INTRODUCTION AND REVIEW OF LITERATURE

The liver is the largest gland in the body. It is both an endocrine and exocrine gland. Releasing several substances directly into the blood stream and secreting bile into a duct system **(William and Harry, 1994).**

The liver primordium arises from the endodermal lining of the forgut during the middle of the third week of gestation. The hepatic diverticulum is situated at the ventral part of the forgut, cranial to its opening into the yolk sac. **(Hamilton et al., 1962).**

The liver is situated in the right upper quadrant of the abdominal cavity with its rounded upper surface conforming to the dome of diaphragm **(Fawcett, 1998).**

The liver is well known as the major organ for gathering, transforming and accumulating drug metabolites, beside neutralizing and eliminating the various toxic substances **(Leeson et al., 1992).**

This organ is covered by a thin connective tissue capsule (Glisson's capsule) and the liver or hepatic tissue itself is made up of two main constituents namely, the parenchyma and stroma **(Snell, 1984).**

Normally the liver has a minimal Content of connective tissue in its interior, it presents a remarkably uniform appearance and structural subunits which are not easily identifiable. It is possible, however, to detect a repeating pattern of roughly polygonal areas in which fenestrated plates

of parenchymal cells (hepatocytes) are arranged redially around central vein **(David, 1993).**

The liver is completely divided on its anterior surface into large right lobe and smaller left lobe by the attachment of peritoneal falciform ligament on the inferior and posterior surfaces. There are two additional lobes the quadrate and the caudate lobe delineated by the presence of inferior vena cava, attachment of the lesser omentum, ligamentum teres and the gall bladder **(Snell, 1984).**

The classical lobule is the basic anatomical and functional unit of the liver and at some corners of these polygonal areas there are small triangular areas of connective tissue "the portal areas" enclosing a branch of the portal vein, a branch of the hepatic artery, a small branch of the bile duct and a lymph vessel. The branch of the portal vein is wide and thin walled, that of hepatic artery is narrower with thick wall delivering blood to the sinusoids between the hepatocytes and the small branch of bile duct recognizable by its linings of simple cuboidal epithelium carrying bile towards the porta hepatis. The thin walled lymphatics drain lymph in the same direction **(David, 1993).**

Hepatocytes appear hexagonal in cross section and have three distinct types of surfaces. One faces the sinusoid and its surface is greatly increased by extension of numerous microvilli, this surface represents the membrane across which blood hepatocyte exchange occurs the second surface faces the adjacent hepatocytes, and the third surface lies between adjacent hepatocytes near the center of the liver cell plates forming the boundary of the bile canaliculus, this surface also forms microvilli that

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project into the bile canaliculi **(Burkel and Low, 1966 and Fawcett, 1998).**

The cytoplasm of each hepatocyte contain numerous organelles and inclusions the most discrete organelle is the mitochondria, which are rounded or oblong in shape that can attain a length of up to (10 µm).

Each mitochondrion is comprised mainly of an external and internal membranes (0.5nm in thickness) bounding its internal lumen the latter membrane projects intraluminally in the form of small folds, namely the mitochondrial crests or ridges, hanging freely inside those lumens. These ridges, are quite often of the tubular types and the spaces located within these ridges are incontinuity with the spaces lying between the two mitochondrial membranes, such intratubular spaces are usually termed as the outer chamber whilst those found between the ridges are termed the internal chambers. The inner inter-ridgal spaces include a granular matrix of reliable electron density. **(Snell, 1984; Loud, 1987 and Cormack, 1998).** DNA filaments about 30-50 nm in width are noticed **(Nass and Nass, 1963).** RNA containing granules (mitochondrial ribosomes) were observed in the mitochondria suggesting that they may serve as an extra nuclear genetic system or may have a self replication system. There is a multi-enzyme system for manufacture of ATP in mitochondria. Mitochondria are usually located very close to rough endoplasmic reticulum (rER), near the nucleus and along the sinusoidal surface, suggesting a functional relationship among those organelles **(Leeson et al., 1992).**

The cytoplasm of the hepatocytes also possesses a well developed rough endoplasmic reticulum (rER) and smooth endoplasmic reticulum (sER). The rER is distributed around nucleus is close association with mitochondria and towards the vascular and biliary poles, it tends to be arranged in parallel stacks of flattened cisternae, saccules, tubules, and vesicles. It is the site of protein synthesis especially that for secretion **(Luthy et al., 1976 and Grudut et al., 1976).**

Ribosomes are small electron dense particles about 15-30 nm in diameter. Two forms of ribosomes one being attached to rER and another free in the cytoplasm are observed and consist of rRNA and ribosomal protein. They are the site where amino acids are incorprated into proteins **(Novikoff and Essner, 1980).**

