Alcohol and the brain

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Ethyl alcohol (ethanol)

Ethyl alcohol (ethanol) is the most commonly abused drug in the world.

Pharmacokinetics

- is a small lipophilic molecule
- readily crosses all biological membranes
- Rapidly & completely absorbed from GIT
- Has large Vd (distributed to all body tissues)
- Volume of distribution = Total body water (0.5-0.7 L/kg).
- Crosses placenta and excreted in milk

Metabolism of ethanol

Metabolism in gastric mucosa & liver.

- Oxidation of ethanol to acetaldehyde via alcohol dehydrogenase or cyt-p450 (CYP2E1).
- Oxidation of acetaldehyde to acetate via aldehyde dehydrogenase which also reduces NAD+ to NADH.
- Acetate ultimately is converted to CO_2 + water.

Metabolism of ethanol

- **At low ethanol conc.** minor metabolism by microsomal ethanol-oxidizing system **(MEOS) mainly CYP-450 (CYP2E1).**

- Upon continuous alcohol use, this enzyme is stimulated and contribute significantly to **alcohol metabolism & tolerance.**

Alcohol Metabolism (the major pathway)
90-98% in the liver

CH_3CH_2OH (Ethanol)

NAD+

Alcohol dehydrogenase , cytosolic enzyme

NADH

CH_3CHO (Acetaldehyde) more toxic than alcohol

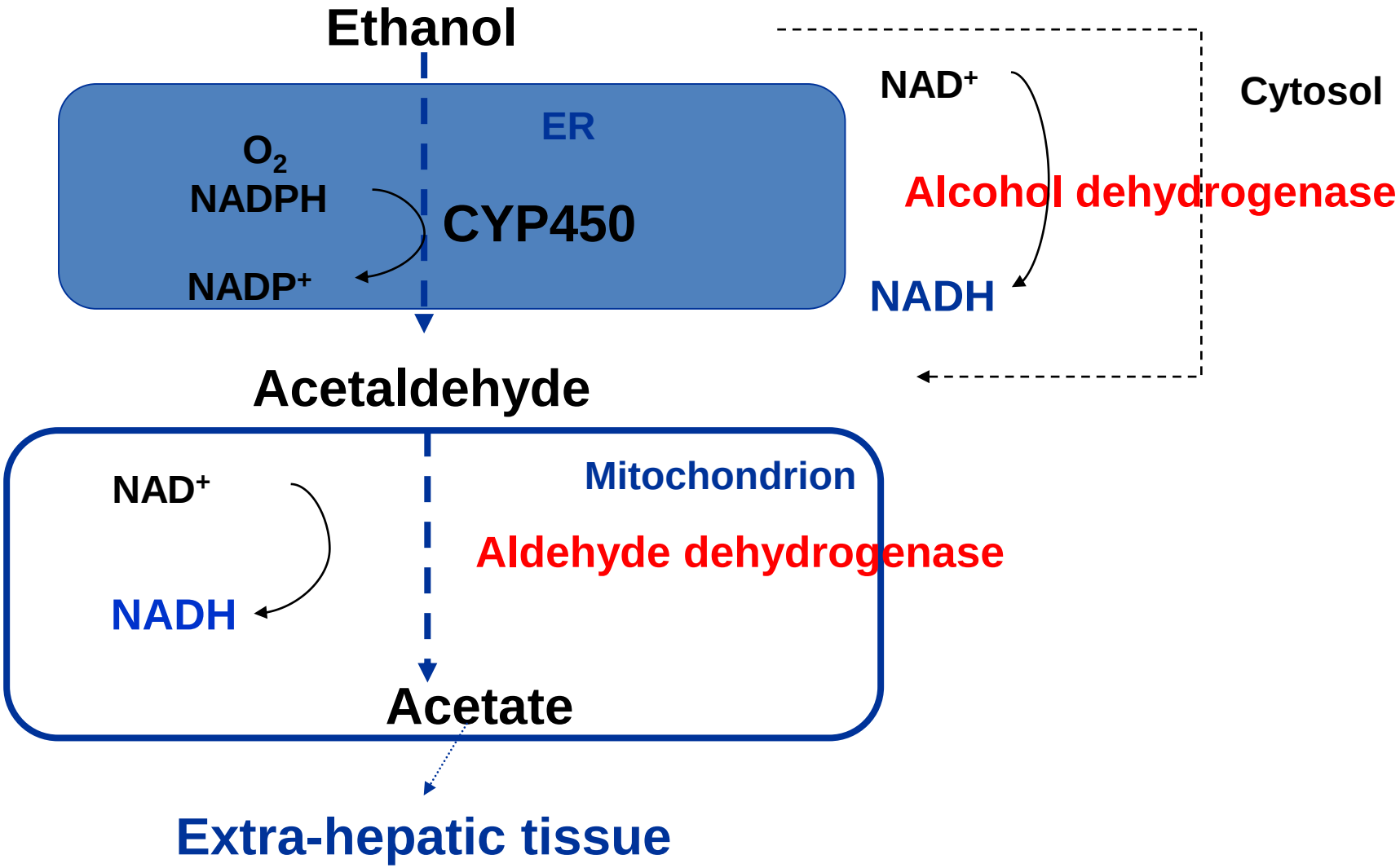
NAD+

aldehyde dehydrogenase , mitochondrial enzyme

NADH

CH3COOH (Acetic acid)  CO2 +water

Hepatic Cellular Processing of alcohol



NAD^+/NADH: nicotinamide adenine dinucleotide

Metabolism of ethanol

- **Acute alcohol** consumption inhibits CYP450 2E1 so decrease metabolism of other drugs taken concurrently as (warfarin, phenytoin).

- **Chronic alcohol** consumption induces CYP450 2E1, which leads to significant increases in ethanol metabolism **(Tolerance)** & metabolism of other drugs as warfarin taken with it **(Drug interactions).**

Genetic variation of alcohol metabolism

Aldehyde Dehydrogenase Polymorphism

- Asian populations (including Chinese, Japanese, Taiwanese, Korean) have genetic variation in aldehyde dehydrogenase resulting in a variant allele ALDH2*2
- The rate of metabolism of alcohol is slower than other populations.
