

## HEPATOTOXICITY |

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### 9.1 INTRODUCTION

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Liver is metabolically the most active organ of the body; the cells of liver are involved in varieties of functions which are crucial for survival. Liver is susceptible to toxic insult as it receives a high concentration of absorbed toxicants and for being the primary site for metabolism of xenobiotics. Though liver has capacity to regenerate, extensive or chronic exposure to toxicants can cause serious liver injuries. Many liver toxicants damage the essential ordered microstructure of liver, essential for performing important metabolic functions. In this unit, we will see how certain toxicants interact with liver and cause toxicity.

## Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ understand reasons of susceptibility of liver to toxic insult;
- ❖ know the functional anatomy of liver;
- ❖ know various pathological conditions caused by toxicants; and
- ❖ learn how various hepatotoxic substances cause damage to liver.

**Table 9.1: Overall functions of liver**

Metabolism/processing of nutrients (carbohydrate, lipid, amino acids)
Synthesis (gluconeogenesis, lipoproteins, blood proteins, hormones, heme, lymph)
Storage (carbohydrates, vitamins, minerals)
Excretion of xenobiotics in bile
Metabolism of xenobiotics
Immunological functions
Digestion of food

## 9.2 FUNCTIONS AND SUSCEPTIBILITY OF LIVER TO TOXIC INSULT

Liver is the largest organ and is metabolically more active than any other organ of the body. Liver is also an important organ from toxicological point of view since it is the main organ of metabolism and excretion of xenobiotics (via bile). General functions of liver are given in table 1.

Liver is often a target organ for several toxicants. The reasons for susceptibility of liver to toxic insult are:

- i. Liver is the first organ which receives nutrients and xenobiotics absorbed from the intestine via portal vein. Thus, liver is exposed to a high concentration of xenobiotics absorbed from gastrointestinal tract.
- ii. Liver has the highest concentration of xenobiotic metabolizing enzymes. In cases wherein toxicants are rendered more toxic or reactive after metabolism, liver is the first organ where these reactive metabolites cause lesions.
- iii. Cells of liver (hepatocytes) are in close contact with blood due to fenestrated capillary system in liver. This directly exposes hepatocytes to xenobiotics.

- iv. Liver cells have a high number of various membrane transport proteins which can actively and selectively concentrate toxicants.

### **9.2.1 Functional Anatomy of Liver**

Liver receives blood from *i*) intestine via 'hepatic portal vein', which carries absorbed material and, *ii*) 'hepatic artery' which supplies oxygenated blood to liver. The blood is drained through central veins which open in hepatic vein. At microscopic level, liver is organized into hexagonal structural units 'lobules' (Fig. 9.1b). The bulk of liver is comprised of 'hepatocytes' which are arranged linearly in each lobule called 'hepatic cords' separated by 'sinusoids' (Fig. 9.1b). Sinusoids are wide capillaries in which the endothelial lining is discontinuous (fenestrated endothelium) allowing free movement of substances from blood to the hepatocytes (Fig. 9.1d). At the corners of lobules lies 'portal triad' which contains branches of 'hepatic portal vein', 'hepatic artery' and 'bile duct'.

Sometimes, the microscopic structure of liver is viewed in a different manner—the 'hepatic acinus' is considered the functional unit of liver (Fig. 9.1c). This view better explains the way blood flows in the liver at microscopic level. Blood entering via branches of portal vein and hepatic artery mixes and enters into the sinusoids (Fig. 9.1d). Here, blood comes in contact with hepatocytes and exchange of matter takes place between blood and the hepatocytes. The blood from sinusoids slowly moves towards the central vein and finally leaves liver via hepatic vein (Fig. 9.1d). Note that bile in canaliculus flow is in reverse direction because bile is produced by hepatocytes by secreting the components into bile canaliculi. The bile in canaliculi flows towards the bile duct and then pours into the intestinal lumen via a common bile duct (Fig. 9.1 D).

