PHARMACOLOGY OF THE LIVER AND THE BILIARY TRACT

PANCREATIC ENZYME REPLACEMENT THERAPY

DRUGS PROMOTING GASTROINTESTINAL MOTILITY

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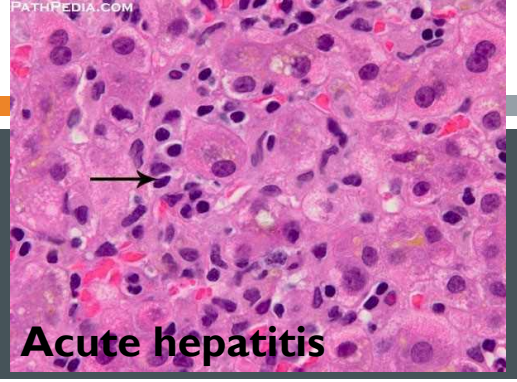
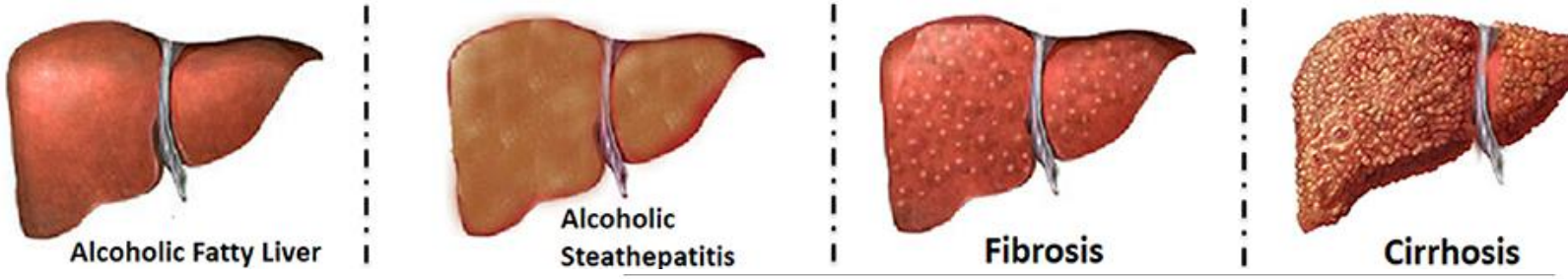
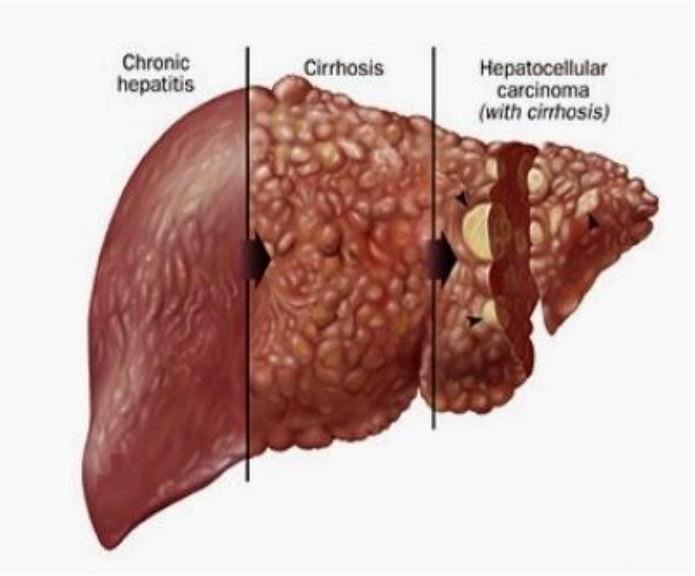
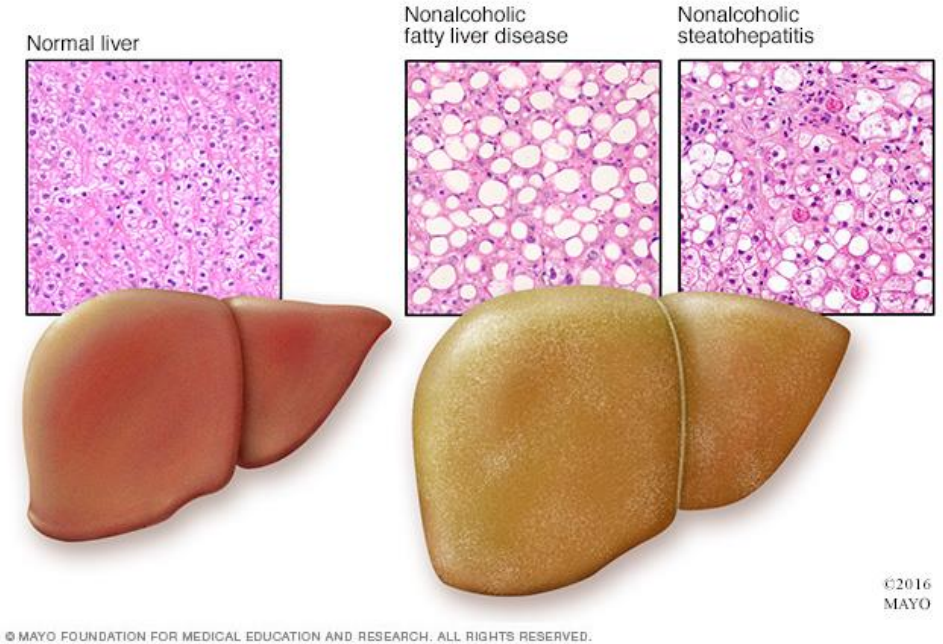
LIVER DISEASE/HEPATIC DISEASE



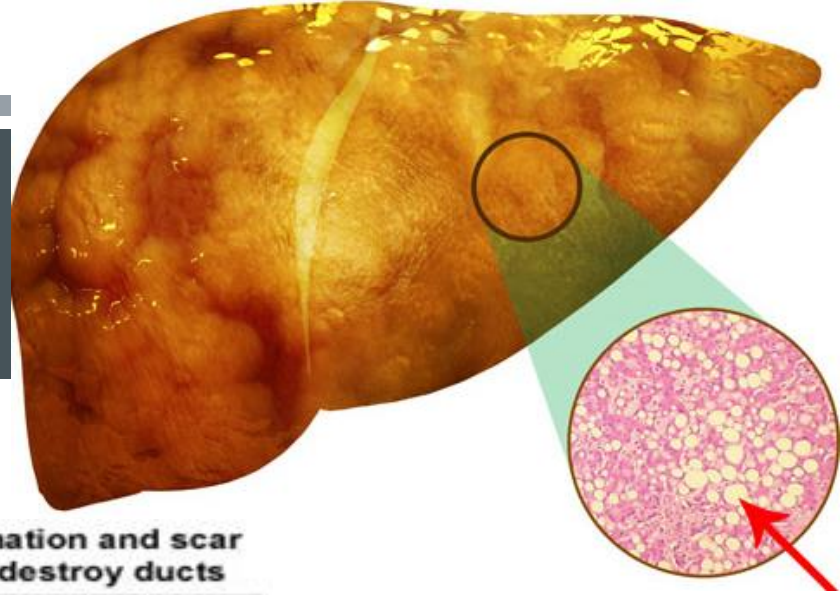
- Hepatitis = inflammation of the liver
  - various viruses (viral hepatitis)
  - liver toxins (e.g. alcoholic hepatitis)
  - autoimmunity (autoimmune hepatitis)
  - hereditary conditions
- Alcoholic liver disease
  - alcohol overconsumption
  - fatty liver disease,
  - alcoholic hepatitis,
  - cirrhosis.
- "drug-induced" or "toxic" liver disease
  - various drugs
- Fatty liver disease (hepatic steatosis)
  - reversible condition
  - large vacuoles of triglyceride fat accumulate in liver cells
- Non-alcoholic fatty liver disease
  - a variety of disease associated with obesity and metabolic syndrome.



