INTRODUCTION
AND REVIEW OF LITERATURE

Vitamin A is a generic term to all compounds other than carotenoids that exhibit the biological properties of retionl. Retinoids, refer to the chemical entity retionl and other related naturally occuring derivatives and synthetic analoges *(Martin, 1983)*.

Vitamin A has important functions in the body. It plays an essential role in the function of the retina. It is necessary for growth and differentiation of the epithelial tissues and also for growth of bone, reportduction and embryonic development *(Mandel and Cohn, 1985)*.

The recommended daily requirement of vitamin A is 1500 I.U. for infants and children up to 3 years. There-after, the recommended amount increases with age up to 5000 I.U. for adolescents and adults including pregnant women.However, during lactation, 8000 I.U. daily is recommended *(Roels, 1970)*.

In the intestine, retinol esters are hydrolyzed and the formed retinol is readily absorbed from the normal gastrointestinal tract. If the amount ingested is not much greater than the requirement, absorption is complete; however, when an excess amount is taken, some of the retinol

escapes in the feces. Most of the absorbed vitamin is stored in the liver as retinol esters. Retinol is then mobilized from the liver, the esters are hydrolyzed at first and then bound to retinol binding protein which is synthesized in the hepatocytes. The complex then enters the circulation and delivers retinol to the target tissues leaving the retinol binding protein behind and the retinol enters its target cell *(Kanai, Raz and Goodman, 1986; Peterson and Berggard 1971; Mahoney, Margolis, Knauss and Labbe, 1980)*.

The mechanism of vitamin A toxicity is incompletely understood. It appears that hypervitaminosis A occurs when hepatic stores of the vitamin and the retinol binding protein carrier system become saturated due to excessive intake of retinol or hepatic damage. At this time, the cells become exposed to unbound retinol, The surface active properties of vitamin A apparently produce labile cell membranes leading to damage of the membranous cell organells with the release of their contents which in turn may be involved in the other effects of hypervitaminosis A *(Smith and Goodman, 1976)*.

Only commercial vitamin preparations and liver contain sufficient vitamin A to produce acute or chronic toxicity. A large intake of the provitamin β carotene containing foods does not induce vitamin A intoxication because only limited

amounts of carotene are converted into vitamin A *(Mahoney et al., 1980)*.

Chronic hypervitaminosis A results, in general, from chronic intake of 3000 IU/Kg/day *(Hayes and Hegsted, 1973)*.Most frequently, this intake in children is the result of overzealous prophylactic vitamin therapy on the part of the parents. In adults, toxicity has resulted from extended self medication, excessive intake of certain foods containing large amounts of vitamin A or the use of high doses of retinoids for the therapy of acne or other skin lesions *(Herbert, 1982)*. Also, chronic hypervitaminosis A can occur by daily ingestion of liver, even from herbivorous animals like chicken *(Mahoney et al., 1980)*.

Acute vitamin A intoxication occurs in man by ingestion of more than 2,000,000 I.U. of vitamin A in an adult *(Hayes and Hegsted, 1973)*. This intake occurs by eating liver from polar bears, seals and sharks especially the former species, where the concentration of vitamin A is very high reaching up to 18,000 IU/gm *(Rodahl and Moore, 1943; Lonie, 1950; Knudson and Rothman, 1953)*.

Early signs and symptoms of chronic retinoid intoxication include dry and pruritic skin,skin desquamation , erythematous dermatitis, disturbed hair growth, fissures of the lips, pain and tenderness of bones and hepatomegaly.

Increased intracranial pressure may give rise to headache, vomiting, diplopia, visual field defects, papilledema and bulging fontanelles in infants without focal signs of cerebral damage. These neurologic manifestations are reversible after withdrawal of vitamin A. Hence, some authors regard chronic hypervitaminosis A as one of the causes of the syndrome of benign intracranial hypertension *(Feldman and Schlezinger, 1970; Muenter, Perry and Ludwig, 1971; Lombaert and Carton, 1976)*.

These manifestations develop after one to three months of vitamin A administration *(Shaywitz, Siegel and Pearson, 1977)*. Improvement usually begins within three weeks of withdrawing the supply of the vitamin *(Bowman and Rand, 1980)*.

In cases of acute intoxication, signs and symptoms include drowsiness, irritability or irresistalbe desire to sleep, severe headache, dizziness, vomiting, papilledema and in infants, bulging of fontanelles due to increased intracranial pressure. These manifestantions develop within 8-12 hours after administration of retinol. They disappear within 36 hours after cessation of retionl intake *(Bawn, 1962; Mandel and Cohn, 1985)*.

Choroid Plexuses:

The choroid plexuses are folds of pia mater projecting into the brain ventricles constituting paths for the deeper vessels. They are invested by ependyma.

The choroid plexuses of the lateral ventricles bulge from the medial borders and are continuous with each other through interventricular foramina crossing the third ventricle. From this connection, the two choroid plexuses of the third ventricle bulge.