In figure 9.1d, you can make out the main types of cells found in the liver:

- 1) Hepatocytes
- 2) Endothelial cells
- 3) Kupffer cells (macrophages),
- 4) Hepatic stellate cells (fat-storing cells)

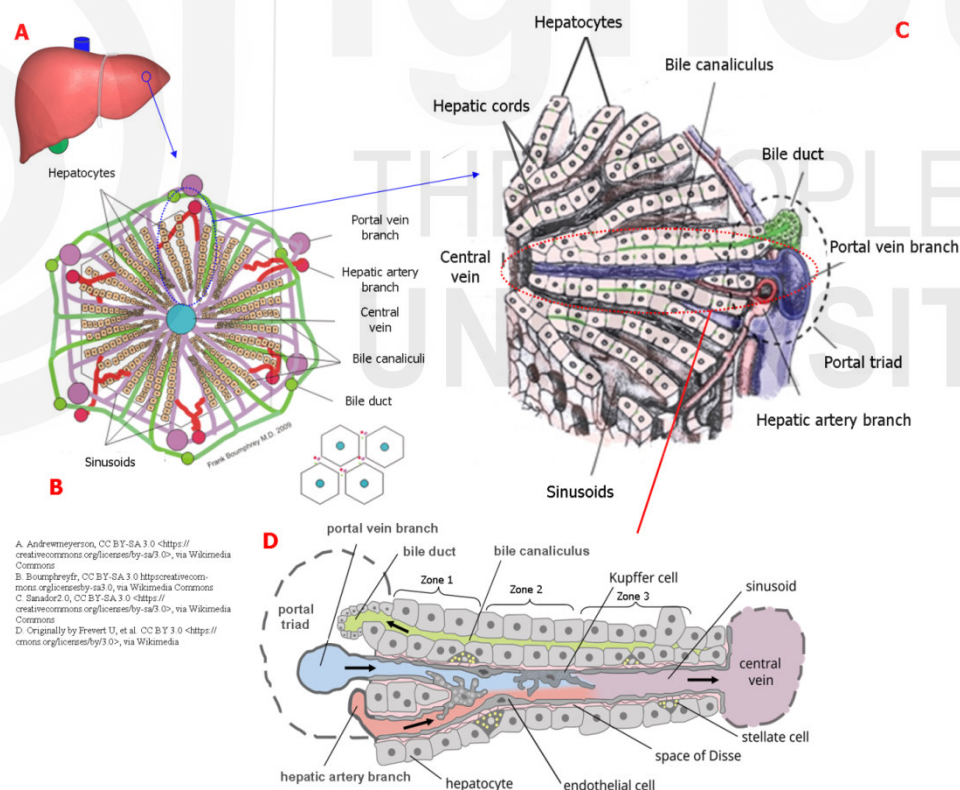
Hepatocytes are the most abundant of all the cell types in the liver (about 60% of total cells) and are responsible for most of the metabolism of nutrients, synthesis and storage of nutrients as given in table 1. Hepatocytes extract or uptake xenobiotics from the sinusoidal blood and metabolize them with the help of xenobiotic metabolizing enzymes. The primary function of Kupffer cells is to engulf and degrade (i.e. phagocytosis) particulate matter (e.g. bacteria) and remove them from the blood.

### **9.2.2 Liver Zonation**

Under the microscope, at structural level, all the hepatocytes of liver look alike. However, there exists a difference in biochemical functions (therefore enzymes, transporters, metabolites, etc.) among hepatocytes arranged along the entire length of hepatic cords in liver acinus (Fig. 9.1d). So, on the basis of

biochemical functions, and composition of biomolecules in the hepatocytes, acinus can be divided into three zones, viz. 1, 2 and 3. Let us explain this phenomenon with an example: processes which consume more oxygen or energy (such as protein secretion, gluconeogenesis, beta-oxidation, etc.) are carried out by hepatocytes which are closer to the portal triad i.e. zone 1, whereas less energy or oxygen demanding processes (such as xenobiotic metabolism, glycolysis, ketogenesis, glycogen synthesis, etc.) take place in hepatocytes which are nearer to the central vein or zone 3 (Fig.9.1d). These differences are due to the fact that the oxygen (and nutrients) content in blood closer to the portal triad (blood to which zone 1 hepatocytes are exposed) is higher (60-65 mm Hg); and as the blood moves towards zone 3, metabolic activities in hepatocytes of zone 1 and 2 removes oxygen. Blood reaching zone 3 thus has only half the original amount of oxygen. The phenomenon of gradual differences (in the biochemical functions, enzymes, transporters, etc.) in hepatocytes moving from one end to another along the hepatic cord is called 'liver zonation'.