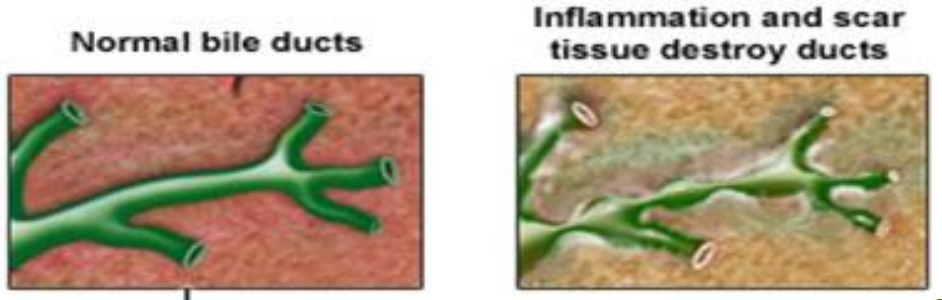


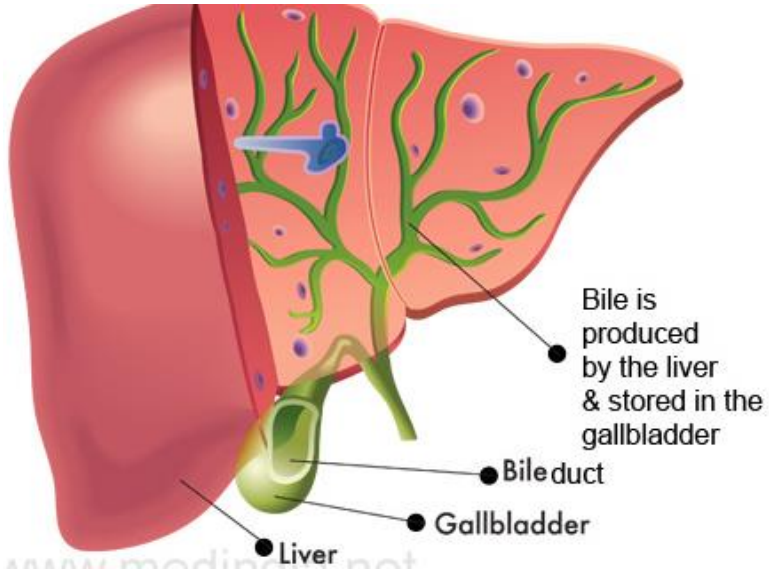


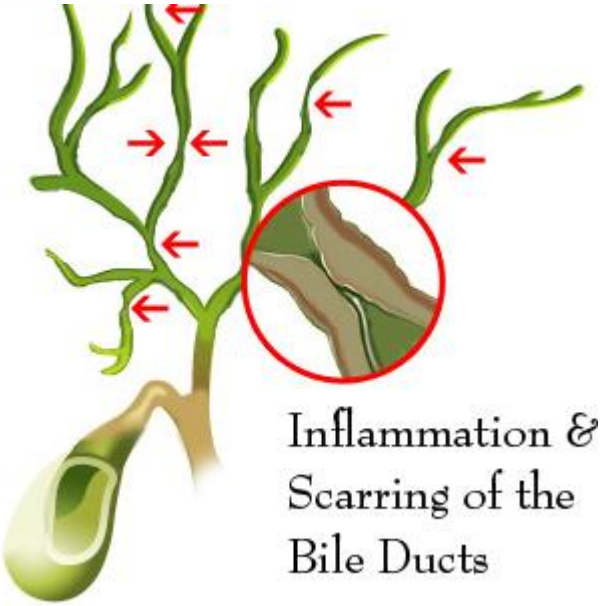
LIVER DISEASE/HEPATIC DISEASE



- Hereditary diseases
  - Hemochromatosis = accumulation of iron in the body
  - Wilson's disease
  - alpha 1-antitrypsin deficiency
  - glycogen storage disease type II
  - Gilbert's syndrome = genetic disorder of bilirubin metabolism
- Cirrhosis = formation of fibrous tissue (fibrosis) in the place of liver
- Primary liver cancer
  - hepatocellular carcinoma and/or cholangiocarcinoma
  - angiosarcoma and hemangiosarcoma of the liver
- Primary biliary cirrhosis = a serious autoimmune disease of the bile capillaries
- Primary sclerosing cholangitis =chronic inflammatory disease of the bile duct (? autoimmune in origin)
- Budd–Chiari syndrome
  - caused by occlusion of the hepatic vein







DRUG-INDUCED LIVER DISEASE

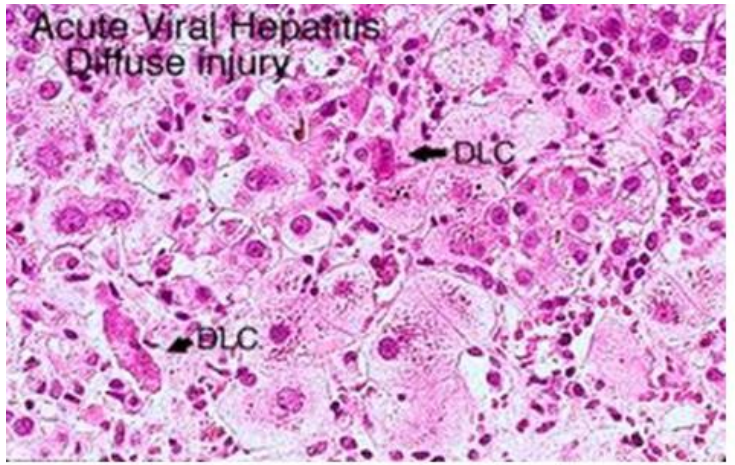
- Mild elevations in blood levels of liver enzymes without symptoms or signs of liver disease
- Hepatitis
- Necrosis
- Cholestasis (decreased secretion and/or flow of bile)
- Steatosis
- Cirrhosis
- Mixed disease
  - both hepatitis and necrosis of liver cells
  - hepatitis and fat accumulation
  - cholestasis and hepatitis
- Fulminant hepatitis with severe, life threatening liver failure
- Blood clots in the veins of the liver (Budd Chiari syndrome)