In the fourth ventricle, the pia mater projects forming three fringed masses in the form of the letter T. These masses are designated as the median and lateral choroid plexuses of the fourth ventricle *(Davis & Coupland, 1967)*

The choroid plexus has many leaf-like processes which are supplied by small arteries or arterioles. Each arteriole gives rise to a capillary plexus which becomes tortuous producing elevations in the epithelium called villi. Thus, the choroid plexus is known to consist of a single layer of epithelium surrounding a core of connective tissue with small blood vessels *(Ham & Cormack, 1979)*.

The epithelium that covers the villi of the plexus develops from the ependyma. As was first described *(Purkinje, 1836)*, this epithelium consists of a single layer

of cuboidal or low columnar cells. The nuclei are spherical, and located in a central or a basal position. Each possesses up to three nucleoli and is enclosed by a porous double membrane, the nuclear envelope, *(Millen and Rogers, 1956)*.

These cuboidal epithelial cells have an apical microvillous border. The microvilli present, are membrane-bound cytoplasmic projections which can be classified into two types: one is symmetrical, finger-like structure, while the other (clavate microvillous) is relatively shorter, rounded or club-shaped *(Dohrmann and Bucy, 1970)*. Occasional cilia can be seen as a persistant embryological remnant along the microvillous surface and the number of these per an epithelial cell varies *(Masuzawa and Sato, 1983)*. Lateral cell membranes are closely approximated and junctional complexes of zonulae adherens and occludens are noted near the ventricular surface encircling apical regions of the cells. The basal plasma membrane is infolded and rests on a basement membrance. This basement membrane has been suggested to be a part of the blood brain barrier *(Dempsey and Wislocki,1955)*.

Numerous mitochondria are dispersed throughout the cytoplasm. They measure 400-600 nm in length and 200-300 nm in width. Rough endoplasmic reticulum is also seen throughout the cytoplasm. It presents many vesicles which measure 300-350 nm in diameter. A Golgi apparatus is located

in a paranuclear position and it consists of elliptical vesicles lined by smooth membranes. Polyribosomes, lysosomes and multivesicular bodies are also present throughout the cytoplasm. On the other hand, pinocytotic vesicles are particularly numerous at the apical, basal and lateral membranes *(Wislocki and Lodman, 1958)*.

The space between the choroidal basement membrane and the capillaries of the choroid plexus is filled with a loose connective tissue stroma composed primarily of fibroblasts along with variable amounts of collagen fibrills. Macrophages and several leucocytes are also present *(Wislocki and Lodman, 1958)*.

The capillaries of the choroid plexus consists of thin endothelium resting on a definite basement membrane. The cytoplasm of the endothelial cells is extremely attenuated, fenestrated or characteristically perforated.

The structurs of the human choroid plexus points out to its multiple functions. It is capable of water transport through its fenestrated capillaries, active fluid transport through the infolded basal plasma membranes, absorption and secretion through its microvilli, high metabolic activity due to mitochondrial concentration and transport of substances of high molecular weight through pinocytotic vesicles *(Dohrmann and Bucy, 1970)*.

The choroid plexus plays a major role in the production of cerebrospinal fluid (C.S.F.). Extrachoroidal sites, such as the ventricular ependyma, the intracranial subarachnoid space, the spinal arachnoid space and the parenchyma of the brain also share in the C.S.F. production *(Hassin, 1924; Pollay and Curl, 1967; Sato and Bering, 1967 and Sato and Amano, 1972)*. The exact mechanism of C.S.F. production is not fully understood. Anyhow, evidence has accumulated showing that C.S.F. is formed largely by active secretion rather than merely by ultrafiltration or dialysis of the plasma *(Davson, 1955; Becker, 1961; Welch, 1962 and Wright, 1972)*. The epithelium covering the choroid plexus shows a large number of intracellular organelles required for the active transport process. The active secretion of C.S.F. by the choroid plexuses involves active transport of sodium via A.T.P.ase system and chloride by the carbonic anhydrase system *(Tschirgi, Frost and Taylor, 1954; Vates, Bonting and Opplet, 1964; Smith, Roberts and Fisher, 1974; Masuzawa, Saito and Sato, 1981)*.

The C.S.F. produced in the lateral ventricles passes through the interventricular foramina to the third ventricle. Then, it passes with that produced in the third ventricle through the cerebral aqueduct to the fourth ventricle. Here, more C.S.F. is added by the choroid plexus of the fourth ventricle. Then, a small amount of C.S.F.

passes into the central canal of the spinal cord while the greater amount passes through the three aperatures of the fourth ventricle to the subarachnoid space. The greater amount of the latter portion sweeps on the surface of the brain while a small portion passes into the vertebral canal *(Davis and Coupland, 1967)*.

The C.S.F. is absorbed mainly via the arachnoid villi into the dural sinuses and the spinal veins and to a minor degree, it may pass along the sheaths of the cranial nerves into the cervical lymphatics and also into the perivascular spaces. Its pressure is normally about 100 mm. of water. It depends on a balance between its rate of secretion and its rate of absorption *(Heisey, Held and Pappenheimer, 1962)*.