PHARMACOLOGY

TEAM 432

Hepatotoxic Drugs

Objectives

- Clarify the role of liver in drug detoxification
- Elaborate types (patterns) of hepatotoxicity
- Classify hepatotoxins
- Explain how a drug can inflict hepatotoxicity
- Contrast the varied clinical presentation of hepatotoxicity
- Discuss possibilities of diagnosis
- Enlist the possible treatment

Color Guide

Slides = Black
Females notes= Green
Female slides=purple
Males slides= Blue
Explanation=Orange

This lecture is also based on dr.Omnia's lecture. Cases,questions and imprtant points that are mentioned by her are written

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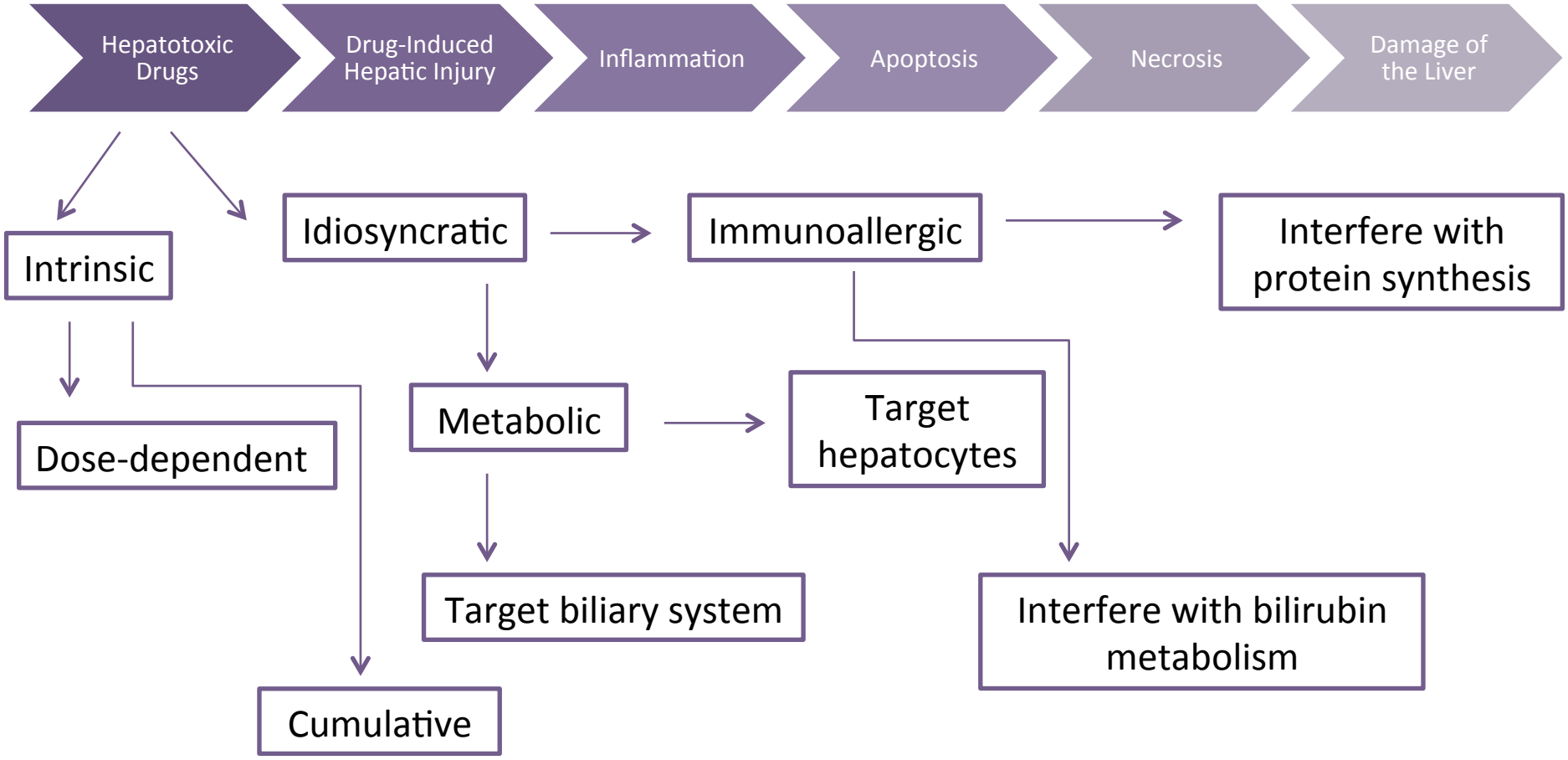
Mind Map