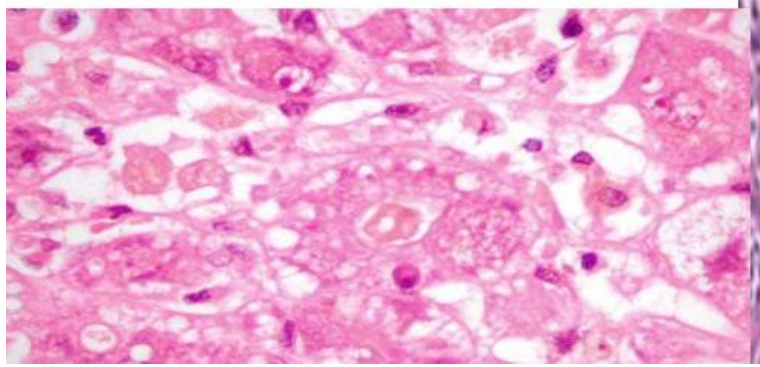
MILD ELEVATIONS IN BLOOD LEVELS OF LIVER ENZYMES

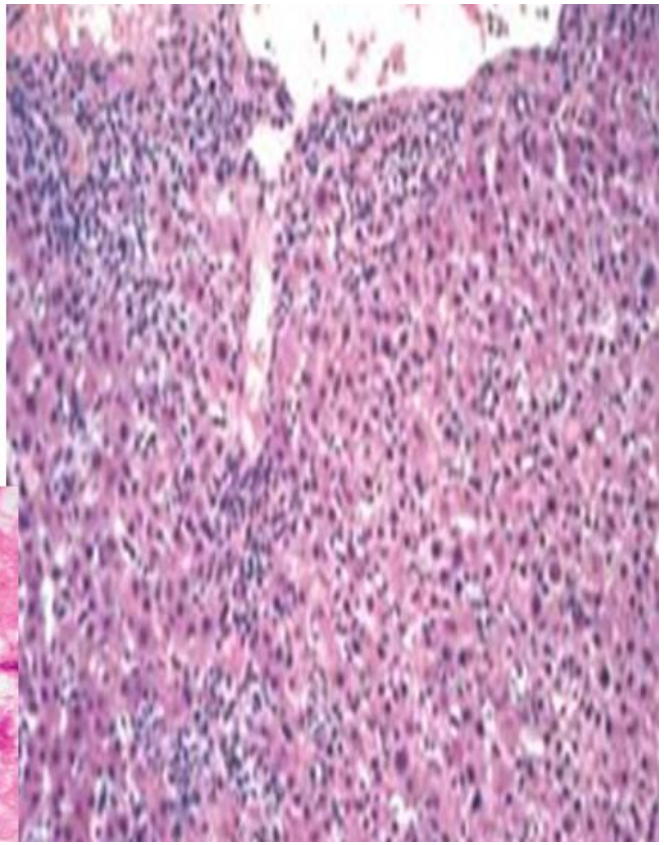
- statins
- some antibiotics
- some antidepressants
- some antidiabetics
- tacrine
- aspirin
- quinidine

DRUG-INDUCED ACUTE HEPATITIS

- acetaminophen (acute liver failure/fulminant hepatitis)
- phenytoin
- Aspirin
- isoniazid
- diclofenac
- amoxicillin/clavulanic acid
- tetracycline
- methotrexate
- azathioprine

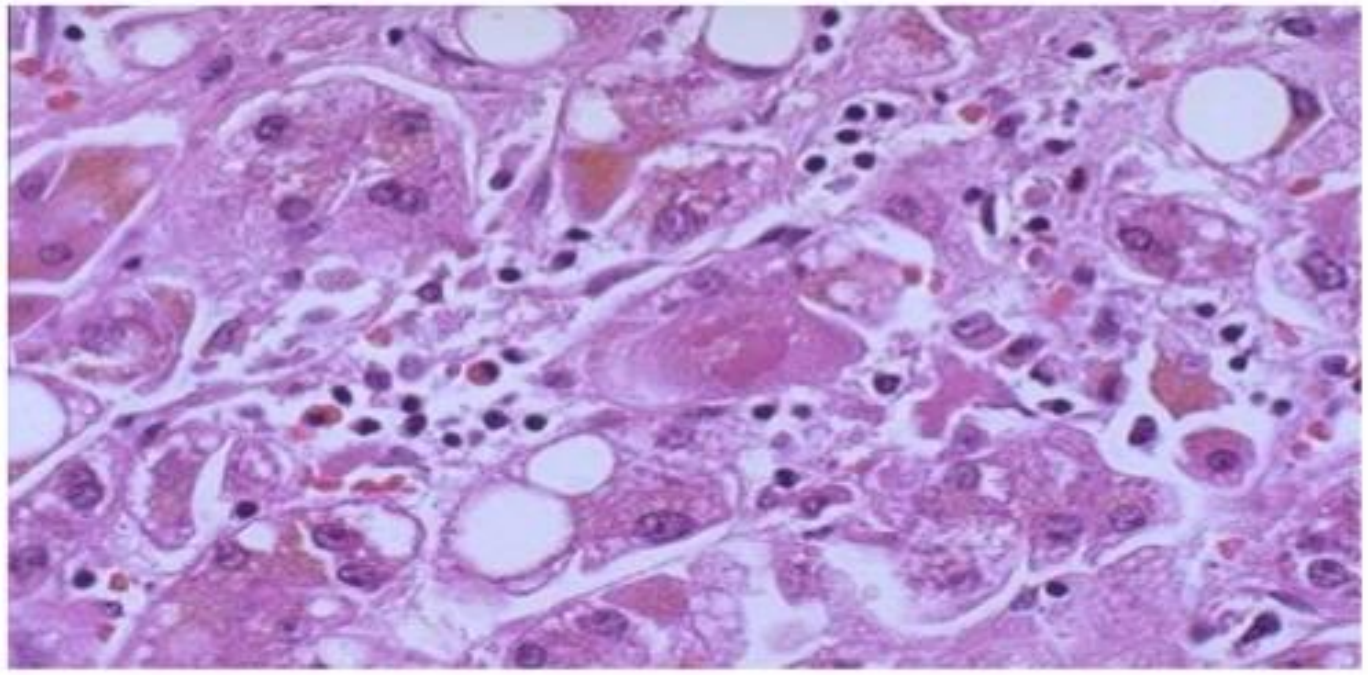






DRUG-INDUCED CHRONIC HEPATITIS

- minocycline
- nitrofurantoin
- phenytoin
- propylthiouracil
- fenofibrate
- methamphetamine ("ecstasy")
- methyl-dopa
- dantrolen

