Acknowledgement

*First and foremost, I always feel indebted to "**ALLAH**" the most beneficent and merciful.*

Words cannot express the depth of my gratitude to my teacher **Prof. Dr. Yahia Abdel-Rahim Hamimy** *Professor* ***Prof. of Anaesthesia and Intensive Care*** *, faculty of Medicine, Ain Shams University, for his valuable suggestions, generous assistance, kind support and continuous encouragement throughout this work.*

My great appreciation and thanks to **Prof. Dr. Alfred Maurice said Boktor,** ***of Anaesthesia and Intensive Care*** *, Faculty of Medicine, Ain Shams University, for his unlimited help, kind support, valuable supervision, guidance and advice.*

Finally, I would like to express may appreciation to every one who directly or indirectly gave a hand in accomplishment of this work.

INTRODUCTION

The number of patients with cirrhosis who require surgery is on the rise. Despite advances in antiviral therapeutics, the prevalence of cirrhosis secondary to hepatitis C continues to increase, as does the prevalence of cirrhosis due to chronic alcoholic liver disease. Additionally, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are gaining more attention, especially in association with metabolic syndrome and obesity. At the same time, the amount of medications and treatments aimed at improving survival among patients with cirrhosis has been increasing. Therefore, it can be expected that a growing number of patients with liver disease, both known and as yet undiagnosed and asymptomatic, will undergo surgery. ***(Del Olmo JA et al., 2003)***

An estimated 1 in 700 patients admitted for elective surgery has abnormal liver enzyme levels. Some authors have estimated that as many as 10% of patients with advanced liver disease will undergo surgery in the last 2 years of their lives.(***Garrison RN, et al1984)***

Identification of the surgical risk is imperative in the care of any patient, especially as patients develop an increasing number of chronic comorbid medical conditions. Patients with

liver disease are at particularly high risk for morbidity and mortality in the postoperative period due to both the stress of surgery and the effects of general anesthesia. Compared 135 patients with cirrhosis with 86 patients without cirrhosis, all undergoing nonhepatic general surgery. ***(Del Olmo JA et al., 2003)*** At 1 month, mortality rates were 16.3% for patients with cirrhosis compared with 3.5% in the control group. What is further evident in the literature is that decompensated liver disease increases the risk of postoperative complications (eg, acute hepatic failure, infections including sepsis, bleeding, poor wound healing, and renal dysfunction). Assessing risk in these patients is a challenging but important endeavor. ***(Del Olmo JA et al., 2003)***

The liver is vital for protein synthesis, coagulation homeostasis, glucose homeostasis, bilirubin excretion, drug metabolism, and toxic removal, among other critical functions. In general, the liver has substantial functional reserve because of its dual blood supply: portal-venous (75%) and hepatic-arterial (25%). Hence, clinical manifestations of liver damage occur only after considerable injury.

AIM OF THE WORK

This article focuses on the challenges of perioperative care of patients with liver disease.

PHYSIOLOGY Of The LIVER

The liver is the largest internal organ in the body, constituting about 2.5% of an adult's body weight. During rest, it receives 25% of the cardiac output via the hepatic portal vein and hepatic artery. The hepatic portal vein carries the absorbed nutrients from the GI tract to the liver, which takes up, stores, and distributes nutrients and vitamins. The liver plays an important role in maintaining blood glucose levels. It also regulates the circulating blood lipids by the amount of very low density lipoproteins (VLDLs) it secretes. Many of the circulating plasma proteins are synthesized by the liver. In addition, the liver takes up numerous toxic compounds and drugs from the portal circulation. It is well equipped to deal with the metabolism of drugs and toxic substances. The liver also serves as an excretory organ for bile pigments, cholesterol, and drugs. Finally, it performs important endocrine functions.