Hepatotoxic Drugs
Drug-Induced Hepatic Injury
Inflammation
Apoptosis
Necrosis
Damage of the Liver
Intrinsic
Idiosyncratic
Immunoallergic
Interfere with protein synthesis
Dose-dependent
Metabolic
Target hepatocytes
Target biliary system
Interfere with bilirubin metabolism
Cumulative

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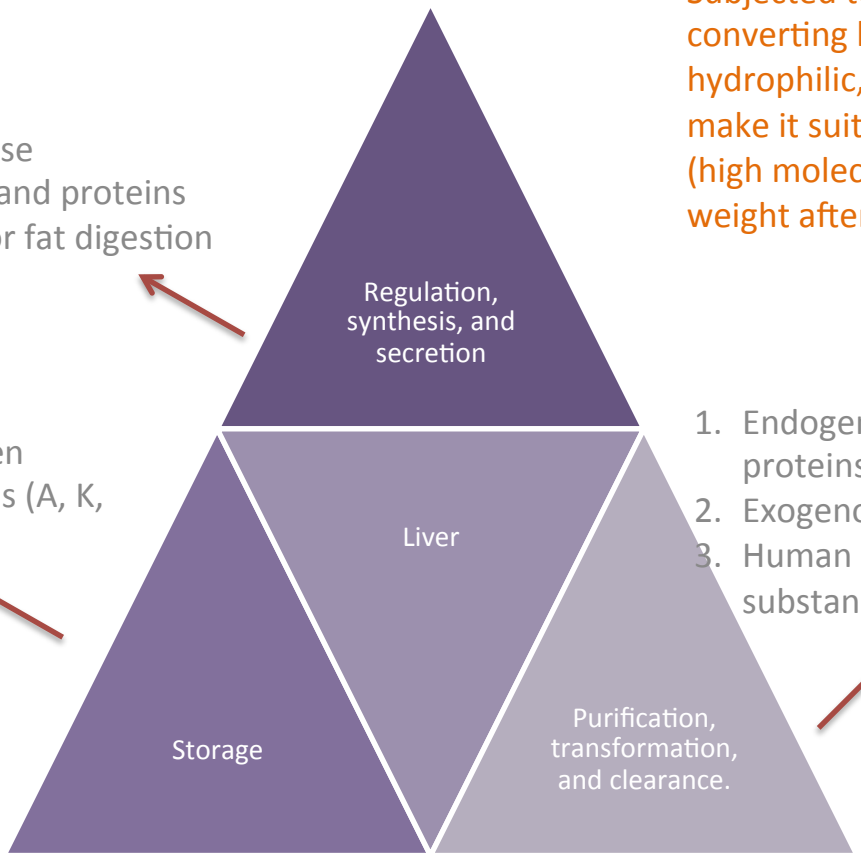
Functions of the Liver

Subjected to Metablism.The net result is converting lipophilic drugs into the hydrophilic,inactive and easily excreted form to make it suitable for elimination through the bile (high molecular weight) or urine (low molecular weight after going through the blood circulation).

1. Utilization of glucose
2. Synthesis of lipids and proteins
3. Secretion of bile for fat digestion



1. Glucose as Glycogen
2. Fat soluble vitamins (A, K, E, D)
3. Minerals

1. Endogenous substances (Steroids, Cholesterol, FA, proteins)
2. Exogenous substance (Drugs and toxins)
3. Human body indetifies it almost all drugs as a foreign substance (xenbiotic)

1. Phase 1: Oxidation, reduction, hydrolysis, hydration. Catalyzed by CYT P450. This phase makes the drug ready to be conjugated and may yield intermediates that are toxic to the liver.

2. Phase 2: Conjugation with a moiety (Acetate, glutathione, Glucuronic acid..)

Liver is the metabolic clearing house

Hepatotoxic Drugs

Why is the liver the site of major ADR?

1. The liver is the organ that comes in contact with a drug after its absorption from the GIT.
2. It produces enzymes that can convert drugs (Protoxins) into intermediates (Toxins) before being conjugated for elimination.