- Can develop **“Acute acetaldehyde toxicity”** after alcohol intake characterized by nausea, vomiting, dizziness, headache, vasodilatation, and facial flushing and prevent them from becoming alcoholic.

Alcohol excretion

- Excreted unchanged in urine (2-8%).
- Excretion unchanged via lung **(basis for breath alcohol test).**
- Rate of elimination is zero-order kinetic (not concentration-dependent) i.e. rate of elimination is the same at low and high concentration.

Mechanism of action of alcohol

- It is a CNS depressants
- **Acute alcohol** causes:
  - **Enhancement the effect of GABA** (inhibitory neurotransmitter) **on its GABA receptors** in brain leading to CNS depression
  - **Inhibition of glutamate action** (excitatory neurotransmitter) **on NMDA receptors** leading to disruption in memory, consciousness, alertness.

Chronic alcohol leads to

up-regulation of NMDA receptors & voltage sensitive Ca channels (Ca influx to nerve cells) leading to alcohol tolerance & withdrawal symptoms (tremors, exaggerated response & seizures).

Acute actions of alcohol

In mild-moderate amounts

CNS depression

- relieves anxiety, euphoria (feeling of well-being).
- Nystagmus, slurred speech, impaired judgment, ataxia
- Sedation, hypnosis, loss of consciousness

CVS depression

- Myocardial contractility depression
- **Vasodilatation** due to:
  - ✓ Vasomotor center depression
  - ✓ Direct smooth muscle relaxation caused by acetaldehyde

Acute actions of ethanol :

In severe amounts

- Severe CNS depression
- Respiratory depression.
- Respiratory acidosis
- Nausea, vomiting, aspiration of vomitus.
- CVS depression
- Volume depletion
- Hypotension
- Hypothermia
- Coma, death.

Chronic ethanol abuse (alcoholism) is associated with many complications

- **Tolerance, dependence, addiction, behavioral changes**
- **Liver**: hepatic cirrhosis & liver failure.
- **CVS:** hypertension, myocardial infarction
- **CNS:** cerebral atrophy, cerebellar degeneration, and peripheral neuropathy. Wernicke encephalopathy or Korsakoff psychosis may occur.
- **GIT system:** irritation, inflammation, bleeding, nutritional deficiencies
- **Endocrine system:** gynecomastia & testicular atrophy
- Hematological disorders, neoplasia.