Each ribosome consists of a large and a small subunits **(Florendo, 1989)** several ribosomes aggregated and attached to strands of messenger RNA to form polysomes, which are usually in the spiral form. The free ribosomes synthesize the structural proteins of cell itself, a process particularly active during development and regeneration **(Redman and Sabatini, 1966).**

In case of attached ribosomes, the large subunits are the site of attachments, the attached ribosomes have been demonstrated to synthesize the secretory proteins **(Redman, 1969)** which are transmitted to cisternal lumen of rER through channels in the large subunits, then via the smooth endoplasmic reticulum to the Golgi apparatus to be discharged at the sinusoidal surface by excytosis. This traditional view, full established for other protein secreting glands, has been disputed for the liver by **(Lin and Change 1975).** The rER cooperate with the smooth

one in the synthesis of enzymes associated with lysosomes and peroxisomes within the cell **(Orlandil and Koch, 1975).**

Smooth endoplasmic reticulum (sER) cisternae are more tubular, devoid of ribosomes and more likely to appear as interconnected channels of variable shapes and sizes rather than of flattened cisternae, it arise from rER **(Feldman et al., 1980).** It is responsible for the oxidation, conjugation and methylation processes. It neutralizes and detoxifies certain hormones and toxic substance such as alcohol and insecticides and it is responsible for glycogen breakdown in the liver cells **(MacSween and Scothorne, 1979).**

The nucleus is round or oval in shape and about 10μm in diameter but its size may vary from cell to cell. It is central in position approximately 25% of hepatocytes are binucleated.. In the interior of the nucleus one or more nucleoli are embedded. These nucleoli are the site of synthesis of three forms of RNA **(Fawcett, 1998 and O'Kellely, 1998).**

Each nucleus has a well demarkated nuclear membrane (7 nm in thickness) and the nucleoplasm contains aggregations of electron dense coarse granules or particles of heterochromatin while euchromatin is usually visible in the form of a loose net work of fine fibrils. The heterochromatin is often aggregated on the inner surface of nuclear membrane **(Leslie et al., 1992) (Motta et al., 1997).**

The outer and inner membranes are fused with each other forming nuclear pores about 70 nm in diameter. Multiple prominent nucleoli are

usually present. They disperse and disappear during cell division (nucleolus is usually present), but reappear in the telophase of mitosis.

Nucleolus is usually basophilic when stained with haematoxylin and eosin as seen with the light microscope. The nucleolus consists of 3 distinct components, the first component is one to several pale staining regions composed of nucleolar organizer DNA sequences of bases that code for rRNA, the pars fibrosa and pars granulosa form a thread like structure called the nucleoclonema by light microscope **(Bruni and Porteer, 1965; Jones et al., 1998).**

Peroxisomes (microbodies) are ovoid membrane bounded granules and were renamed to reflect their role in the metabolism of hydrogen peroxide **(DeDuve and Baudhuin, 1966).** Peroxisomes occupy 2% of total hepatocellular volume. They are limited by a single membrane and their matrix is finally granular. Peroxisomes may occur randomly within the cell but thin membranes are usually intimately associated with the membranes of adjacent sER **(Stemlieb and Quintana, 1977).** Peroxisomes contain a variety of oxidases and a large quantity of the catalaze. The catalaze mediate decomposition of peroxides to water **(Rods et al., 1981).**

Peroxisomes which remain attached to the endoplasmic reticulum circulate within the endoplasmic reticulum to detoxify accumulating hydrogen peroxide (H_2O_2), perioxssomes protect the cell from the effect of H_2O_2 **(Rods and The mann, 1981 ; Hinkle, 1982 and William and Harry, 1994).**

Golgi apparatus consists of three to five parallel flat saccules or cisternae each having one convex and another concave surface with

numerous vesicles and vacuoles beside it. The convex surface represents the forming face where materials synthesized by ER transformed into the Golgi apparatus by vesicules. The concave surface represents the maturing face from which materials are released into cytoplasm in a packed form. The Golgi apparatus in hepatocytes concentrates and transfers the secretory products, such as the low density lipoprotein **(Stein and Stein, 1967)** and albumin **(Glumann and Ericrson, 1970)** toward the cell surface facing the space of Disse.

Lysosomes, present in hepatic cell vary in appearance, they contain lipofuscin and ferritin like substance (which may be stored in large amount in iron storage disease). There are about 25 microbodies per liver cell **(De Duve and Baudhuin, 1966).**

The Centriole is found near Golgi apparatus in hepatic cells. Also the cytoplasm of hepatocytes contains two prominent cell inclusions first one is glycogen found in the form of granules and second is fat **(Greep and Weiss, 1973 and Erson and Scottl, 1976).**

Microfilaments and microtubules are structures that provide a supporting cytoskeleton and are not peculiar to hepatocytes. microfilaments are found near the periphery of the hepatocyte **(Holborow et al., 1975)** and are well developed along the plasma membrane facing the bile canaliculus and the space of Disse **(French and Davis, 1975).**

