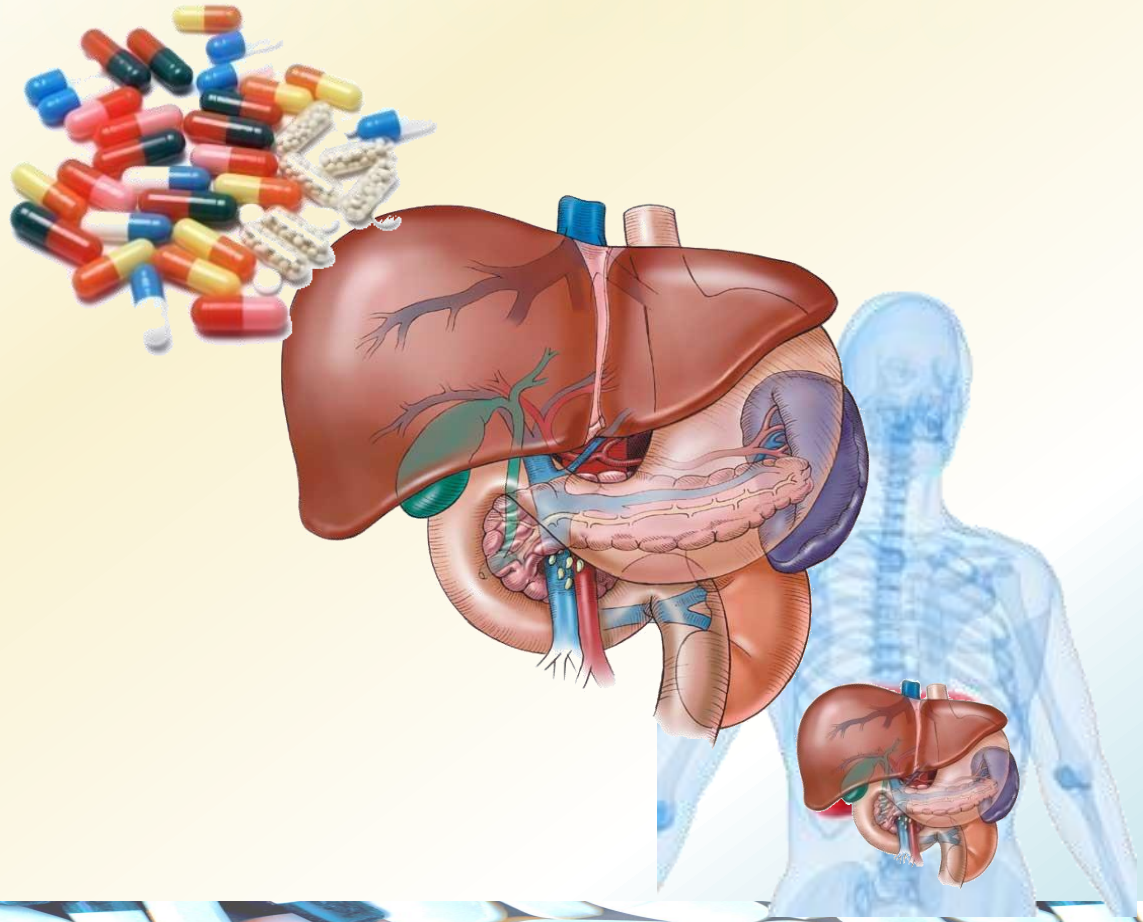
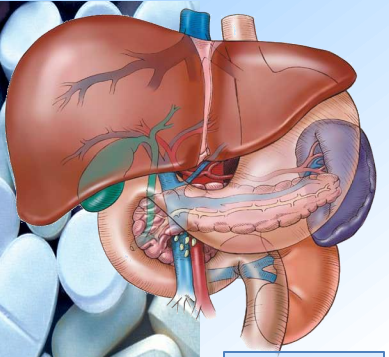
HEPATOTOXIC DRUGS