Chronic alcohol use (Alcoholism)

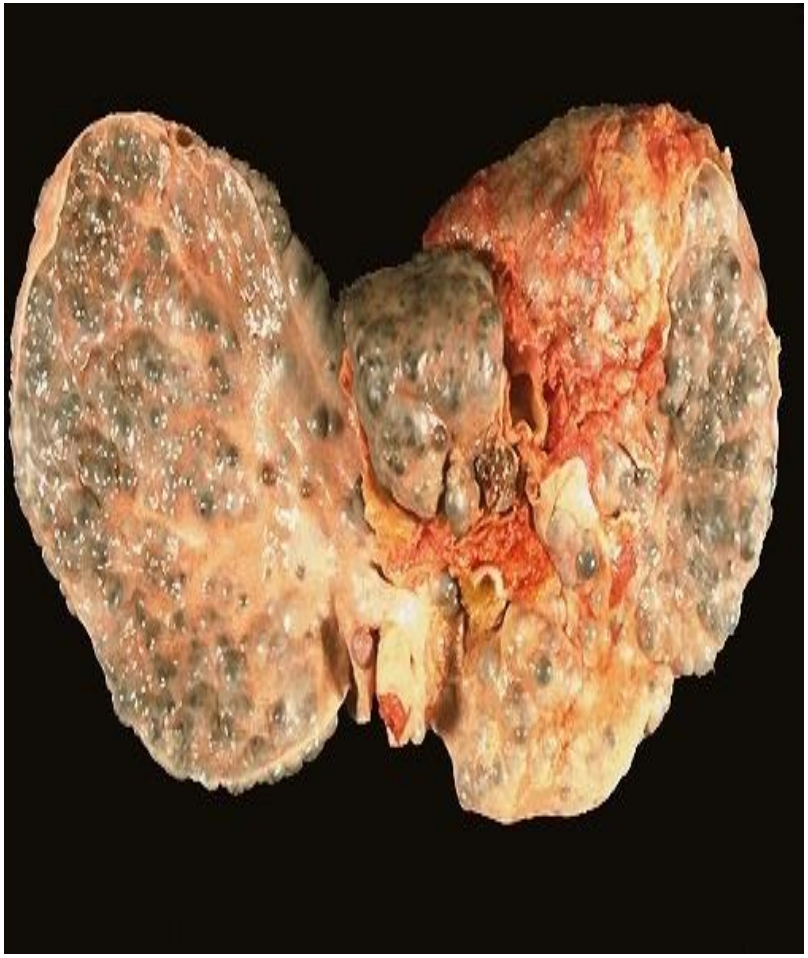
Liver

The most common medical complication of alcoholism occurs with liver

- Reduction of gluconeogenesis
- Fatty liver/ alcoholic steatosis
- Hepatitis
- **Hepatic cirrhosis**: jaundice, ascites, bleeding, encephalopathy.
- Irreversible liver failure.