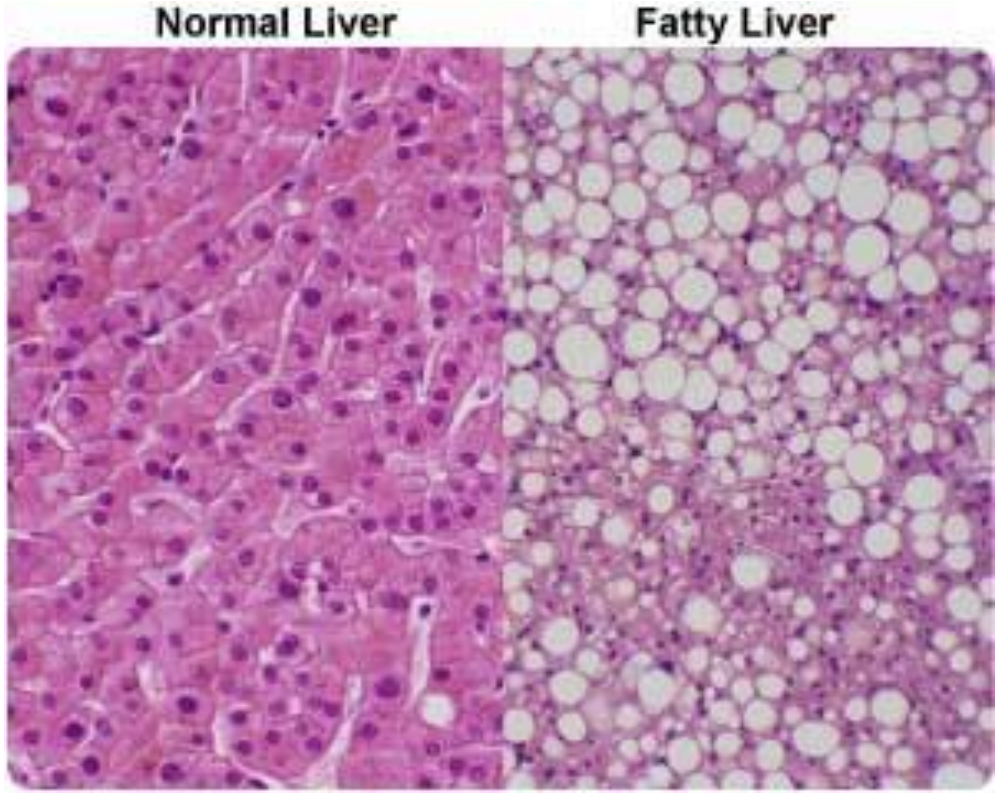


DRUG-INDUCED CHOLESTASIS

- erythromycin
- chlorpromazine
- sulfamethoxazole and trimethoprim
- amitriptyline
- carbamazepine
- ampicillin
- ampicillin/clavulanic acid
- rifampin
- captopril
- estradiol
- birth control pills (oral contraceptives)
- anabolic steroids
- naproxen
- amiodarone
- haloperidol
- imipramine
- tetracycline
- phenytoin

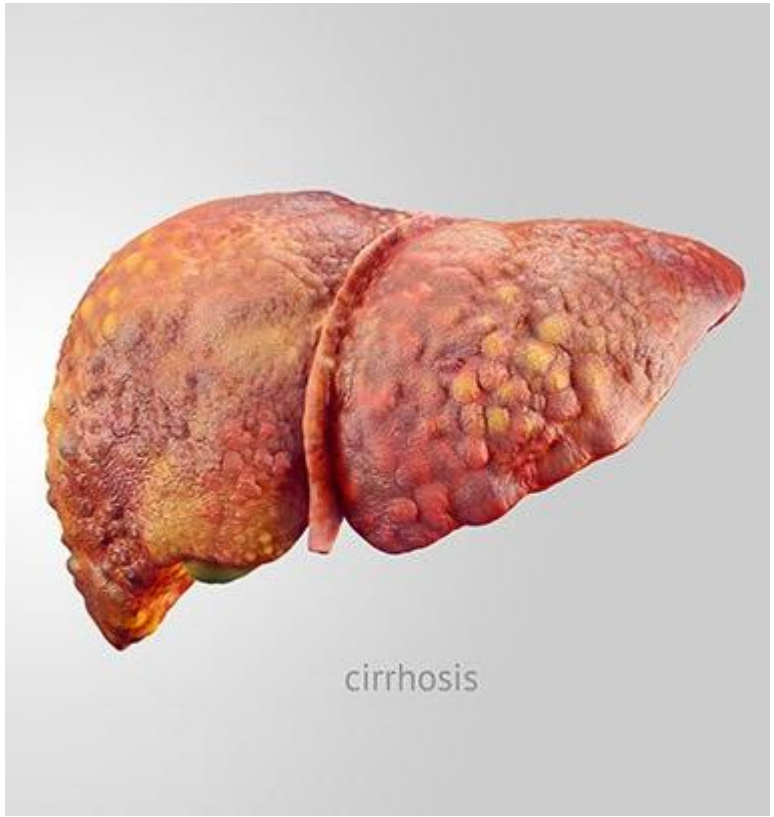
DRUG-INDUCED STEATOSIS

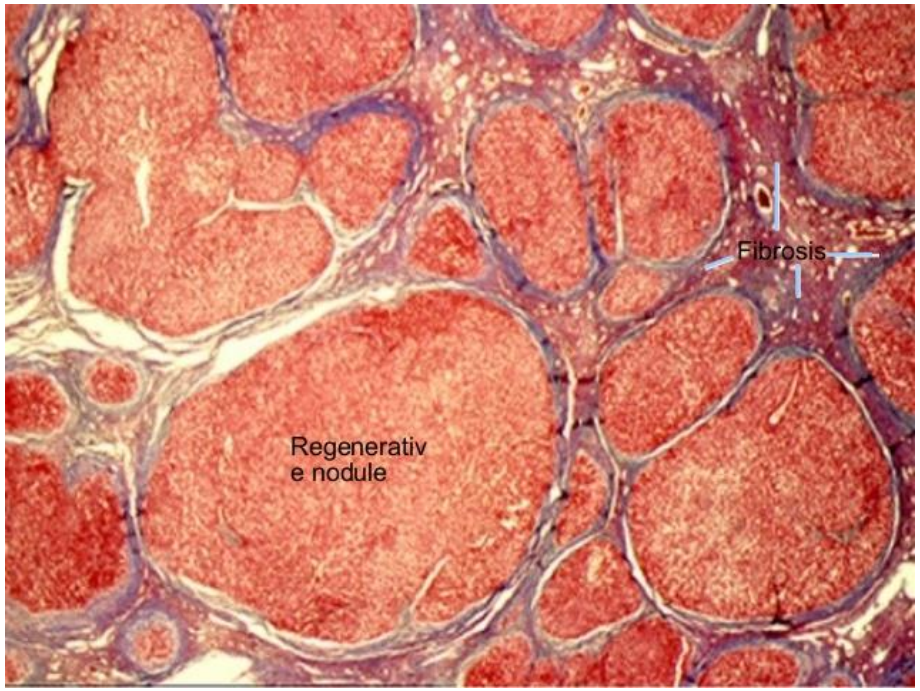
- total parenteral nutrition
- methotrexate
- griseofulvin
- tamoxifen
- steroids
- valproate
- amiodarone
- high doses of intravenous tetracycline or amiodarone