THE ANATOMY OF THE LIVER

The liver is essential to the normal physiology of many organs and systems of the body. It interacts with the cardiovascular and immune systems, it secretes important

substances into the GI tract, and it stores, degrades, and detoxifies many substrates. ***(Arias 1994)***

Hepatocytes

Hepatocytes are highly specialized cells. The bile canaliculus is usually lined by two hepatocytes and is separated from the pericellular space by tight junctions, which are impermeable and, thus, prevent the mixing of contents between the bile canaliculus and the pericellular space. The bile from the bile canaliculus drains into a series of ducts, and it may eventually join the pancreatic duct near where it enters the duodenum. Drainage of bile into the duodenum is partly regulated by a sphincter located at the junction between the bile duct and the duodenum, the sphincter of Oddi. The pericellular space, the space between two hepatocytes, is continuous with the perisinusoidal space. The perisinusoidal space, also known as the space of Disse, is separated from the sinusoid by a layer of sinusoidal endothelial cells. Hepatocytes possess numerous, finger-like projections that extend into the perisinusoidal space, greatly increasing the surface area over which hepatocytes contact the perisinusoidal fluid.

Endothelial cells of the liver, unlike those in other parts of the cardiovascular system, lack a basement membrane. Furthermore, they have sieve-like plates that permit the ready exchange of materials between the perisinusoidal space and the sinusoid. Electron microscopy has demonstrated that even particles as big as chylomicrons (80 to 500 nm in diameter) can penetrate these porous plates. Although the barrier between the perisinusoidal space and the sinusoid is permeable, it does have some sieving properties. For example, the protein concentration of hepatic lymph, assumed to derive from the perisinusoidal space, is lower than that of plasma by about 10%. ***(Arias 1994)***

Kupffer cells also line the hepatic sinusoids. These are resident macrophages of the fixed monocyte-macrophage system that play an extremely important role in removing unwanted material (e.g., bacteria, virus particles, fibrin-fibrinogen complexes, damaged erythrocytes, and immune complexes) from the circulation. Endocytosis is the mechanism by which these materials are removed. Some perisinusoidal cells contain distinct lipid droplets in the cytoplasm. These fat-storage cells are called stellate cells or Ito cells. The lipid droplets contain vitamin A. Through

complex and typically inflammatory processes, stellate cells become transformed to myofibroblasts, which then become capable of both secreting collagen into the space of Disse and regulating sinusoidal portal pressure by their contraction or relaxation. Stellate cells may be involved in the pathological fibrosis of the liver. ***(Arias 1994)(fig 1)***

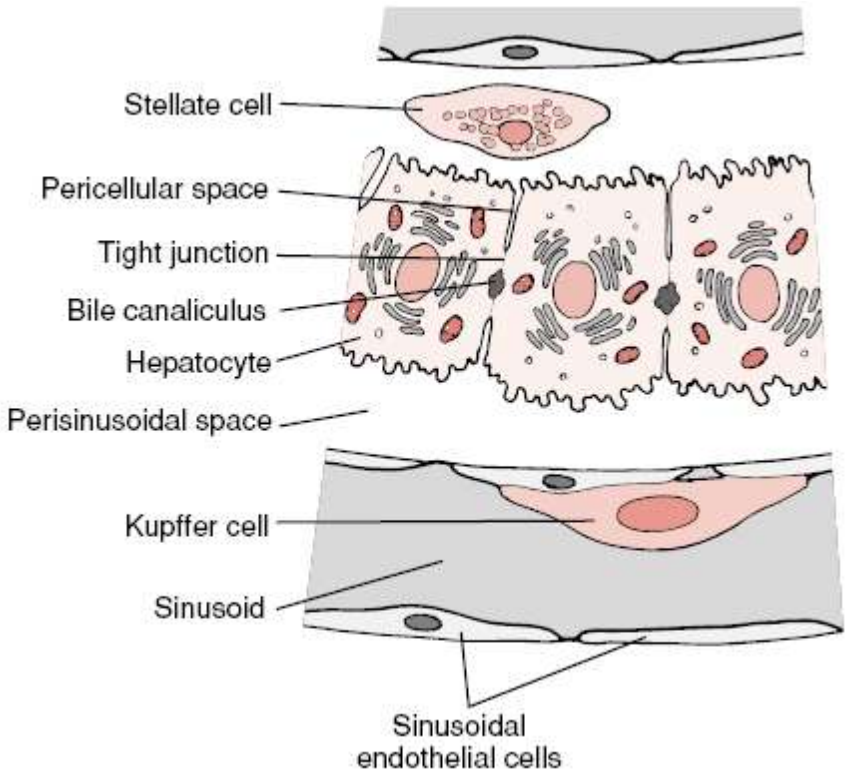

Fig 1 The relationship between hypocytes, the perisinusoidal space and the sinusoid.