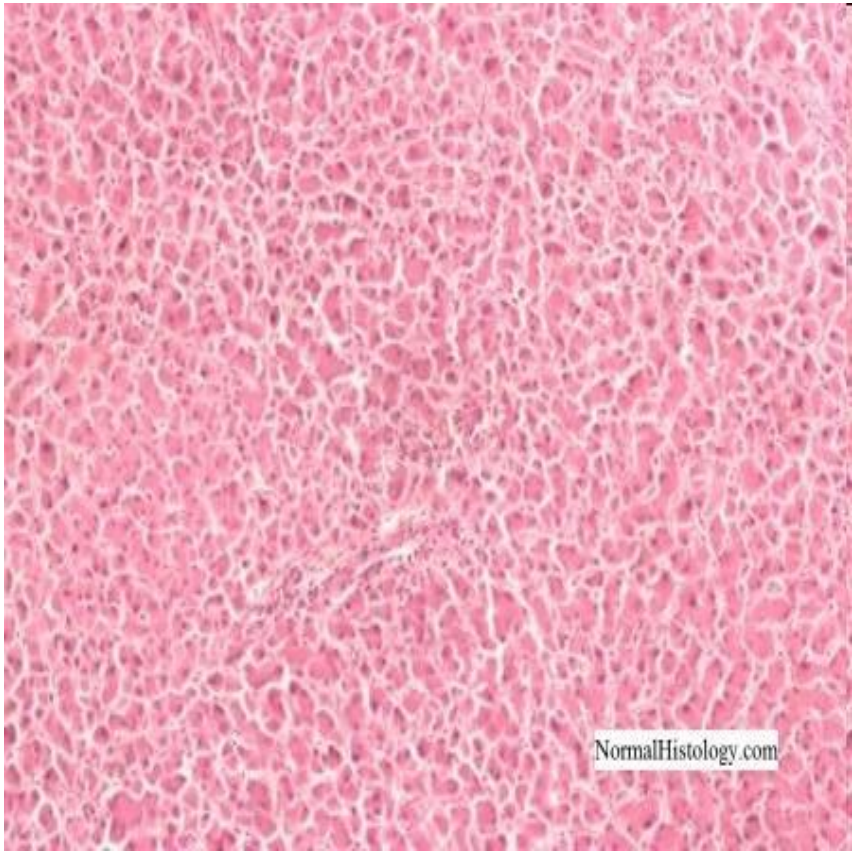
Healthy Liver

Liver in chronic alcoholics

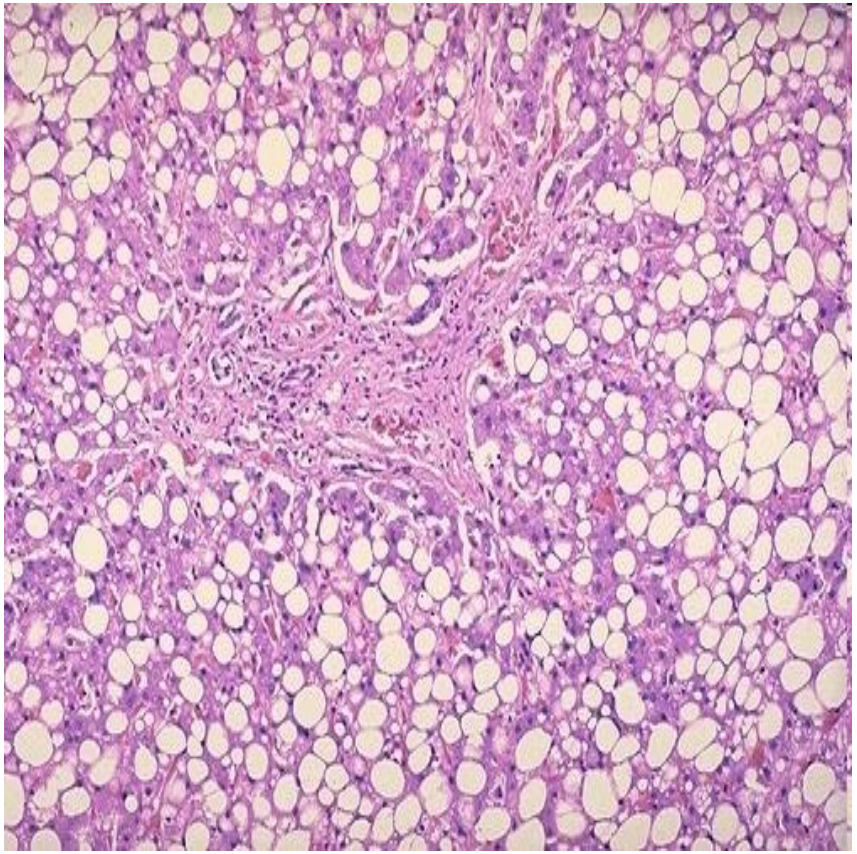


Healthy Liver *vs* Fatty Liver

Normal liver

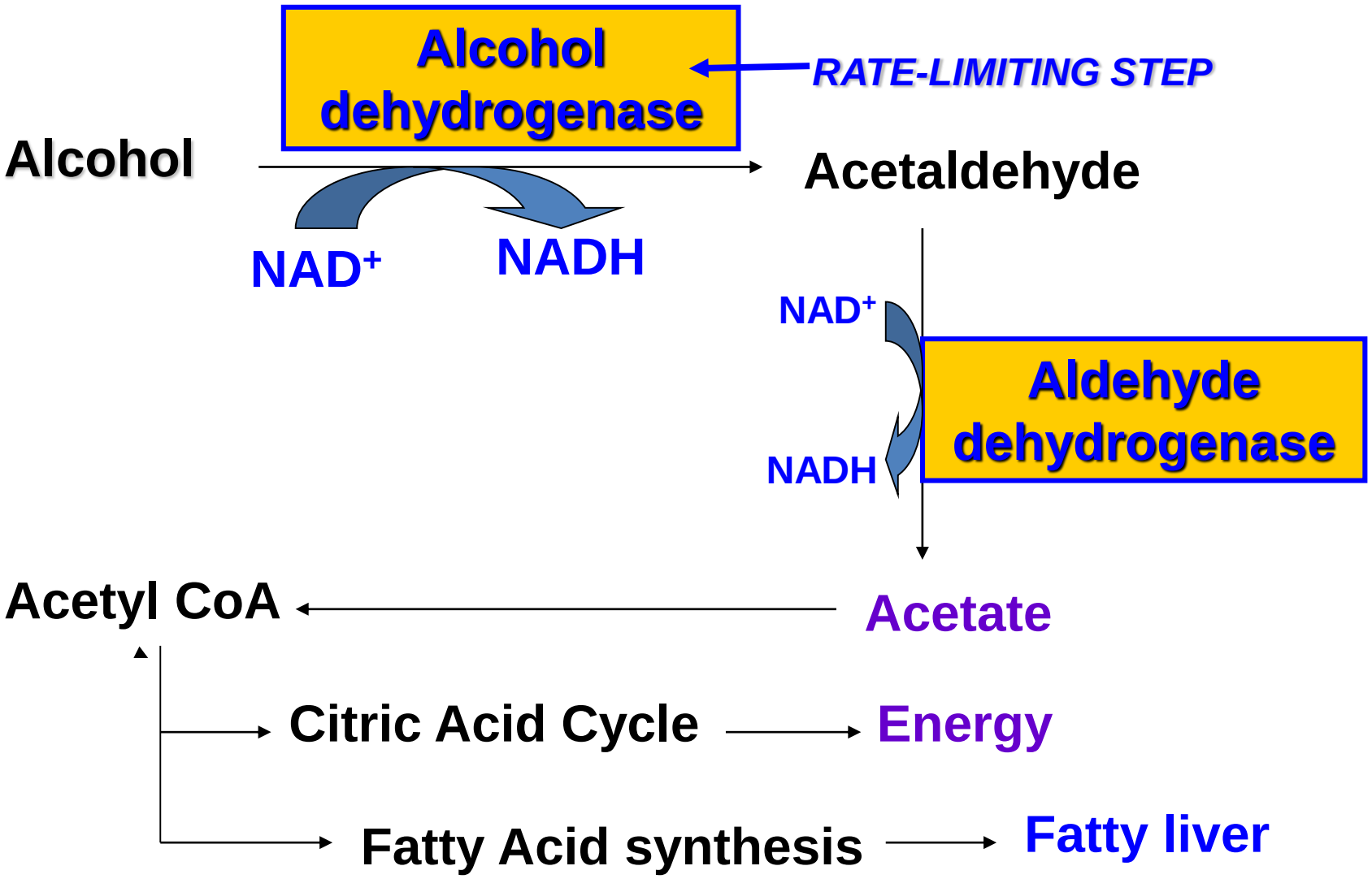


Fatty liver



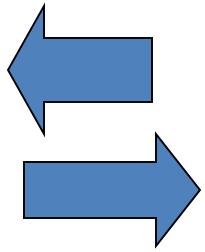
Acetaldehyde is more toxic than alcohol →causing inflammation and fat cell proliferation

Hepatic Ethanol Metabolism

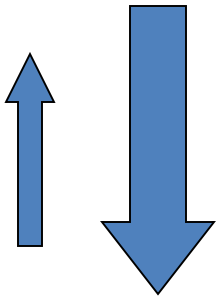


Alcoholic Liver Disease

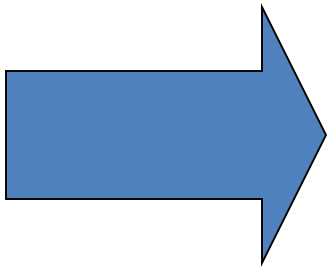
Steatosis



Normal



Steatohepatitis



Cirrhosis

Gastrointestinal system

- Gastritis, hemorrhagic esopahgitis, ulcer diseases, pancreatitis (due to direct toxic action on epithelium).
- Diarrhea
- Deficiency of vitamins.
- Exacerbates nutritional deficiencies
- weight loss, and malnutrition
- **In heavy drinkers**: increased risk of oral and esophageal cancer.