DRUG-INDUCED CIRRHOSIS

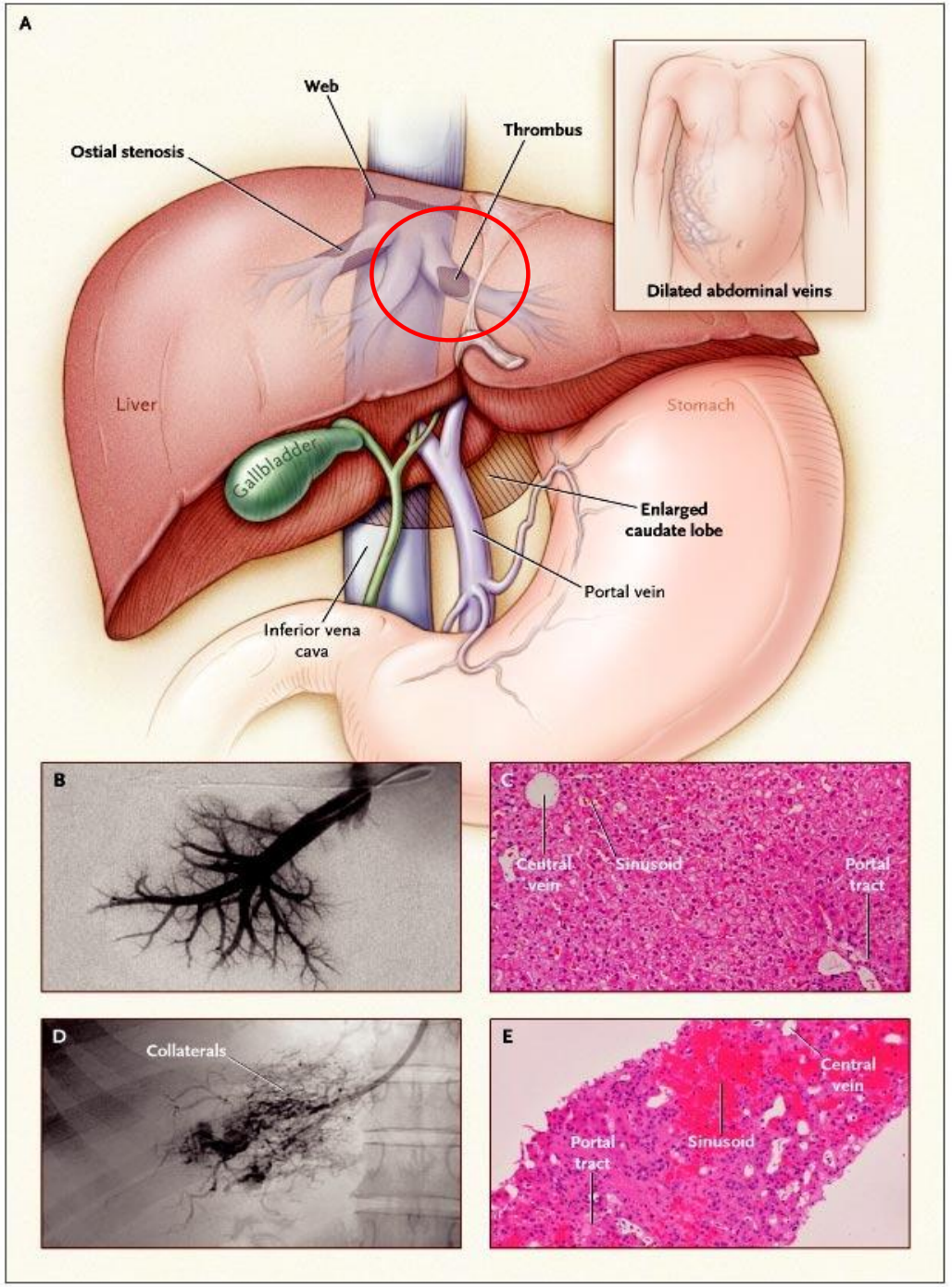
- alcohol
- methotrexate
- amiodarone
- methyldopa





DRUG-INDUCED BUDD CHIARI SYNDROME

- birth control pills (oral contraceptives)
- Pyrrolizidine alkaloids found in certain herbs
  - e.g., borage, comfrey



TREATMENT OF DRUG-INDUCED LIVER DISEASE

- withdrawal of the offending drug
- spontaneous recovery
- Specific therapies
- oral N-acetylcysteine
  - acetaminophen overdoses
- Cholestyramine
  - acute liver injury due to leflunomide
  - chronic cholestasis induced by terbinafine
- Carnitine administration
  - specific antidote for valproate hepatotoxicity (!!! iv.)
- Ursodeoxycholic acid
- reduce the severity of liver injury
- Charcoal depuration
  - for paracetamol toxicity
  - prevents further absorption of the drug if administered within 3–4 hours following an acute ingestion
- Corticosteroids
  - Liver injury associated with hypersensitivity features (eosinophilia, rash and fever)
  - antiepileptic drugs