Example: Paracetamol is metabolized by CYT P450 into an intermediate (NABQI) that causes centrilobular injury to the liver.

Not all drugs can cause injury to the liver but the ones that do are called hepatotoxins, the toxicity potential of the drug depends on:

- The chemical composition of the drug itself
- The nature of its reactive metabolite
- The conjugation reactions related to it
- Availability of the drug
- Mitochondrial effects of the drug
- Drug formulation

Not important

Hepatotoxic Drugs

How can a drug induce hepatotoxicity?

The drug or it's reactive metabolite form either covalent bonds or non-covalent interactions with target molecules

Not important

Covalent interactions (Irreversible)	
Binding to protein ➔	Immunogenic reaction
Binding to DNA ➔	Carcinogenesis
Non-covalent interactions	
Lipid peroxidation ➔	Formation of cytotoxic oxygen radicals which impairs mitochondrial function
Depletion of GSH reactions ➔	Oxidative stress
Modification of Sulfhydryl groups ➔	Impair of Ca^{+2} hemostasis which results in inhibition of protein synthesis

Do Hepatotoxins cause liver disease in all persons?

For reasons not completely understood, they only cause liver disease in some persons. It is believed that the underlying metabolic state of the liver plays an important role. This metabolic state is a reflection of a person's **environmental host factors** and **genetic makeup**.

Hepatotoxic Drugs

Intrinsic Hepatotoxin: Supertheraputic dose, it inflicts direct dose dependent hepatotoxicity.
Belongs to Type A (Predictable/Direct) ADR.

Dr.Omnia said you have only to memorize Drugs in Red

Hepatotoxins		
Intrinsic		
Dose-dependent (Increased dose)	Cumulative	Mixed
Acetaminophens(paracetamol)	Amiodarone	Alcohol
Statins	Oral contraceptives	Methotrexate
Salicylates		

Hepatotoxic Drugs

important

Idiosyncratic Hepatotoxin: Normal dose of the drug, inflicts indirect dose independent hepatotoxicity.
Belongs to type B (Unpredictable/Bizzar) ADR.appear with a theraputic dose

Hepatotoxins			
Idiosyncratic			
Immunoallergic (Hypersensitivity)		Metabolic	
Target the biliary system which leads to the accumulation of bile in the liver	Target the hepatocytes causing viral hepatitis-like pattern	Interfere with bilirubin metabolism	Interfere with protein synthesis
Inflammatory Cholestasis	Viral hepatitis-like pattern		
Chlorpromazine	Isoniazide anti TB	Erythromycin	Corticosteroids
Chlorpropamide	Phenytoin anti epiliptic	Rifampicin anti TB	Tetracycline
Erythromycin	Methyldopa anti hypertension		

N.B. The bile itself is injurious to the liver in addition to the toxic effect of the drug itself.

Drug Induced Hepatic Injury = (DIHI)

INCIDENCE of DIHI:

10% of all cases of hepatitis → young adults

40% of cases → older than 50.

People are divided according to their susceptibility to DIHI into:

- **Tolerators** ➔ **No injury**
- **Adaptors** ➔ **Mild transient injury but adapt** (slight increase in liver enzymes but no symptoms)
- **Susceptibles** ➔ **Develop overt symptoms depending on existing predisposing factors** (can be managed)
- **In Threat ; DIHI accelerates beyond initial targets due to ➔ loss of synthetic & clearance function of hepatocyte**

Individual drugs tend to have CHARACTERISTIC SIGNATURE depending on 3 things:

1) A particular latency period

(((Short {hrs-dys} ,,, Intermediate {1-8 wks} ,,, Long { 4-12 mths})))

2) A clinical pattern

(((Asymptomatic ,,, Symptomatic injury to {1-hepatocytes, 2- biliary, 3- both})))

3) A particular histo-pathological pattern (not required - for further knowledge)

Each point will be discussed in details on the next slides.