The zonal differences also make one zone more susceptible to toxic insult than another. For example, zone 3 has the highest concentration of CYPs. A toxicant (such as paracetamol) activated by CYPs therefore would cause more damage to zone 3 hepatocytes. Similarly, allyl alcohol causes toxicity in zone 1, because of its higher uptake and activation in this zone.



**Fig. 9.1: Functional anatomy of liver: (A) external morphology, (B) a 'lobule' showing organization of 'hepatocytes' and various 'vessels', (C) 'hepatic acinus' (a portion) showing linear arrangement of hepatocytes– 'hepatic cords', 'sinusoids', 'bile canaliculus' and blood vessels (D) various cells of liver, and direction of flow of blood and bile.**

(Source: b) Boumpheyfr, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons d) Wikimedia Commons)

## SAQ 1

### a) State whether the following statements are true or false:

- i) Kupffer cells are the most abundant cells in liver (True/False).
- ii) Presence of high concentration of metabolizing enzymes makes liver susceptible to toxic insult (True/False).
- iii) Zone 1 of hepatic acinus receives highest concentration of oxygen (True/False).
- iv) Central vein in the hepatic lobules supplies fresh blood to the liver. (True/False).

### b) Fill in the blanks with appropriate words:

- i) The function of Kupffer cells is.....
- ii) Hepatic stellate cells are also known as .....
- iii) .....is considered as functional unit of liver.

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## 9.3 TYPES OF LIVER INJURIES

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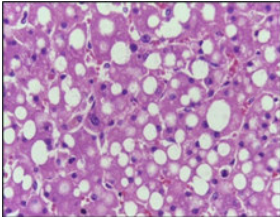
As we discussed above, liver is susceptible to several toxicants. The effects of various toxicants may range from mild reversible cell injury or necrosis to irreversible alteration in microscopic and macroscopic structure of the liver (such as cirrhosis). Extensive damage to the architecture limits liver to perform essential functions leading to liver failure, which may be fatal. We have seen the basic structural plan of liver and major types of cells in the previous section. In this section, we will discuss pathological changes in liver caused by toxicants.

### 9.3.1 Necrosis

Liver necrosis is death of liver cells, particularly, the hepatocytes. Necrosis may be restricted to a small part of liver and affect only few cells (focal) or involve a large area of the liver (massive necrosis). A cell undergoing necrosis swells up and the cellular contents including the enzymes, proteins and metabolites leak out. Appearance of enzymes alanine aminotransferase (ALT) and aspartate amino transferase (AST) in blood has been used to monitor liver damage. Both the enzymes are predominantly found in liver. Necrosis is usually an acute injury and may not be critical due to extraordinary regenerating capacity of liver. Massive necrosis exceeding beyond the capacity to repair leads to serious liver damage or liver failure.

### 9.3.2 Fatty Liver (Steatosis)

Fatty liver is a condition of excessive deposition of 'triglycerides' in the hepatocytes. The deposition of fat droplets displaces nucleus to the periphery of the cell (Fig. 9.2). Fatty liver does not necessarily indicate a state on non-functional hepatocytes and is reversible if the stimulus causing fatty liver is