DECISION TO STOP DRUG ADMINISTRATION

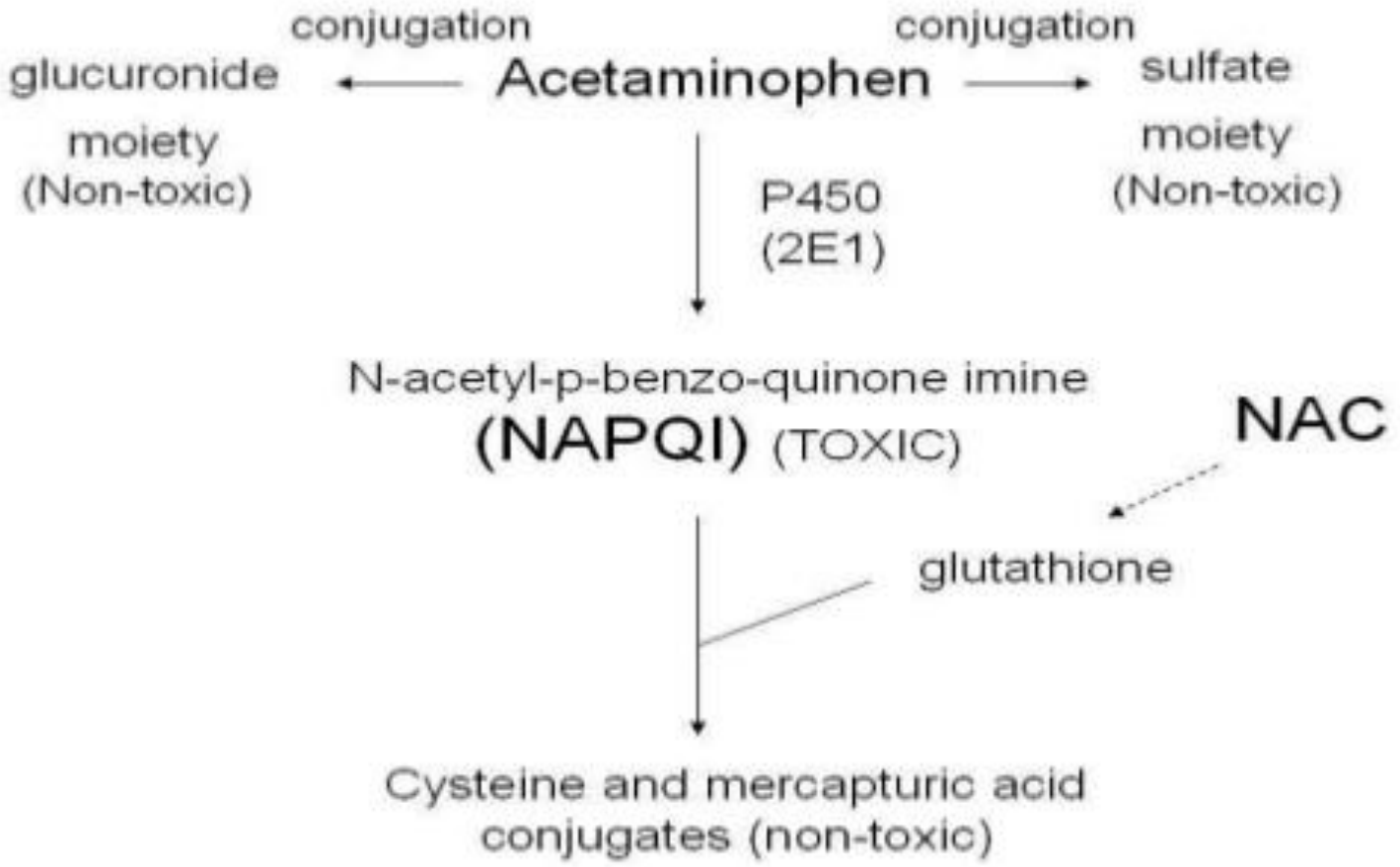
- **Suggested by the FDA guidance:**
- ALT or AST >8 ULN
- ALT or AST >5 ULN for more than 2 weeks
- ALT or AST >3 ULN and (TBL >2 ULN or INR >1.5)
- ALT or AST >3 ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

HEPATOPROTECTIVE AGENTS

- N-Acetylcysteine
- Penicillamine
- S adenosyl methionine (SAM)
- Herbal medications
- Cardiotropin 1
- Anti oxidants
  - Vitamins
  - Melatonin
  - Glutathione
  - Beta carotene

HEPATOPROTECTIVE AGENTS

N-Acetylcysteine (NAC)