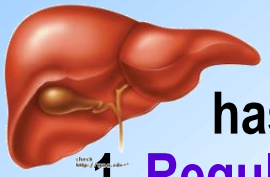




HEPATOTOXIC DRUGS

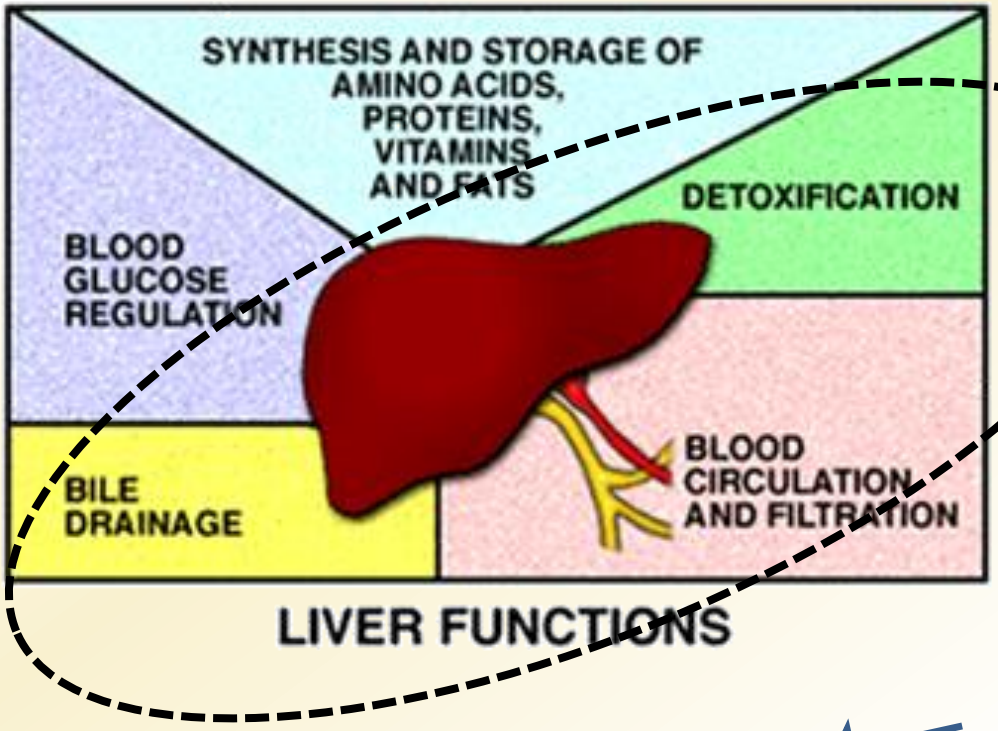
ILOs

- Define the role of liver in drug detoxification
- Discuss the types (patterns) of hepatotoxicity
- Classify hepatotoxins
- Explain how a drug can inflict hepatotoxicity
- State the pathological consequences of hepatic injury
- Contrast the varied clinical presentation of hepatotoxicity
- Enlist the possible treatment



has multiple functions (>5000) ➔ can be categorized into:

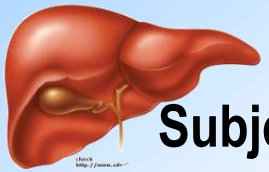
1. Regulation, synthesis & secretion. ➔utilization of glucose, lipids & proteins + bile for digesting fats.
2. Storage. ➔ Glucose (as glycogen), fat soluble vitamins (A, D, E & K) & minerals
3. Purification, transformation & clearance ➔ of endogenous (steroid hormones, cholestrol, FA, & proteins..) & exogenous (drugs, toxins, herbs…etc) chemicals.



Human body identifies almost all drugs as foreign substances i.e. XENOBIOTIC

Has to get rid of them

"METABOLIC CLEARING HOUSE"



HEPATOTOXIC DRUGS

Subjects drugs to chemical transformation (METABOLISM) ➔ to become inactive & easily excreted. Since most drugs are lipophilic ➔ they are changed into hydrophilic water soluble products ➔ suitable for elimination through the bile or urine

Such metabolic transformation usually occur in 2 PHASES:

Phase 1 reactions
Oxidation, Reduction, Hydrolysis, Hydration
Catalyzed by CYT P-450

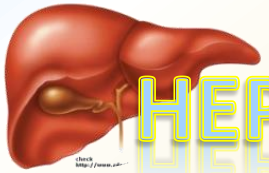
Yields intermediates ➔
polar, transient, usually highly reactive ➔
far more toxic than parent substrates ➔
may result in liver injury

Drug Induced Liver Injury (DILI)

Phase 2 reactions
Conjugation with a moiety (acetate, a.a., glutathione, glucuronic a., sulfate)