**Fig. 9.2: Microscopic view of liver hepatocytes containing fat droplets (white spaces), displacing the nucleus (blue stained) towards periphery.** *Image courtesy: Calicut Medical College, CC BY-SA 4.0* [<https://creativecommons.org/licenses/by-sa/4.0>](https://creativecommons.org/licenses/by-sa/4.0/), via [Wikimedia Commons](https://commons.wikimedia.org/wiki/File:Microscopic_view_of_liver_hepatocytes_containing_fat_droplets_(white_spaces)_displacing_the_nucleus_(blue_stained)_towards_periphery.jpg) (Source: Calicut Medical College, CC BY-SA 4.0 [httpscreativecommons.org/licenses/by-sa/4.0](https://creativecommons.org/licenses/by-sa/4.0/), via [Wikimedia Commons](https://commons.wikimedia.org/wiki/File:Microscopic_view_of_liver_hepatocytes_containing_fat_droplets_(white_spaces)_displacing_the_nucleus_(blue_stained)_towards_periphery.jpg))

removed. However, accumulation of fat makes liver susceptible to injury by other hepatotoxicants. Fatty liver may progress into a more serious condition—cirrhosis. The reason for accumulation of fat in the liver are: increased supply of fat to the liver from adipose tissue and diet, and decreased metabolism and impaired transport of triacylglycerol from liver to adipose tissue. Liver transports triacylglycerol packed in the form of VLDL (Very Low Density Lipoproteins). VLDLs are vesicles made of various lipids and proteins. Thus, toxicants interfering with the synthesis of VLDL proteins, phospholipids, and movement of VLDL across cell membrane can cause accumulation of fat in the liver. Ethanol, CCl<sub>4</sub>, tamoxifen and valproic acid are few examples of toxicants which promote fat deposition in the liver.

### 9.3.3 Cholestasis

Refer to figure 1 and follow the direction in which bile flows. Bile is formed when the components of bile (bile salts, conjugated bilirubin, phospholipids, cholesterol, ions, and water) are transported by hepatocytes across the cell membrane into bile canaliculi. The transportation of bile components is facilitated by several membrane transport proteins. The metabolites of xenobiotics are secreted by hepatocytes in the bile by the same membrane transport system. Bile from several bile canaliculi is eventually poured into the bile duct from where it moves to larger ducts and finally secreted in the intestine via common bile duct. The formation and adequate flow of bile through bile ducts is necessary for normal physiological functions such as digestion and excretion of metabolites of xenobiotics and endogenous substances.

In cholestasis, the flow of bile is reduced, and in extreme situations, the flow stops. It is due to the impairment in secretion of bile components by hepatocytes or obstruction to the flow of bile through ducts. Inflammation and accumulation of dead cell debris in the bile ducts are the reasons for obstruction to bile flow. The accumulating bile components in hepatocytes begin to appear in the blood. The yellowing of skin and eyes due to presence of excess amount of bile pigments in blood is called 'jaundice'.

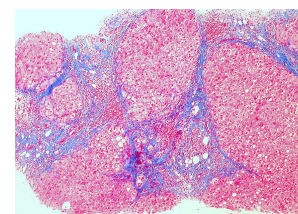
### 9.3.4 Fibrosis and Cirrhosis

Fibrosis (sometimes also called scarring) is replacement of the normal tissue with fibrous tissue, similar to that occur in the wound healing process of skin. Hepatic fibrosis is due to the chronic liver injury caused by toxicants or other factors such as inflammation. During hepatic fibrosis, there is extensive deposition of collagen fibres around the central vein, portal tracts and space of Disse (see Fig. 9.1D). With continuing fibre deposition, an interconnection between scars develops and liver is divided into nodules with hepatocytes. The normal lobular architecture of liver is damaged—a condition known as 'cirrhosis'. The excessive fibre deposition disrupts the characteristic blood flow in liver (as discussed above) which impedes exchange of nutrients and affects normal functioning of liver. Worldwide, viral hepatitis and alcohol abuse are the leading causes of fibrosis and cirrhosis.

## SAQ 2

State whether the following statements are true or false:

- In cholestasis, there is a heavy deposition of fat in the hepatocytes (True/False).
- Presence of alanine aminotransferase (ALT) in the blood may indicate ongoing necrosis of hepatocytes (True/False).
- Fatty liver may be caused by defect in transport of lipids from liver to adipose tissue (True/False).
- Deposition of large amount of cholesterol in hepatocytes causes steatosis (True/False).