The pericanalicular microfilaments seem to provide stability to the bile canaliculus **(Oda et al., 1974).**

Lipid inclusions have been demonstrated by electron microscopy as lipid droplets triglycercide in nature of variable size and density **(Tanikawa et al., 1979 and Shibasakis, 1998).**

Glycogen was also detected as α particles and β-particles which are aggregates of smaller particles arranged in rosettes **(Biava, 1963).**

Bile canaliculi are present between layers of liver cells of each plate, which have no lining and bile enters canalciulus go toward the periphery of the lobule **(Fawcett, 1998).**

The liver blood sinusoids are wider than capillaries and their wall conform to the surface of the plates of heptocyte on either side but one separated from them by a narrow space and are lined by two types of cells Endothelial cells and Kupffer cells. Endothelial cells are greater in number and form a discontinous lining for the wall of sinusoids, they have large fenestrations and the absence of basement membrane allow to percolate unformed blood elements and plasma through sinusoidal wall into the space of Disse **(Fawcett, 1998 and Junqueira et al., 1998).** Kupffer cells are phagocytic cells that are derived from monocytes that lie within the sinusoid and are fixed to its endothelium. They can be easily demonstrated in animals by intravascular injection of vital dyes as trypan blue **(Leslie et al., 1992 and Fawcett, 1998).** They have cytoplasmic projections called pseudopodia **(Boluin 1977; Arias et al., 1982 and Macluskey, 1990).**

Ito cells (lipocyte perisinusoidal cells, stellate cell, fat storing cells or vitamine A storing cells) are usually located in the perisinusoidal recsses located within the space of Disse they are small single oval to

round eccntrically placed nuclei. The most prominent characteristic is the presence of several large lipid vacuoles, also they contain desmin **(Cyokio and Akihisa, 1983)** Which has a supporting function **(Koh et al., 1983 and Cormack, 1998).**

The liver receives approximately 25% of the cardiac out put most of blood that flows through the liver passes through sinusoids, then blood flows from sinusoids into central veins and then into hepatic vein which merge with the inferior vena cava **(Kurti, 1992).**

The liver produces a large volume of lymph from one quarter to one half of the lymph of thoracic duct comes from the liver which contains a large amount of plasma protein. It passes parallel to the branches of the portal vein from interlobular portal areas to porta hepatis. Lymphatics have not been demonstrated within hepatic lobules **(Cormack, 1998 and Rouiller, 1998).**

The liver is innervated mainly by efferent autonomic nerves found in portal triads and also adrenergic endings in space of Disse **(Cormack, 1998).**

Hepatocytes are responsible for converting lipid and amino acids into glucose by means of a complex enzymatic process called gluconeogensis **(Janqueira et al., 1998).** Hepatocytes are responsible for detoxification of certain endogenous and exogenous compounds that are deleterious to body such as ammonia, toxins and various drugs **(Davidsonj and Layne, 1979 and Fawcett, 1998).**

The liver carbohydrates are stored in the form of glycogen and lipids are stored in the form of triglycerides this metabolic function is

important because it supplies body with energy between meals **(Leslie et al., 1992 and Carneiro, 1998).**

The liver is a complex gland, it produces and secretes the bile which is passed into intestinal tract. Bile is composed of bilirubin, bile salts cholesterol, phospholipids, electrolytes and water **(Snell, 1984).** Liver cell produce albumin, prothrombin, fibrinogen and lipoprotein **(Leesons, 1992 and Jinqueirea et al., 1998).**

Hepatocytes have an important accessory function in the immune system of the intestine. Immunoglobulin A is present in bile four times its concentration in the blood **(Cormack, 1998).**

Succinic dehydrogenase is one of the enzymes of citric acid cycle **(Troyer, 1980).** The activity of respiratory enzymes such as succinic dehydrogenase and cytochrome oxidase in the liver is concentrated in peripheral cells of hepatic lobules it is associated with mitochondrial inner membrane **(Chinquoine, 1953; Pullmun, 1962 and Jurima et al., 1994).**

Alkaline phosphatase enzyme increases in liver disease **(Colowick and Kaplan, 1955),** acid phosphates enzyme is widely distributed in animal tissues. Spleen, prostate and liver are the richest sites **(Pearse, 1968 and Barka and Anderson, 1963).**

Function of hepatocytes include the following:

1) secretion of plasma proteins (e.g albumin, fibrinogen and prothrombin), very low density lipoprotein (VLDL), immunoglobulin A (IgA) and other components of bile
2) Storage of absorbed glucose as glycogen.

3) Storage of lipid soluble vitamins A. D,E,K. and B12.

4) Detoxification of steroids, alcohol and toxic exogenous chemicals that have entered the blood stream. **(Cormack, 1998).**

5) Secretion of Bile Salts.