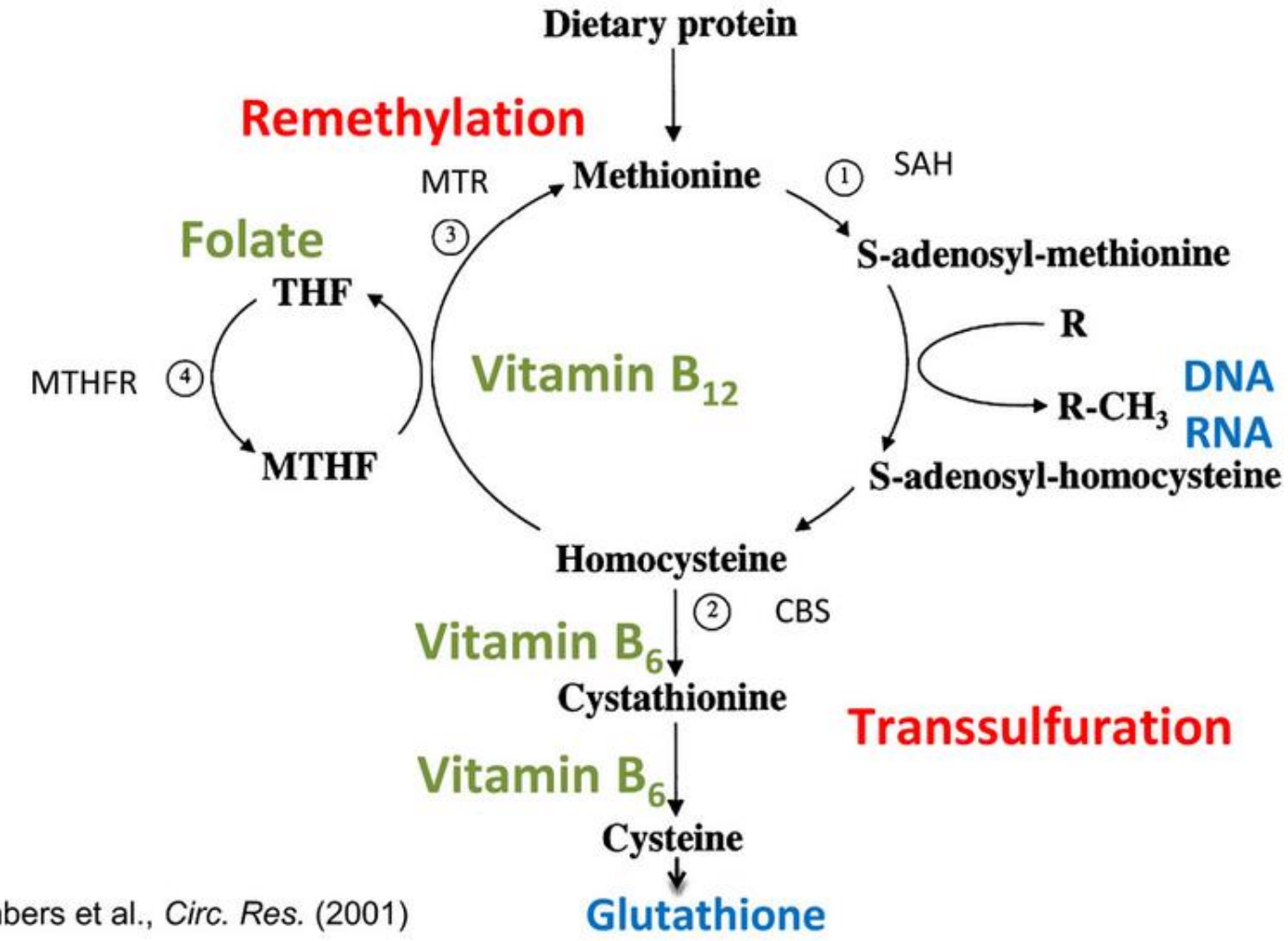
HEPATOPROTECTIVE AGENTS

Penicillamine

- degradation product of penicillin
- without antimicrobial activity
- chelates several metals: copper, lead, iron, mercury → stable water soluble complexes →excreted renally
- Penicillamine + cystine → a stable, soluble, complex
- Antifibrotic effects
  - inhibits lysyl oxidase (necessary for collagen production)
  - directly binds to collagen fibrils, preventing cross- linking into stable collagen fibers
- may have immunomodulatory effects
- reduce IgM rheumatoid factor in humans with rheumatoid arthritis

HEPATOPROTECTIVE AGENTS

- **Methionine and S adenosyl methionine (SAM)**



Chambers et al., *Circ. Res.* (2001)

HEPATOPROTECTIVE AGENTS

Methionine and S adenosyl methionine (SAM)

- in the liver, SAM is a precursor for glutathione, a major endogenous antioxidant that protects cells against injury by scavenging free radicals
- interact directly with reactive oxygen species
- reduces apoptosis and inflammatory cytokines
- Clinical trials:
  - 24-month randomized, placebo-controlled, double-blind, multicenter clinical trial in patients with alcoholic cirrhosis
    - SAM treatment improved survival/delayed the need for liver transplantation in alcoholic liver cirrhosis
  - oral 1.2 g SAM/d for 6 months
  - significantly increased hepatic glutathione concentrations in ALD patients
- Therapeutic indications:
  - acetaminophen and carbon tetrachloride induced liver damage

HEPATOPROTECTIVE AGENTS

Herbal medications

- Silybum marinum
- Eclipta alba
- Foeniculum vulgare
- Trigonella foenum graecum
- Jatropha curcas
- Garcinia mangostana Linn
- Chamomile capitula

HEPATOPROTECTIVE AGENTS

Silybum marinum

- 'milk thistle'
- Silymarin = a complex mixture of four flavonolignan isomers:
  - silybin (60-70%),
  - silychristin (20%),
  - silydianin (10%),
  - isosilybin (5%)

HEPATOPROTECTIVE AGENTS

- **Mechanism of action**
- Stimulation of protein synthesis:
  - accelerates protein and DNA synthesis → repair of damaged hepatocytes and restoration of normal functions of liver
- Anti-inflammatory actions:
  - inhibitory effect on 5-lipoxygenase pathway → inhibitory effect on LTB4 formation
  - parenteral exposure to silymarin → suppression of T- lymphocytes at low doses and stimulation of inflammatory process at higher doses (experimental data)
- Antifibrotic action:
  - inhibits hepatic stellate cells (HSC) conversion into myofibroblast
- Prevent the absorption of toxins into the hepatocytes by occupying the binding sites
- antioxidant activity and free radical scavenging properties
- Silymarin can also interact directly with cell membrane components to prevent any abnormalities in the content of lipid fraction responsible for maintaining normal fluidity.

HEPATOPROTECTIVE AGENTS

- Therapeutic indications:
  - Mushroom intoxication
  - Alcoholic liver disease
  - Hepatic cirrhosis
  - Chronic hepatitis

HEPATOPROTECTIVE AGENTS

Himalaya Liv.52

- protects the hepatic parenchyma and promotes hepatocellular regeneration
- antiperoxidative activity
  - prevents the loss of functional integrity of the cell membrane
  - maintains cytochrome P-450
  - hastens the recovery period and ensures early restoration of hepatic functions in infective hepatitis
- facilitates rapid elimination of acetaldehyde – toxic intermediate metabolite of alcohol metabolism
- prevents fatty infiltration of the liver
- In pre-cirrhotic conditions
  - arrests the progress of the disease and prevents further liver damage

HEPATOPROTECTIVE AGENTS

Cardiotrophin 1 (CT-1)

- a member of the IL-6 family of cytokines
- antiapoptotic effects on hepatocytes
- Reduce the cellular damage cause by ischemia/reperfusion
- Decrease oxidative damage
- Potent anti-inflammatory agent
- has FDA and EMA orphan drug designation for transplantation and acute liver failure
- Therapeutic indications:
  - treatment of acute, subacute, fulminant and chronic hepatitis
  - treatment of hepatic cirrhosis
  - for promoting hepatic regeneration after hepatectomies, after liver transplantation

HEPATOPROTECTIVE AGENTS

Thioctic Acid

- Lipoic acid (LA) = α-lipoic acid = alpha lipoic acid (ALA)
- Marketed as an antioxidant (pharmaceutical drug or dietary supplement)
- scavenge reactive oxygen and reactive nitrogen species
- induces synthesis of endogenous antioxidants like glutathione
- protects against the hepatic effects of carbon tetrachloride
- prevents abnormal fat deposition
- promotes glycogen deposition
- used in:
  - acute and chronic hepatitis
  - alcoholic liver damage
  - Amanita phalloides poisoning

HEPATOPROTECTIVE AGENTS

Insulin – glucagon combination

- In animal studies
  - has been shown to be effective against viral hepatitis
- Human studies
  - have shown that it is also beneficial in alcoholic hepatitis

BILE ACID AGENTS

Ursodiol (ursodeoxycholic acid)

- is a naturally occurring bile acid
- decreases the cholesterol content of bile by reducing hepatic cholesterol secretion.
- stabilize hepatocyte canalicular membranes
- Clinical Use
- for dissolution of small cholesterol gallstones
  - at a dosage of 10 mg/kg/day orally for 12–24 months, dissolution occurs in up to 50% of patients with small (<5–10 mm) noncalcified gallstones
- effective for the prevention of gallstones in obese patients
  - 300 mg twice daily
- the first-line agent used for the treatment of early primary biliary cirrhosis (PBC)
  - 13–15 mg/kg/d in two to four divided doses with food