**Fig. 9.3: Microscopic view of liver showing interconnected fibrous scars dividing the liver parenchyma.** Image courtesy: Nephron, CC BY-SA 3.0 <<https://creativecommons.org/licenses/by-sa/3.0/>>, via Wikimedia Commons

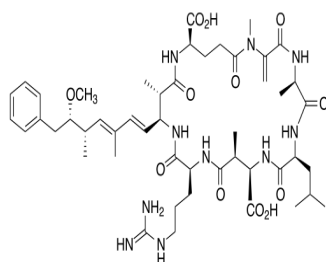
(Source: Ed Uthman from Houston, TX, USA, CC BY 2.0 <https://creativecommons.org/licenses/by/2.0/>, via Wikimedia Commons)

## 9.4 HEPATOTOXIC AGENTS

A variety of xenobiotics including drugs, natural poisons such as plant and animal toxins, metals, drugs, food additives, etc. can harm liver. In this section, we will see the mechanism of action of major hepatotoxicants.

### 9.4.1 Microcystins

Microcystins is a group of toxins produced by 'cyanobacteria' or 'blue-green algae' growing in lakes and reservoirs. Microcystin-LR is the most common and well-studied of all microcystins. Humans and animals are exposed to microcystins by drinking contaminated water. The main target organ of microcystins is liver, although it has also been reported to affect kidneys and intestine. It is taken up by hepatocytes by transporters OATP (organic anion-transporting polypeptides). A higher number of these transporters on hepatocyte cell membrane accounts for selective hepatotoxicity by microcystins (Fig. 9.4).



**Fig. 9.4: Microcystin-LR.**

(Image courtesy: Charlesy, Public domain, via Wikimedia Commons)

Microcystins causes deformity in hepatocytes and their detachment from each other disrupting the normal architecture. Microcystins bind to cysteine residue of the enzymes - protein phosphatases. These enzymes are responsible for removal of phosphate groups from other proteins and enzymes making them active or inactive. Inhibition of phosphatases causes accumulation of phosphorylated proteins such as those involved in cell signalling and cell proliferation.

### 9.4.2 Amatoxins

It is a group of toxins produced by toxic mushroom *Amanita phalloides*. This toxin is efficiently absorbed from intestine and reaches liver; here, it enters hepatocytes using OATP transporters. It causes necrosis of hepatocytes. Amatoxins are potent inhibitors of RNA polymerase II, which is required for transcription of mRNA. This results in inhibition of protein synthesis and death of the cells (Fig. 9.5).

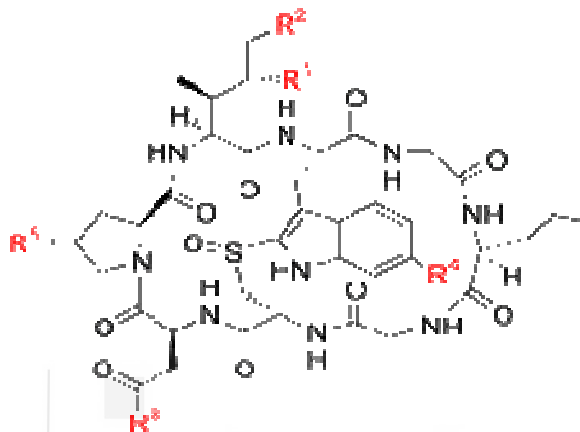


Fig. 9.5: Backbone structure of Amatoxins.

(Image courtesy:Edgar181, Public domain, via Wikimedia Commons)

### 9.4.3 Carbon Tetrachloride

It is a potent and well-studied hepatotoxicant.  $\text{CCl}_4$  is metabolized in liver by CYP450 to trichloromethyl radical ( $\cdot\text{CCl}_3$ ), which after reaction with oxygen, gets converted to trichloromethylperoxyl radical ( $\cdot\text{OCCl}_3$ ). Both the free radicals are highly reactive and can react with proteins in hepatocytes and initiate lipid peroxidation (Fig.9.6). The latter is the process by which free radicals can fragment membrane lipids and damage cell membrane. Damage to cell membrane causes leakage of cellular contents and finally necrosis. Continued exposure to  $\text{CCl}_4$  causes extensive necrosis and replacement of hepatocytes with fibrous mass—fibrosis.