Yields products of increased solubility
- If of high molecular weight ➔ excreted in bile
- If of low molecular weight ➔ to blood ➔ excreted in urine

Hepatotoxicity ➔ Is the Leading cause of ADRs



HEPATOTOXIC DRUGS

DRUG INDUCED LIVER INJURY

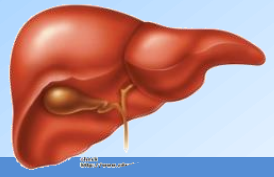
Injury / damage of the liver ➔

Caused by exposure to a drug ➔

Inflict varying impairment in liver functions ➔

Manifests clinically a long range ➔ hepatitis ⇨failure

Inflammation ⇨Apoptosis ⇨ Necrosis



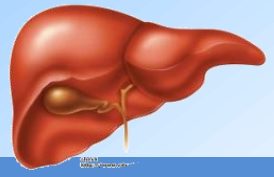
HEPATOTOXIC DRUGS

Why the liver is the major site of ADRs ?

- It is the first organ to come in contact with the drug after absorption from the GIT.
- Being the metabolic clearing house of the body ➔ it expresses the highest levels of drug metabolizing enzymes that converts some drugs(PROTOXINS) into intermediate (TOXINS) before being conjugated for elimination

Drug (Pro-toxin)		Toxin		Injury
Paracetamol	→ *CYT P450* →	NABQI		centrilobular

(NAPBQI) : N-acetyl-p-benzoquinone imine



HEPATOTOXIC DRUGS

Can any drug cause liver-related ADRs ?

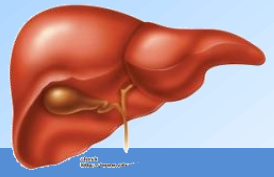
Not all drugs do so.

Drugs that can cause ADRs in the liver (hepatotoxicity) → are called → **HEPATOTOXIN**

TOXICITY POTENTIAL OF THE DRUG

- Chemical composition of the drug itself
- Nature of its reactive metabolite
- Conjugation reactions linked to it & their availability
- Mitochondrial effects of the drug
- Drug formulation

…etc



HEPATOTOXIC DRUGS

1. Nature of a Hepatotoxin
2.Types of drug-induced hepatotoxic ADRs it inflicts ?

If the toxicity of HEPATOTOXIN is inflicted by:

SUPERTHERAPEUTIC or CUMULATIVE DOSE of the drug
➔ INTRINSIC HEPATOTOXIN
The hepatotoxicity it inflicts is ➔ DIRECT HEPATOTOXICITY ➔ belong to TYPE A ADRs: PREDICTABLE / DIRECT

If the toxicity is inflicted by NORMAL DOSE of the drug ➔ IDIOSYNCRATIC HEPATOTOXIN
The hepatotoxicity it inflicts is ➔ INDIRECT HEPATOTOXICITY ➔belong to TYPE B ADRs: UNPREDICTABLE / BIZZAR / IDIOSYNCRATIC

Types of drug-induced hepatotoxic ADRs ?

1. DIRECT HEPATOTOXICITY caused by INTRINSIC HEPATOTOXIN

Type A *Dose-dependent hepatotoxicity*

Direct increased dose dependent hepatotoxicity

- Acetaminophen — Increased Dose
- Salicylates — Increased Dose
- Statins — Increased Dose
- Amiodarone — Cumulative Dose/effect
- Methotrexate — Increased & Cumulative
- Oral contraceptives — Cumulative Dose/effect
- Alcohol — Increased & Cumulative Doses/effect

Direct cumulative hepatotoxicity

2. INDIRECT HEPATOTOXICITY caused by IDIOSYNCRATIC HEPATOTOXIN

Type B *Dose-independent hepatotoxicity* ➔ divided into:

- Hypersensitivity or immunoallergic reactions
- Metabolic-idiosyncratic reactions

2.a. Immunoallergic Idiosyncratic Hepatotoxicity

Type B

A drug or its metabolite binds to hepatic membranes or proteins ➔act as hapten to induce a variety of immune reactions

Inflammatory cholestasis	Viral hepatitis-like pattern
Chlorpromazine. Chlorpropamide. Erythromycin.	Isoniazid. Phenytoin. Methyldopa.