Hepatic Artery

The hepatic portal vein provides about 70 to 80% of the liver's blood supply, and the hepatic artery provides the rest. Hepatic portal blood is poorly oxygenated unlike that from the hepatic artery. The portal vein branches repeatedly, forming smaller venules that eventually empty into the sinusoids. The hepatic artery branches to form arterioles and then capillaries, which also drain into the sinusoids. ***(Arias 1994)***

Liver sinusoids can be considered specialized capillaries. As mentioned earlier, the hepatic sinusoid is extremely porous and allows the rapid exchange of materials between the perisinusoidal space and the sinusoid. The sinusoids empty into the central veins, which subsequently join to form the hepatic vein, which then joins the inferior vena cava. ***(Arias 1994)***

Hepatic blood flow varies with activity, increasing after eating and decreasing during sleep. Blood flow to the intestines and spleen and, in turn, in the portal vein is predominantly regulated by the splanchnic arterioles. In this way, eating results in increased blood flow to the intestines

followed by increased liver blood flow. Portal vein pressure is normally low. Increased resistance to portal blood flow results in portal hypertension. Portal hypertension is the most common complication of chronic liver disease and accounts for a large percentage of the morbidity and mortality associated with chronic liver diseases**. *(Arias 1994)***

Hepatic Lymphatic System

The hepatic lymphatic system is present in three main areas: adjacent to the central veins, adjacent to the portal veins, and coursing along the hepatic artery. As in other organs, it is through these channels that fluid and proteins are drained. The protein concentration is highest in lymph from the liver.

In the liver, the largest space drained by the lymphatic system is the perisinusoidal space. Disturbances in the balance of filtration and drainage are the primary causes of ascites, the accumulation of serous fluid in the peritoneal cavity.

Ascites is another common cause of morbidity in patients with chronic liver disease. ***(Arias 1994)***

Liver Regeneration

Of the solid organs, the liver is the only one that can regenerate. There appears to be a critical ratio between functioning liver mass and body mass. Deviations in this ratio trigger a modulation of either hepatocyte proliferation or apoptosis, in order to maintain the liver's optimal size. Peptide growth factors—such as transforming growth factor-_ (TGF-_), hepatocyte growth factor (HGF), and epidermal growth factor (EGF)—have been the best-studied stimuli of hepatocyte DNA synthesis. After these peptides bind to their receptors on the remaining hepatocytes and work their way through myriad transcription factors, gene transcription is accelerated, resulting in increased cell number and increased liver mass. ***(Arias 1994).***

Alternatively, a decrease in liver volume is achieved by enhanced hepatocyte apoptosis rates. Apoptosis is a carefully programmed process by which cells kill themselves while maintaining the integrity of their cellular membranes.

In contrast, cell death that results from necroinflammatory processes is characterized by a loss of cell membrane integrity and the activation of inflammatory

reactions. Liver cell suicide is mediated by proapoptotic signals, such as tumor necrosis factor (TNF). ***(Arias 1994)***

METABOLISM OF DRUGS AND XENOBIOTICS

Hepatocytes play an extremely important role in the metabolism of drugs and xenobiotics—compounds that are foreign to the body, some of which are toxic. Most drugs and xenobiotics are introduced into the body with food. The kidneys ultimately dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble). This is because reabsorption of a substance by the renal tubules is dependent on its hydrophobicity. The more hydrophobic (nonpolar, lipid-soluble) a substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds. ***(Liska 1998)***

Two reactions (phase I and II), catalyzed by different enzyme systems, are involved in the conversion of xenobiotics and drugs into hydrophilic compounds. In phase I reactions, the parent compound is biotransformed into more polar compounds by the introduction of one or more polar

groups. The common polar groups are hydroxyl (OH) and carboxyl (COOH). Most phase I reactions involve oxidation of the parent compound. The enzymes involved are mostly located in the smooth ER; some are located in the cytoplasm. For example, alcohol dehydrogenase is located in the cytoplasm of hepatocytes and catalyzes the rapid conversion of alcohol to acetaldehyde. It may also play a role in the dehydrogenation of steroids. ***(Liska 1998)***