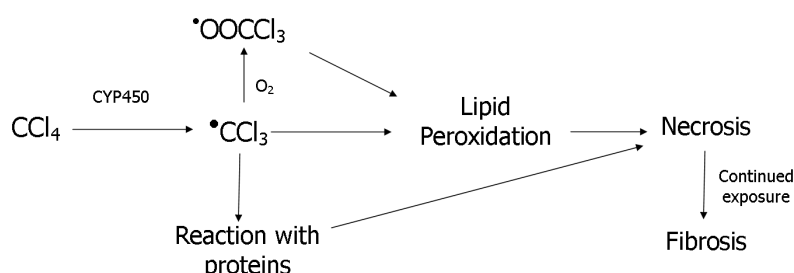


Fig. 9.6: Mechanism of hepatotoxicity by carbon tetrachloride.

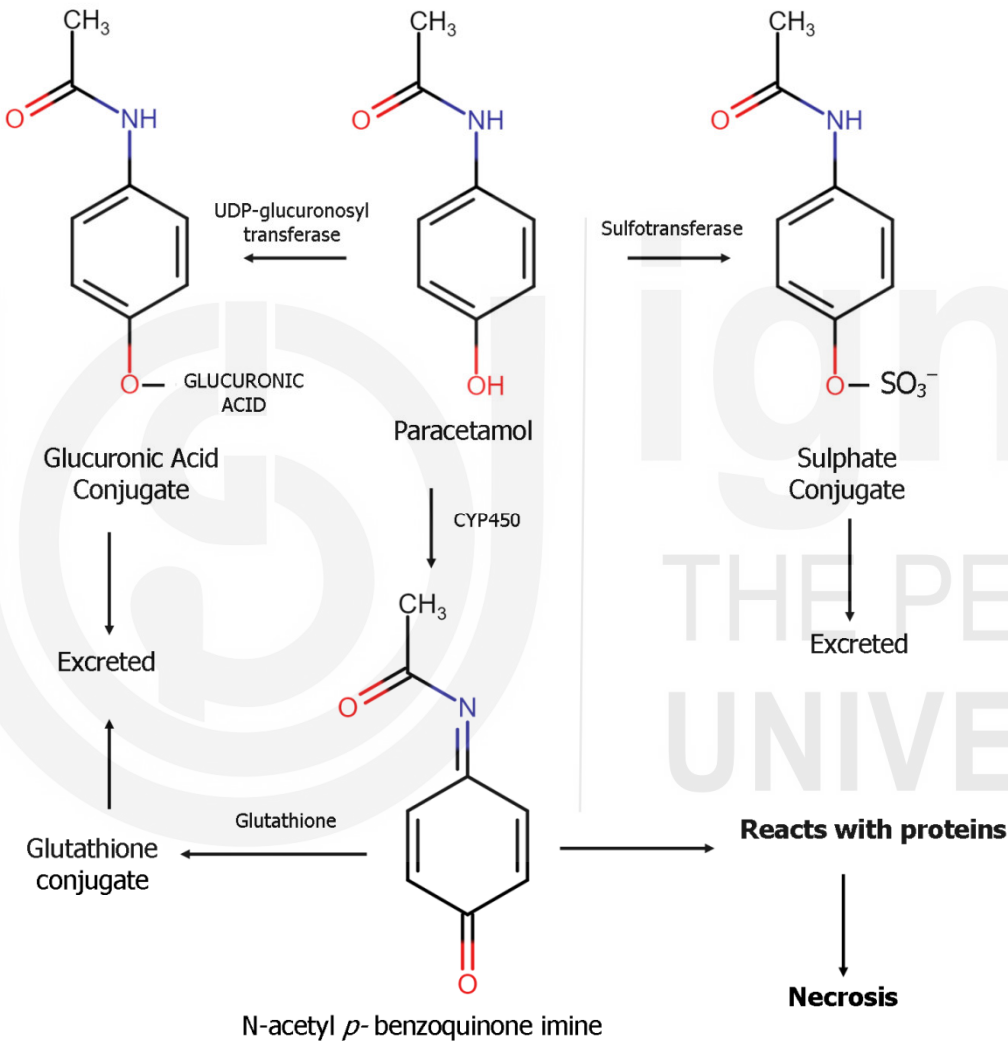
(Source: CCL4 toxicity Rajesh Chaudhary)