2. INDIRECT HEPATOTOXICITY caused by IDIOSYNCRATIC HEPATOTOXIN

2.b. Metabolic Idiosyncratic Hepatotoxicity

Type B

The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis….etc

Interfere with bilirubin metabolism

- **Erythromycin**
- **Rifampicin**

Interfere with protein synthesis

- **Corticosteroids**
- **Tetracycline**

N.B. Not all drugs fall neatly into one of these categories, and overlapping mechanisms may occur with some drugs

HOW CAN A DRUG INDUCE HEPATOTOXICITY ?

Drug or its reactive metabolites can form covalent bonds with target molecules or alter the target molecule by non-covalent interactions or both

COVALENT INTERACTIONS

It is adduct formation between the metabolite of the drug & cellular macromolecules

If covalent binding to protein ➔ immunogenic reaction

If binding to DNA ➔ carcinogenesis

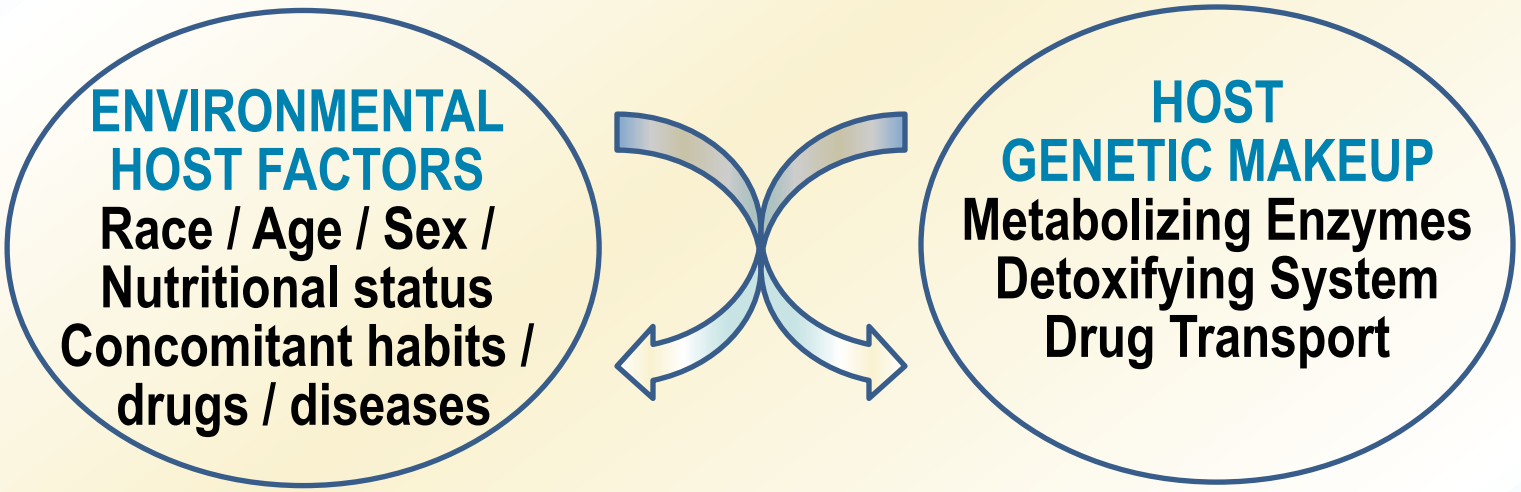
NON-COVALENT INTERACTIONS

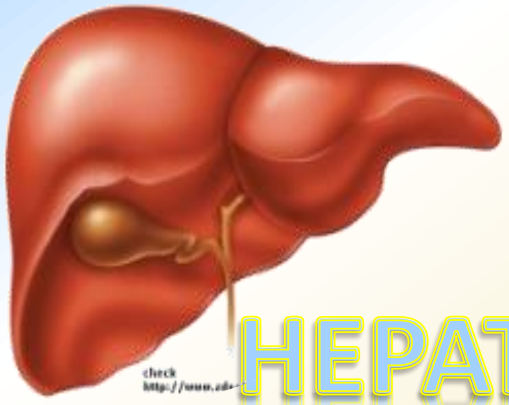
- Lipid peroxidation ➔ generation of cytotoxic oxygen radicals
- Impairment of mitochondrial respiration
- Depletion of GSH reactions ➔ 'oxidative stress'
- Modification of sulfhydryl groups ➔ impair Ca^{2+}homostasis
- Protein synthesis inhibition

…..etc

Do hepatotoxins cause liver disease in all persons ?

