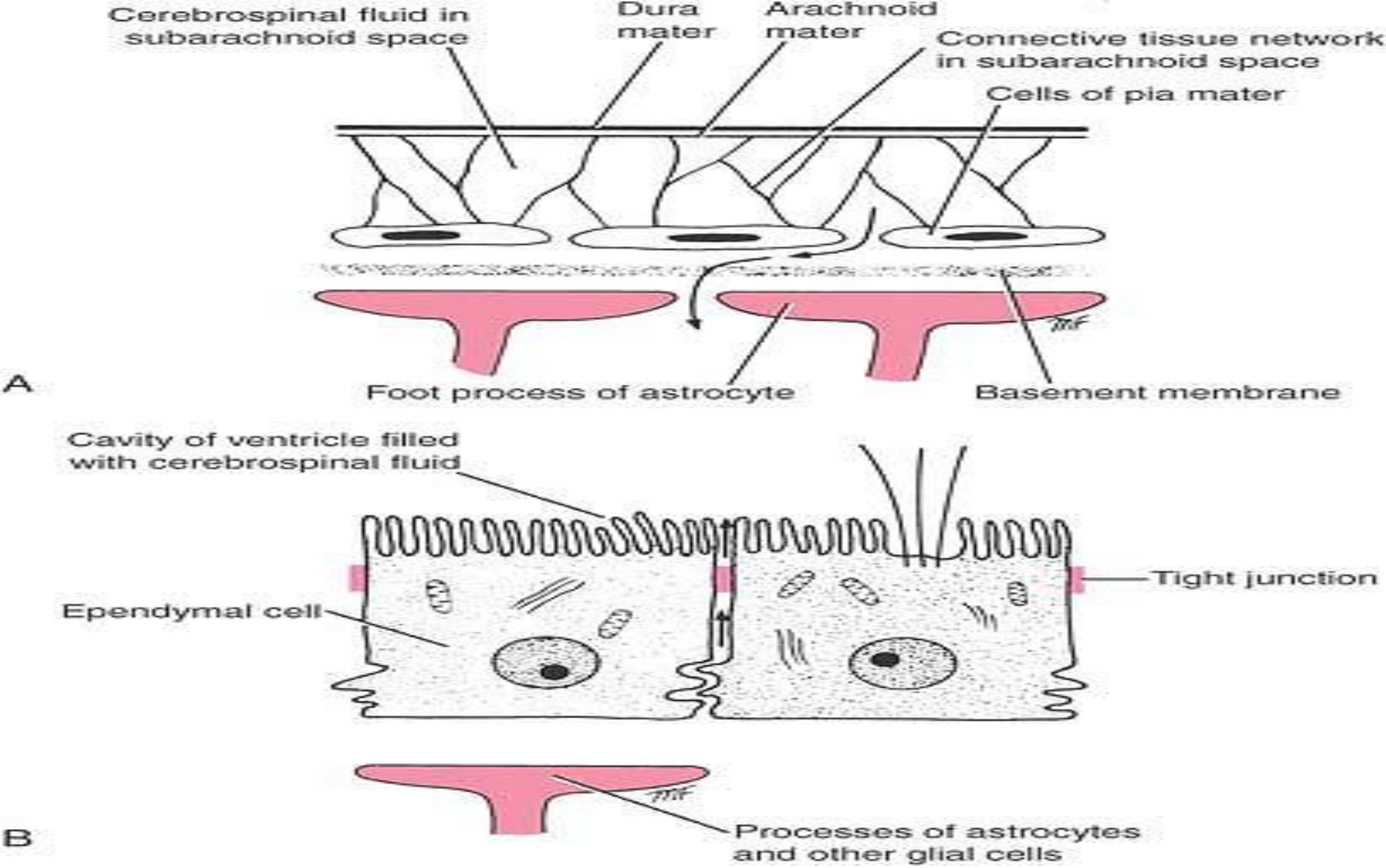
# *Cerebrospinal Fluid Brain Interface*

- Although vital dyes given by intravenous injection do not gain access to most brain tissues, if the dyes are injected into the subarachnoid space or into the ventricles, they soon enter the extracellular spaces around the neurons and glial cells.
- Thus, there is no comparable physiologic barrier between the cerebrospinal fluid and the extracellular compartment of the central nervous system.
- It is interesting, however, to consider the structures that separate the cerebrospinal fluid from the nervous tissue. Three sites must be examined:

(1) the pia-covered surface of the brain and spinal cord,

(2) the perivascular extensions of the subarachnoid space into the nervous tissue

(3) the ependymal surface of the ventricles




**section of the cerebrospinal fluid-brain interface. A: Outer surface of the brain. B: Ventricular surface of the brain.**

- The pia-covered surface of the brain consists of a loosely arranged layer of pial cells resting on a basement membrane
- Beneath the basement membrane are the astrocytic foot processes.
- No intercellular junctions exist between adjacent pia cells or between adjacent astrocytes; therefore, the extracellular spaces of the nervous tissue are in almost direct continuity with the subarachnoid space.
- The prolongation of the subarachnoid space into the central nervous tissue quickly ends below the surface of the brain, where the fusion of the outer covering of the blood vessel with the pial covering of the nervous tissue occurs. The ventricular surface of the brain is covered with columnar ependymal cells with localized tight junctions
- Intercellular channels exist that permit free communication between the ventricular cavity and the extracellular neuronal space.
- The ependyma does not have a basement membrane, and there are no specialized astrocytic foot processes because the neuroglial cells are loosely arranged.

## ***Functional Significance of the Blood Brain and Blood Cerebrospinal Fluid Barriers***

- In normal conditions, the blood-brain and blood cerebrospinal fluid barriers are two important semipermeable barriers that protect the brain and spinal cord from potentially harmful substances while permitting gases and nutriments to enter the nervous tissue

## Blood-Brain Barrier in the Fetus and Newborn

- In the fetus, newborn child, or premature infant, where these barriers are not fully developed, toxic substances such as bilirubin can readily enter the central nervous system and produce yellowing of the brain and kernicterus.  This is not possible in the adult.

## Brain Trauma and the Blood-Brain Barrier

- Any injury to the brain, whether it be due to direct trauma or to inflammatory or chemical toxins, causes a breakdown of the blood-brain barrier, allowing the free diffusion of large molecules into the nervous tissue. It is believed that this is brought about by actual destruction of the vascular endothelial cells or disruption

## Drugs and the Blood-Brain Barrier

- The systemic administration of penicillin results in only a small amount entering the central nervous system.
- This is fortunate, because penicillin in high concentrations is toxic to nervous tissue. In the presence of meningitis, however, the meninges become more permeable locally, at the site of inflammation, thus permitting sufficient antibiotic to reach the infection.
- Chloramphenicol and the tetracyclines readily cross the blood-brain barrier and enter the nervous tissue. The sulfonamide drugs also easily pass through the blood-brain barrier.
- Lipid-soluble substances such as the anesthetic agent thiopental rapidly enter the brain after intravenous injection.
- On the other hand, water-soluble substances such as exogenous norepinephrine cannot cross the blood-brain barrier. Phenylbutazone is a drug that becomes bound to plasma protein, and the large drug protein molecule is unable to cross the barrier.
- Most tertiary amines such as atropine are lipidsoluble and quickly enter the brain, whereas the quaternary compounds such as atropine methylnitrate do not.
- In Parkinson disease, there is a deficiency of the neurotransmitter dopamine in the corpus striatum.
- Unfortunately, dopamine cannot be used in the treatment, as it will not cross the blood-brain barrier.

# Suggested Readings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