1) latency period

important

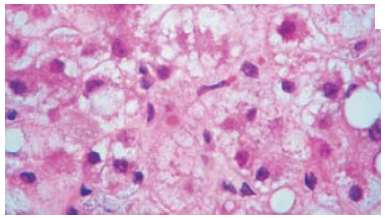
Latency period	How:		Examples
Short (hrs-dys)	Direct dose-dependent Hepatotoxicity	occurs after a threshold of toxicity is reached	*Acetaminophen, Paracetamol* **(toxic dose)**
Intermediate (1-8 wks)	Direct cumulative OR Indirect Immunoallergic Idiosyncratic Hepatotoxicity	may continue to evoke even after drug withdrawal	*amiodarone* **(cumulative) / phenytoin, isoniazid (idiosyncratic)**
Long (1-12 mths)	Indirect Metabolic Idiosyncratic Hepatotoxicity	Unpredictable most problematic	*tetracyclines, oral contraceptives*

2) histo-pathological pattern

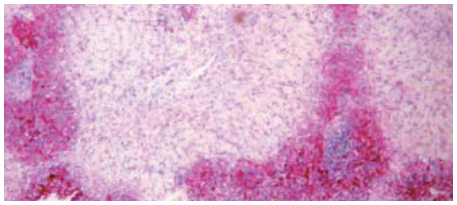
Not required

No universal histo-pathological pattern of DIHI exist.
The commonest are: Hepatocellular necrosis, Cholestasis & Steatosis (Any one agent may produce different types of injury in different patients)

Ballooning & degeneration of hepatocyte

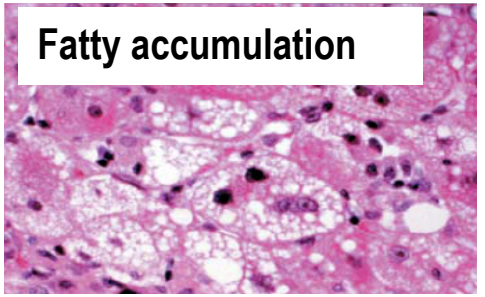


Centrilobular & midzonal necrosis



Cholistatic injury with damaged bile duct

Fatty accumulation



3) Clinical Patterns

important

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

Some PATTERNS of ASYMPTOMATIC drug-induced liver disease

ALT(asymptomatic aminotranferases)	≥ 2 fold rise.	Examples:	Phenytoin, Statins, Sulfonamides, Sulfonylureas

Some PATTERNS of SYMPTOMATIC drug-induced liver disease

Hepatic injury	Hepatocellular(apoptosis or necrosis)>> cytotoxic	Cholestatic(canalicular or ductal	Mixed
	Flu-like, malaise,anorexia muscle aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored,	Jaundice.Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light. There is hyperbilirubinemia.	Target both hepatocytes and biliray system
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

important

Case 1. 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.

- Tip:How to differentiate between drugs studied in this lecture and drugs in the previous lecture?
- The key word is: "***Jaundice***" once you see it relate the case to this lecture, in the previous one only liver disease

Q1- Which one of the following drugs is the likely cause of her symptoms?

a. Cyclosporine b. Multivitamines
c. Isoniazid (see schedule slide 4) d. Domperidone

Which type of hepatotoxin it is considered?
Indirect hepatotoxin (immunoallergic idiosyncratic hepatotoxicity)

What is the hepatotoxic pattern inflicted by the drug?
Symptomatic heptaocellular (viral hepatitis like pattern)

= Hepatocellular

Case 2. 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 for long receiving statins 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 acetominophen 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 (see schedule slide 4) c. Acetominophen d. Statins

Which type of hepatotoxin it is considered?

Indirect hepatotoxin (immunoallergic idiosyncratic hepatotoxicity)

What is the hepatotoxic pattern inflicted by the drug?

Symptomatic pattern (Inflammatory Cholestasis)

How is DIHI diagnosed?

Not important

DILI is most often diagnosis by

A] Thorough history

B] Exclusion of;

- Viral hepatitis
- Autoimmune disorders
- Alcohol intake
- Metabolic and genetic disorders
- Hemodynamic dysfunction
- Billiary abnormalities.

C] Perform of relevant investigations as;

- Liver enzymes; ALT, ALP
- Ultrasonography, CT scan, MRI
- Biopsy……etc

N.B. Early recognition is essential to minimize injury

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Indirect hepatotoxin (immunoallergic idiosyncratic hepatotoxicity)

What is the hepatotoxic pattern inflicted by the drug?
Symptomatic pattern (Inflammatory Cholestasis)

important

What are the lines of treatment?

lines of treatment

1) Immediate withdrawal	of any suspected drug		
2) No specific treatment	Symptomatic	If severe allergic reaction	Corticosteroids(in hepatotoxic)
		If pruritus →enhance bile acid excretion	Cholestyramine (anti histaminic wont work)
		If cholestatic liver injury	Ursodeoxycholic acid (Ursodiol)decreases inflam in bile duct
		If coagulopathy or encephalopathy develop	treat accordingly
	Supportive	High carbohydrate, moderate protein diet adequate in calories	
3) Specific antidotes	N-acetylcysteine →	acetaminophen toxicity(NABQI antidote)	
	L-carnitine →	valproate toxicity	
4) Emergency liver transplantation	for drug induced fulminant hepatic failure		

What are the pathophysiological consequences of hepatotoxins?