Most hepatotoxins cause liver disease only in certain persons depending on:





HEPATOTOXIC DRUGS

DRUG INDUCED LIVER INJURY

DRUG INDUCED HEPATIC INJURY

Is DIHI common ?

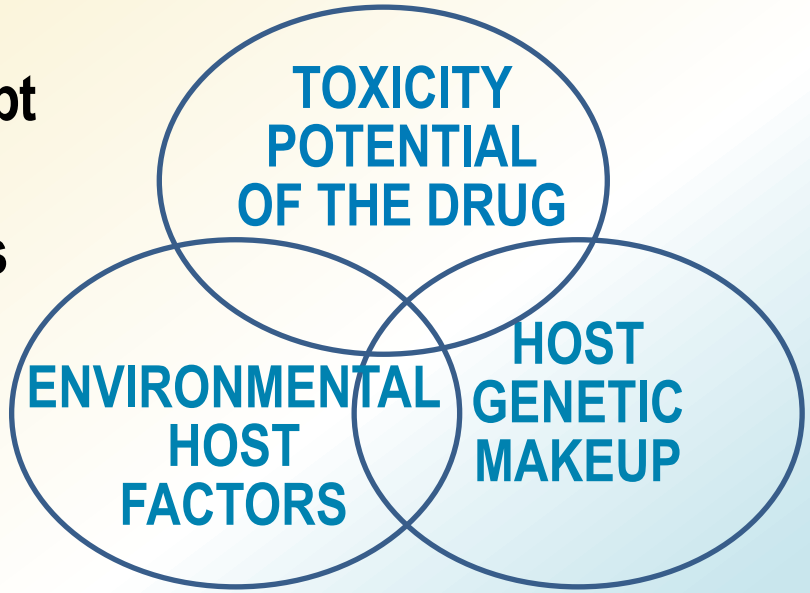
INCIDENCE of DILI

Drugs produce about 10% of all cases of hepatitis in young adults and 40% of cases in patients older than 50 years.

Are certain persons or population more susceptible ?

Upon exposure to hepatotoxins people are categorized as;

- Tolerators → No injury
- Adaptors → Mild transient injury but adapt
- Susceptibles →Develop overt symptoms depending on existing predisposing factors
- In Threat ; DILI accelerates beyond initial targets due to →loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells provoke apoptotic & necrotic signals



What are the presenting manifestations?

Individual drugs tend to have ➔ **CHARACTERISTIC SIGNATURE** ➔ composed of: A particular latency period
A clinical pattern
A particular pathological finding

LATENCY PERIOD ➔ short (hrs/dys), intermediate (1-8ws), long (1-12ms)

- In Direct dose-dependent Hepatotoxicity ➔Latency period ➔ SHORT as it occurs after a threshold of toxicity is reached
  ➔*acetaminophen* (toxic dose)
- In Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity ➔Latency period ➔ INTERMEDIATE ➔but may continue to evoke even after drug withdraw → amiodarone(cumulative)/phenytoin, isoniazid (idiosyncratic)
- In indirect metabolic idiosyncratic hepatotoxicity → latency period → usually long → unpredictable → most problematic → tetracycline, oral contraceptives.

CLINICAL PATTERNS

The clinical presentation could be of variable intensity, ranging from asymptomatic ↑of liver enzymes → → → fulminant hepatic failure

Some drugs just induce → ASYMPTOMATIC ↑ IN AMINOTRANSFERASES

- Phenytoin
- Statins
- Sulfonamides
- Sulfonylureas

Other drugs induce → SYMPTOMATIC MANIFESTATIONS

- If injury targets hepatocytes → apoptosis or necrosis → HEPATITIS (cytotoxic) develops→ rapid onset of malaise, severe anorexia and jaundice + ↑ in alanine aminotransferases (ALT)
- If injury targets biliary system (canalicular or ductal) → CHOLESTASIS develop → jaundice ± severe pruritus predominate → ↑ in alkaline phosphatase (ALP) ± hyperbilirubinaemia
- If injury targets both hepatocytes & biliary system → MIXED TYPE

Some PATTERNS of SYMPTOMATIC drug-induced liver disease

Hepatic injury	Hepatocellular	Cholestatic	Mixed
	Flu-like, malaise, m. aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored,	Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light	
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
Examples	Acetaminophen NSAIDs Isoniazid Amiodarone	Chlorpropamide Erythromycin Rifamycin Oral contraceptives	Phenytoin Carbamazepine Sulfonamides ACE Inhibitors

- A long standing rheumatoid arthritic patient developed tuberculosis 2 month ago. Today she was received in E.R complaining of yellowish discoloration of skin, severe anorexia, vomiting and flue like manifestations since two days. She is very weak and looks toxic.