BILE ACID AGENTS

Obeticholic acid

- is a synthetic derivative of the naturally occurring bile acid chenodeoxycholate
- reduce liver injury by decreasing hepatic concentrations of more toxic endogenous bile acids
- is a ligand for the nuclear farnesoid X receptor, which modulates hepatic inflammation, fibrosis, gluconeogenesis, lipid synthesis, and insulin sensitivity.
- was recently approved for the treatment of PBC at a dose of 5–10 mg/day orally in combination with ursodiol in patients who have had an inadequate response to ursodiol monotherapy
- Adverse effects:
- severe pruritus in up to 25% of patients (! at the10 mg dose)

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PANCREATIC ENZYME REPLACEMENT THERAPY

DRUGS PROMOTING GASTROINTESTINAL

PANCREATIC ENZYME SUPPLEMENTS

- Exocrine pancreatic insufficiency
  - cystic fibrosis, chronic pancreatitis, or pancreatic resection
- steatorrhea
- azotorrhea
- vitamin malabsorption
- weight loss
- **Treatment of pancreatic enzyme insufficiency**
- Pancreatic enzyme supplements (a mixture of amylase, lipase,and proteases)
- Pancreatin
- Pancrelipase

PANCREATIC ENZYME SUPPLEMENTS

- Pancreatin
  - an alcohol-derived extract of hog pancreas
  - relatively low concentrations of lipase and proteolytic enzymes
- Pancrelipase
  - has approximately 12 times the lipolytic activity and more than 4 times the proteolytic activity of pancreatin
  - non-enteric-coated – Pancrelipase enzymes are rapidly and permanently inactivated by gastric acids (+PPI/H_2 antagonists)
  - enteric-coated preparations
  - the preparations differ in their content of lipase, protease, and amylase (may not be interchangeable)
  - administered with each meal and snack
- Adverse effects:
  - high doses
  - diarrhea and abdominal pain
  - hyperuricosuria and renal stones (high purine content of pancreas extracts)

PHARMACOLOGY OF THE LIVER AND THE BILIARY TRACT

PANCREATIC ENZYME REPLACEMENT THERAPY

DRUGS PROMOTING GASTROINTESTINAL

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

- **= prokinetic agents**
- medications that enhance coordinated GI motility and transit of material in the GI tract
- Agents that increase lower esophageal sphincter pressures – for GERD
- Drugs that improve gastric emptying – for gastroparesis and postsurgical gastric emptying delay
- Agents that stimulate the small intestine – for postoperative ileus or chronic intestinal pseudoobstruction
- Agents that enhance colonic transit – treatment of constipation

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

CHOLINOMIMETIC AGENTS

- Bethanechol
  - stimulate muscarinic M3 receptors on muscle cells and at myenteric plexus synapses
  - treatment of GERD and gastroparesis (in the past)
- Neostigmine
  - acetylcholinesterase inhibitor
  - enhance gastric, small intestine, and colonic emptying
  - Intravenous neostigmine is used for the treatment of hospitalized patients with acute large bowel distention (known as acute colonic pseudo-obstruction or Ogilvie's syndrome)
- Adverse effects:
  - excessive salivation, nausea, vomiting, diarrhea, bradycardia

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Dopamine Receptor Antagonists

- Metoclopramide and domperidone
- dopamine D2-receptor antagonists
- increase esophageal peristaltic amplitude
- increase lower esophageal sphincter pressure
- enhance gastric emptying
- have no effect on small intestine or colonic motility
- antinausea and antiemetic effect (dopamine receptors in the CTZ of the brainstem)

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Dopamine Receptor Antagonists

- Mechanisms of action of metoclopramide
  - dopamine receptor antagonism
  - 5HT4 receptor agonism
  - vagal and central 5HT3 antagonism
  - possible sensitization of muscarinic receptors on smooth muscle
- Mechanisms of action of domperidone
  - dopamine D_2 receptor antagonism

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Dopamine Receptor Antagonists

- Therapeutic Uses
- Gastroesophageal reflux disease
  - are not effective in patients with erosive esophagitis
- Impaired gastric emptying
  - due to postsurgical disorders (vagotomy, antrectomy)
  - diabetic gastroparesis
- Nonulcer dyspepsia
- Prevention and treatment of vomiting
  - Prevention of chemotherapy-induced emesis
- Postpartum lactation stimulation – Domperidone
- Metoclopramide injection
  - adjunctive measure in medical or diagnostic procedures: upper endoscopy or contrast radiography of the GI tract

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Dopamine Receptor Antagonists

- Adverse Effects
- Restlessness, drowsiness, insomnia, anxiety, agitation
- Extrapyramidal effects
  - dystonias, akathisia, parkinsonian features
  - Tardive dyskinesia, sometimes irreversible – in patients treated for a prolonged period with metoclopramide
- Elevated prolactin levels
  - galactorrhea, gynecomastia, impotence, and menstrual disorders

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Serotonin Receptor Agonists

- restricted because of serious adverse cardiac events
- tegaserod
  - is only available as an emergency investigational new drug
- cisapride
  - available only via a limited-access protocol for patients with GERD, gastroparesis, intestinal pseudoobstruction, refractory severe chronic constipation, and neonatal enteral feeding intolerance
  - **serious and occasionally fatal cardiac arrhythmias: ventricular tachycardia, ventricular fibrillation, and torsades de pointes**
  - 5HT4 agonist
  - Weak 5HT3 antagonistic properties
  - may directly stimulate smooth muscle
- prucalopride
  - approved in Europe and Canada for symptomatic treatment of chronic constipation in women
  - 5HT4 receptor agonist
  - facilitates cholinergic neurotransmission
  - acts throughout the length of the intestine, increasing oral-cecal transit and colonic transit without affecting gastric emptying

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Motilin and Macrolide Antibiotics

- **Motilin**
- a 22–amino acid peptide hormone secreted by enteroendocrine M cells and by some enterochromaffin cells of the upper small bowel
- a potent contractile agent of the upper GI tract
- **Erythromycin**
  - can mimic effects of motilin
  - directly stimulate motilin receptors on gastrointestinal smooth muscle
  - increases lower esophageal pressure
  - stimulates gastric and small-bowel contractility
  - has little or no effect on colonic motility
- Therapeutic Uses
  - diabetic gastroparesis
- Adverse Effects
- "dumping" of relatively undigested food into the small bowel
- Rapid development of tolerance (~28 days)
- GI toxicity, ototoxicity, pseudomembranous colitis,
- induction of resistant strains of bacteria,
- QT prolongation, and sudden death

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Miscellaneous Agents for Stimulating Motility

- Sincalide
- C-terminal octapeptide of CCK
- for stimulating the gallbladder or pancreas
- for accelerating barium transit through the small bowel for diagnostic testing of these organs
- Agents under evaluation
  - Camicinal
    - Novel motilin receptor agonist
  - Relamorelin
    - a ghrelin receptor agonist
  - velusetrag and naronapride
    - novel 5HT4 agonists

THAK YOU FOR YOUR ATTENTION!