1. **Disruption of the hepatocyte**

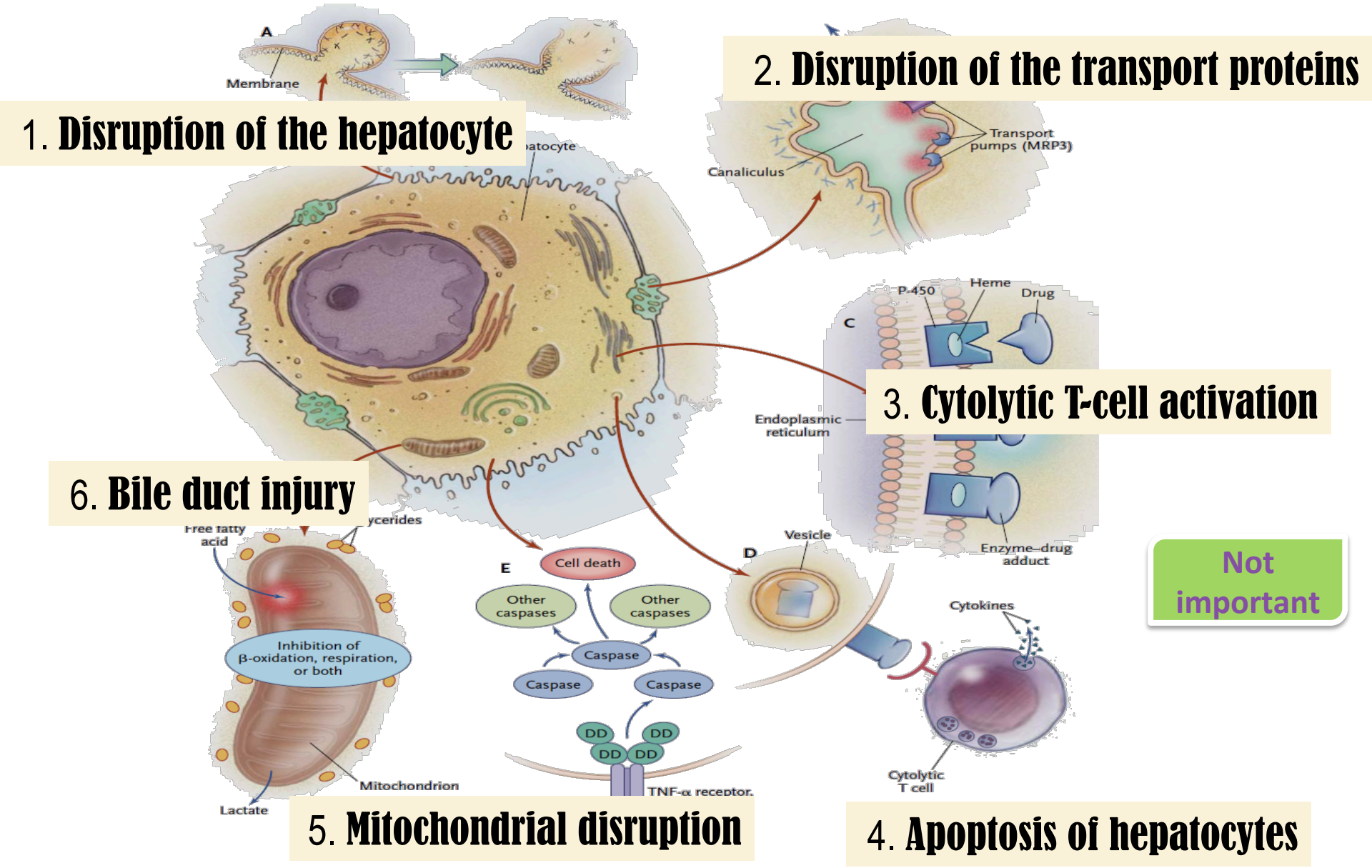
2. **Disruption of the transport proteins**

3. **Cytolytic T-cell activation**

4. **Apoptosis of hepatocytes**

5. **Mitochondrial disruption**

6. **Bile duct injury**



Not important

What are the pathophysiological consequences of hepatotoxins?