### 9.4.4 Paracetamol

It is a safe drug and available as over-the-counter drug for relieving pain and fever. However, overdosing of paracetamol can cause serious liver injury which may be fatal if not intervened. Paracetamol poisoning causes death of

hepatocytes. Refer to fig. 9.7, under normal or therapeutic dose, most of paracetamol is metabolized in the liver via glucuronidation and sulfonation reactions and the harmless metabolites are excreted in bile and urine. However, in the event of overdosing, the two enzymes (see figure) getsaturated and a significant amount of paracetamol is metabolized by CYP450 to produce a toxic metabolite called N-acetyl

benzoquinone imine (NAPQI). This metabolite is detoxified by glutathione conjugation, which also gets depleted on increased production of NAPQI. Thus, overdosing causes accumulation of NAPQI in hepatocytes that reacts with proteins and initiates toxicity.



**Fig. 9.7: Mechanism of hepatotoxicity by paracetamol.**  
 (Source: PCM metabolism Rajesh Chaudhary)

**9.4.5 Ethanol**

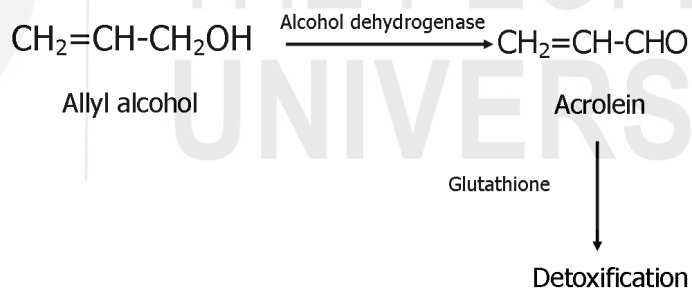
Chronic ethanol abuse is a leading cause of liver damage. Ethanol is metabolized by three pathways using enzymes (CYP450, alcohol dehydrogenase and catalase) and in each of these cases the product is acetaldehyde, which is metabolized to acetate by aldehyde dehydrogenase. Acetate is converted to water molecule and carbondioxide via Krebs cycle.

As we have seen above, excessive or chronic alcoholism causes fatty liver or steatosis. Although the mechanism leading to fat deposition in liver and subsequent events leading to cirrhosis is complex, it may be summarized as follows: *i)* ethanol increases cellular supply of acetate and NADPH which increase triacylglycerol synthesis, *ii)* the acetaldehyde formed from ethanol inhibits proteins involved in the formation and secretion of VLDL. This prevents transport of triacylglycerol from liver to adipose tissues. Both the above steps cause accumulation of triacylglycerol in the liver, which is augmented by the habit of consuming a diet rich in fats. Steatosis makes liver susceptible to several pathological injuries and toxicants, but is not considered enough to cause liver failure.

Continued alcoholism brings in involvement of immune system and necrosis of hepatocytes which is as follows: metabolism of ethanol by CYP450 (as discussed above) causes generation of free radicals which causes necrosis of hepatocytes. Further, acetaldehyde can directly stimulate fibre deposition by stellate cells and also activate Kupffer cells. In summary, necrosis of hepatocytes and stimulation of stellate cells causes fibrosis; that in extreme cases, leads to cirrhosis and liver failure.

#### 9.4.6 Allyl Alcohol

This industrial chemical is preferentially taken up by the hepatocytes of zone 1. It is metabolized by alcohol dehydrogenase to a reactive metabolite 'acrolein', which reacts with the proteins in hepatocytes and can initiate lipid peroxidation (Fig. 9.8). These events lead to necrosis of hepatocytes. A reduced level of glutathione in the hepatocytes aggravates liver injury because acrolein is detoxified by conjugation with glutathione.