Her drug history reveals that she has been 4 month ago on cyclosporine to control the arthiritic exacerbations. A month ago, she was put on isoniazid when she developed T.B. and multivitamins because she is weak. Currently she is given domperidone for the emesis.

Lab results reveals severe elevation in ALT but no elevation in ALP.

Hepatocellular

- Which one of the following drugs is the likely cause of her symptoms?

a. Cyclosporine b. Multivitamines

c. Isoniazid d. Domperidone

- Which type of hepatotoxin is it considered?
- What is the likely hepatotoxic pattern inflicted by the drug?

Treatment????

- A hypercholestrolemic patient was received in E.R complaining of yellowish discoloration of skin, change in color of urine & stools, and severe itching

He has been receiving statins fro the long time for the hypercholestrolemia. Three month ago he was diagnosed as being diabetic and hypertensive and since then he is receiving chlorpropamide for the diabetes and nadolol for the hypertension. The last couple of days he had a flue; for which he was given acetaminophen for muscle aches and nasal drops for his nasal stuffiness.

Lab investigations shows severe elevation in ALP and no significant elevation in ALT

Cholestatic

- Which one of the following drug is the likely cause of his symptoms?

a. Nadolol b. Chlorpropamide c. Acetaminophen d. Statins

- Which type of hepatotoxin it is considered?
- What is the hepatotoxic pattern inflicted by the drug?

Treatment????

HISTOPATHOLOGICAL PATTERNS

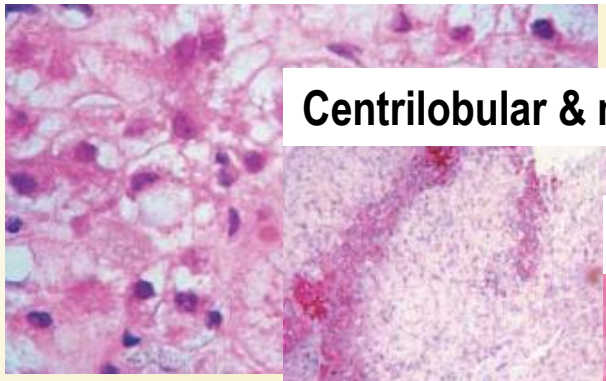
No universal histo-pathological pattern of DIHI exist.

The commonest are; Hepatocellular necrosis
Cholestasis
Steatosis

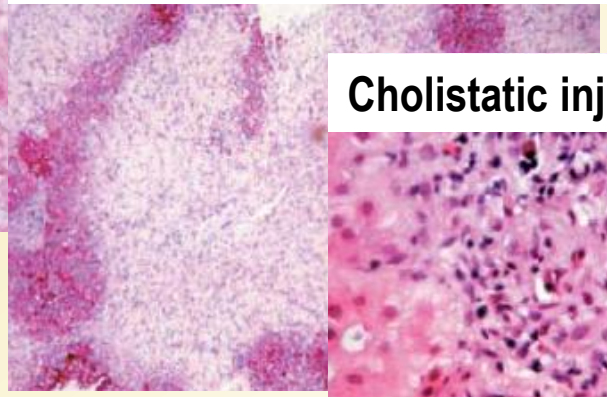
More than one type of injury may occur in the same patient