1. **Disruption of the hepatocyte:** Binding → ↓ ATP & alter Ca homostasis → cytoskeletal disruption → membrane blebs & rupture → cell lysis

2. **Disruption of transport :** Same changes → at canalicular membrane → alter transporter & pumps → interrupt bile flow → cholestasis.

3. **Cytolytic T-cell activation:** Covalent binding of a drug to the P-450 enzyme acts as an immunogen, activating T cells and cytokines and stimulating a multifaceted immune response.

Not important

4. **Apoptosis of hepatocytes:** Immune reaction → ↑TNF-α → activate Fas apoptotic pathways → caspases → apotosis

5. **Mitochondrial disruption:** Binding → ↓ β-oxidation or respiration → activate mitochondrial apoptotic cascade → apoptosis

6. **Bile duct injury:** Toxic metabolites excreted in bile → injury of bile duct epithelium (cholangitis)

SIGNATURE DISEASE		DRUGS CAUSING THE FEATURE
Zonal necrosis		Acetaminophen
Hepatitis;	Viral-like (Immunoallergic)	Phenytoin, Sulfonamides, Halothane
	(Metabolic)	Izoniazid
	Focal	Salicylates & NSAIDs
	Chronic	α - Methyldopa,
Cholistasis;	Bland	O. contraceptives, Androgens, Steroid
	Cholistatic hepatitis	Carbamazepine, Erythromycin
	Ductal	Chlopromazine, Chlopropramide
Steatosis;	Microvesicular steatosis	Valproic a., Tetracyclines, NSAIDs
	Macrovesicular steatohepatitis	Acetaminophen, Methotrexate
	Phospholipidosis	Amidarone, Tamoxifen
Granuloma formation		Sulfonylurea, Izoniazid, Phenytoin
Vascular;	Veno-occlussive	Cyclophosphamide
	Hepatic vein thrombosis	Oral contraceptive
Fibrosis/Chirrohosis		Methotrexate / Alcohol
Neoplasms		Oral contraceptive, Anabolic steroids

Summary

Drugs	Charactarestics
Phenytoin	Asympotomatic in aminotransferases, Mixed symptomatic, inertmediate period
Carbamazepine	Mixed symptomatic
Sulfonamides	Mixed symptomatic
ACE Inhibitors	Mixed symptomatic
Chlorpropamide	Cholestatic symptomatic,immunoallergic idiosyncratic
Erythromycin	Cholestatic symptomatic, metabilic &immunoallergic idiosyncratic
Rifamycin	Cholestatic symptomatic,Metabolic idiosyncratic
Oral contraceptives	Cholestatic symptomatic, Direct cumulative dose,long period
Acetaminophen	Hepatocellular symptomatic,NABQI toxin,Direct increased dose,short period
NSAIDs	Hepatocellular symptomatic
Isoniazid	Hepatocellular symptomatic, immunoallergic idiosyncratic, inertmediate period
Amiodarone	Hepatocellular symptomatic,Direct cumulative dose,inertmediate period
Statins	Asympotomatic in aminotransferases, Direct increased dose
Corticosteriods	Symptomatic severe allergic reaction, Metabolic idiosyncratic

20 years old patient has joint pain one day he experienced severe pain and he took over dose fron The prescribed drug , then he developed Diarrhea, janduce and malaise .. What's the causative drug?

Phenyton
Chlorpropamide
Acetaminophen

Which drug can control the toxicity in the last question?

L-cartinine
N-acetylcysteine
Cholestyramine

1/C
2/B
3/A
4/B

Patient came with hemoptysis, weight loss and fever, she was prescribed to take anti TB, but this drug interfered with the bilirubin metabolism and she developed janduice..Which drug is responsible of her symptoms?

Rifampicin
Isonazid
Tetracycline

25 married female developed pruritis, yellowish discoloration of the skin.She said there is only one drug I've been taken for 5 year.. What's the causative drug?

Amiodarone
Oral contraciptives

PHARMACOLOGY

TEAM 432

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