**Fig.9.8: Activation of allyl alcohol to acrolein by alcohol dehydrogenase in liver.**  
(Source: acrolein Rajesh Chaudhary)

### SAQ 3

a) State whether the following statements are true or false:

- i) Exposure to carbon tetrachloride causes lipid peroxidation in hepatocytes (True/False).
- ii) Under normal therapeutic dose, significant amount of paracetamol is converted to NAPQI which is responsible for necrosis of hepatocytes (True/False).

- iii) Liver is susceptible to amatoxins because they can be selectively accumulated in hepatocytes (True/False).

**b) Fill in the blanks with appropriate words:**

- i) Toxic metabolite of paracetamol is produced by the enzyme.....
- ii) Toxic metabolite of allyl alcohol is produced by the enzyme.....
- iii) Amatoxins are inhibitors of .....

## 9.5 SUMMARY

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- Liver is the largest and most active organ of the body. It performs several functions which are crucial for the survival. There are several toxicants (hepatotoxicants) which specifically damage structure of liver and can cause liver failure.
- Liver is the main organ for xenobiotic metabolism and receives a high concentration of toxicants absorbed from the site of exposure (particularly gastrointestinal tract). Liver contains a high concentration of various xenobiotic metabolizing enzymes and transporters. These factors make liver susceptible to toxic insult.
- Liver has an ordered arrangement of cells and a unique manner of blood flow which is essential for the function of liver. The most abundant cells in liver are the hepatocytes which are arranged linearly around wide capillaries called sinusoids. Hepatocytes perform most of the functions of liver and are main target of toxicants.
- Chronic exposure or exposure to high concentrations of toxicants can cause necrosis or death of hepatocytes, which is repairable up to a certain limit. Massive death of hepatocytes and their replacement with collagen fibres is called fibrosis. Extensive fibrosis may progress to a more serious condition called cirrhosis, in which the liver is divided by fibrous septa into nodules enclosing hepatocytes. This damages the normal functional architecture of the liver and may lead to liver failure.
- Toxicants such as paracetamol, allyl alcohol, carbon tetrachloride can cause acute necrosis, whereas chronic consumption of ethanol can cause steatosis which may progress to fibrosis and cirrhosis.

## 9.6 TERMINAL QUESTIONS

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1. Provide mechanism of action of hepatotoxicity by paracetamol.
2. Explain why liver is susceptible to toxic insult.
3. Briefly describe structure of a hepatic lobule.

## 9.7 ANSWERS

### Self-Assessment Questions

1. a) i) False ii) True iii) True iv) False  
b) i) Phagocytosis  
ii) Fat-storing cells  
iii) Hepatic acinus
2. a) i) False ii) True iii) True iv) False
3. a) i) True ii) False iii) True  
b) i) CYP450  
ii) Alcohol dehydrogenase  
iii) RNA polymerase II

### Terminal Questions

1. In cases of overdosing, paracetamol is metabolized by CYP450 to produce toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). This reactive metabolite is detoxified by glutathione conjugation. However, increased production of NAPQI due to overdosing of the drug depletes glutathione reserve, causing accumulation of NAPQI in hepatocytes which can react with proteins and cause necrosis.
2. The reasons of susceptibility of liver to toxicants are as follows:
  - i) Liver receives a high concentration of toxicants absorbed from gastrointestinal tract.
  - ii) Liver has the highest concentration of xenobiotic metabolizing enzymes and in the event of metabolic activation; the activated xenobiotics immediately react and damage the cellular components of hepatocytes (cell membrane lipids, proteins and DNA).
3. Hepatic lobules are hexagonal structures, the boundary of which is limited by a thin bundle of connective tissue. Lobule is the structural unit of liver. Within a lobule, hepatocytes are arranged in a linear manner called hepatic cords. Along the length of cords lies a wide blood-filled cavity known as hepatic sinusoid. On the corners of lobules, there are hepatic triads—a collection of vessels such as branches of hepatic artery, hepatic portal vein, and bile duct. In the centre of lobule, there is a central vein which collects blood flowing from vessels of hepatic triad through sinusoids.

## 9.8 FURTHER READING

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