Any one agent may produce different types of injury in different patients

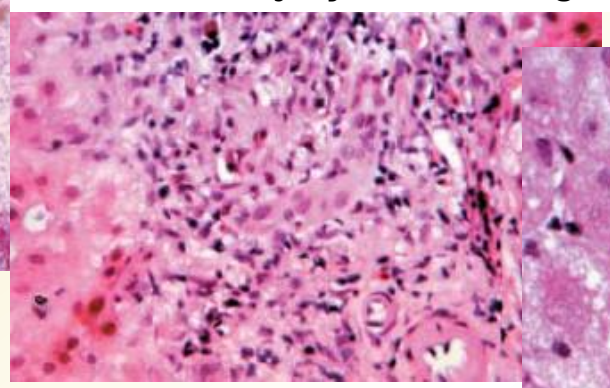
Ballooning & degeneration of hepatocyte



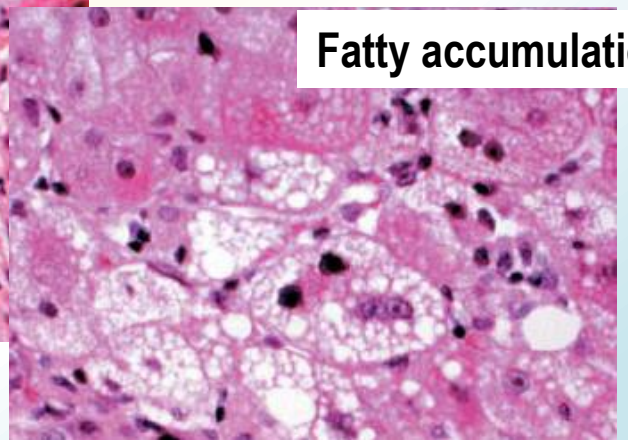
Centrilobular & midzonal necrosis



Cholistatic injury with damaged bile duct



Fatty accumulation



What are the lines of treatment?

Immediate withdrawal ➔ of any suspected drug

No specific treatment ➔ largely symptomatic & supportive

Symptomatic:

If a severe allergic reaction is observed ➔ Corticosteroids

If pruritus ➔ enhance bile acid excretion ➔ Cholestyramine

If cholestatic liver injury ➔ Ursodeoxycholic acid (Ursodiol)

If coagulopathy or encephalopathy develop ➔treat accordingly

Supportive:

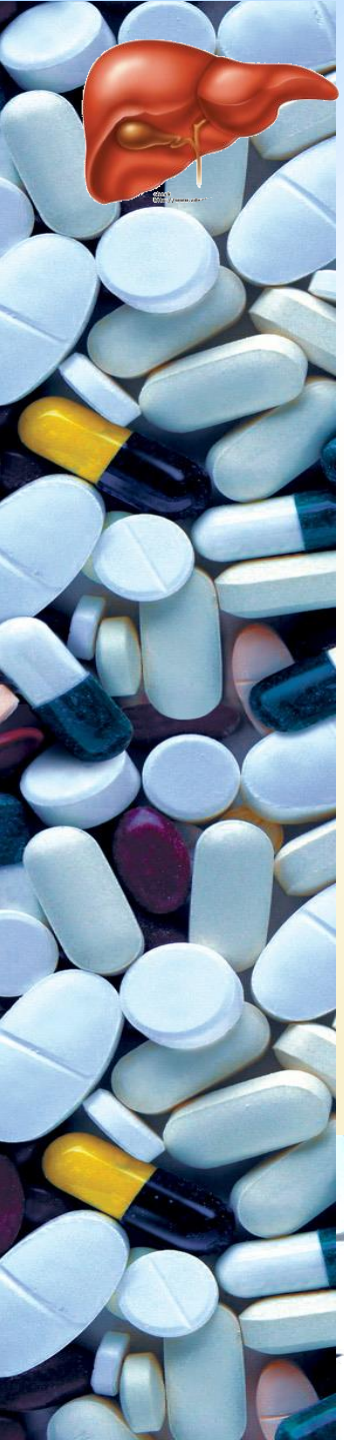
High carbohydrate, moderate protein diet adequate in calories

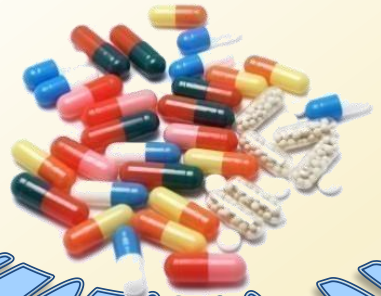
Specific antidotes

N-acetylcysteine ➔ acetaminophen toxicity

L-carnitine ➔valproate toxicity

Emergency liver transplantation ➔for drug induced fulminant hepatic failure





HEPATOXIC DRUGS

GOOD LUCK