The enzymes involved in phase I reactions of drug biotransformation are present as an enzyme complex composed of the NADPH-cytochrome P450 reductase and a series of hemoproteins called cytochrome P450. The drug combines with the oxidized cytochrome P450_3 to form the cytochrome P450_3-drug complex. This complex is then reduced to the cytochrome P450_2-drug complex, catalyzed by the enzyme NADPH-cytochrome P450 reductase. ***(Liska 1998)***

The reduced complex combines with molecular oxygen to form an oxygenated intermediate. One atom of the molecular oxygen then combines with two H_ and two electrons to form water. The other oxygen atom remains bound to the cytochrome P450_3-drug complex and is

transferred from the cytochrome P450_3 to the drug molecule. The drug product with an oxygen atom incorporated is released from the complex. The cytochrome P450_3 released can then be recycled for the oxidation of other drug molecules. ***(Liska 1998) (fig 2)***

In phase II reactions, the phase I reaction products undergo conjugation with several compounds to render them more hydrophilic. Glucuronic acid is the substance most commonly used for conjugation, and the enzymes involved are the glucuronyltransferases. Other molecules used in conjugation are glycine, taurine, and sulfates. ***(Liska 1998)***

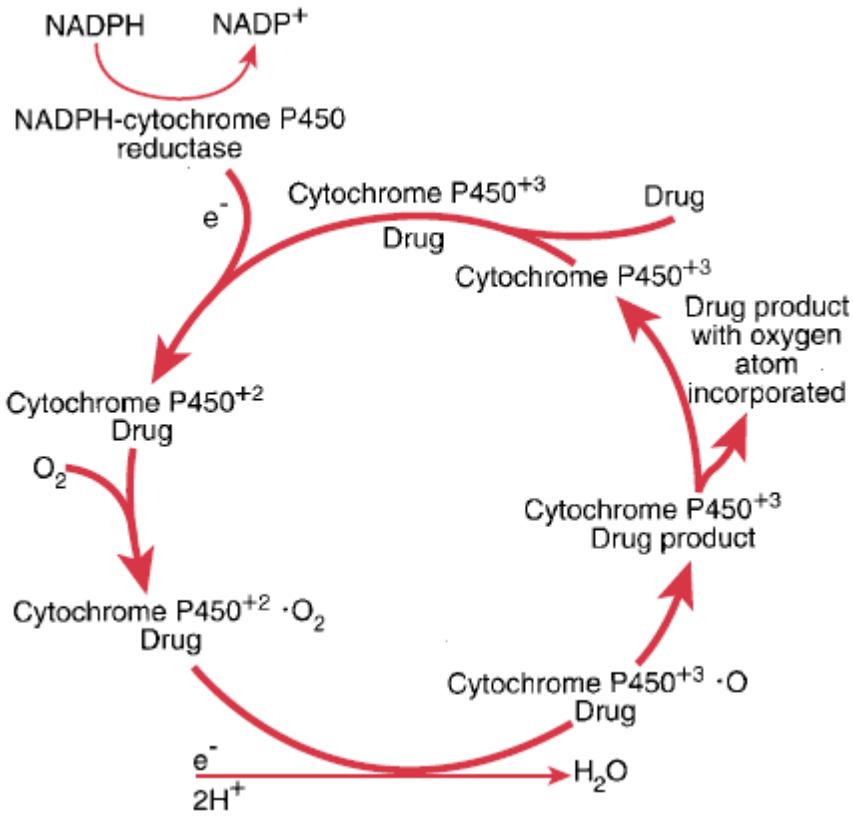

Fig 2 Phase I Reactions in the metabolism of drugs

The enzyme systems in phase I and II reactions are age-dependent. These systems are poorly developed in human newborns because their ability to metabolize any given drug is lower than that of adults. Older adults also have a lower capacity than young adults to metabolize drugs.

Nutritional factors can also affect the enzymes involved in phase I and II reactions. Insufficient protein in