Cardiovascular System

Chronic alcohol abuse can lead to **cardiomyopathy**

- Cardiac hypertrophy
- Congestive heart failure.
- **Arrhythmia** (due to potassium and magnesium depletion)
- **Hypertension**: due to increased calcium & sympathetic activity.

Hematological complications:

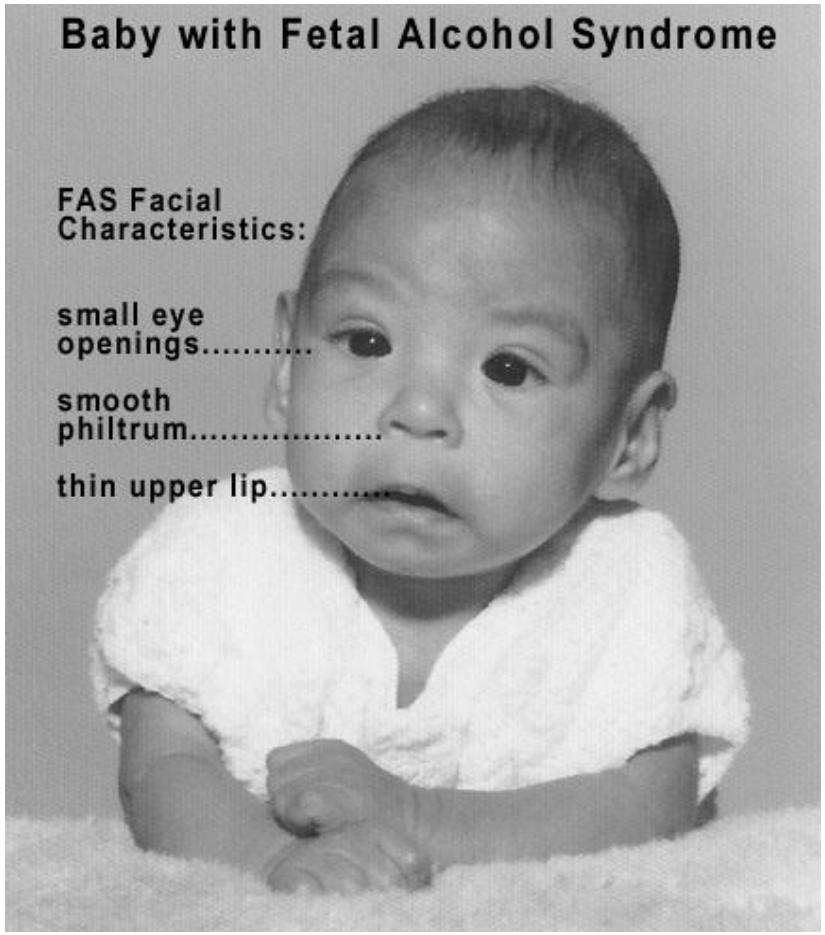
- **Iron deficiency anemia** (due to inadequate dietary intake & GIT blood loss).
- **Megaloblastic anemia**: (due to folate deficiency, malnutrition, impaired folate absorption).
- **Hemolytic anemia**.
- **Bone marrow suppression**
- **Thrombocytopenia** (suppressing platelet formation, prolong bleeding times).
- Impaired production of **vitamin-K dependent clotting factors** leading to prolonged prothrombin time.

Fetal Alcohol Syndrome: Irreversible

- Ethanol rapidly crosses placenta
- Pre-natal exposure to alcohol causes:

- Intrauterine **growth retardation** (due to hypoxia)
- **Congenital malformation (teratogenesis):**
  - Microcephaly
  - Impaired facial development
  - Congenital heart defects
  - Physical and mental retardation.

Fetal Alcohol Syndrome (FAS)



The right brain is an infant's brain that had pre-natal exposure to alcohol.

Endocrine system:

- **Hypogonadism:**

  In women: ovarian dysfunction, amenorrhea, anovulation, hyperprolactinemia, infertility.

  In men: gynecomastia, decreased muscle & bone mass, testicular atrophy, sexual impotence due to inhibition of luteinizing hormone (LH) , decrease in testosterone, estradiol, progesterone.

- **Hypoglycemia & ketoacidosis** due to impaired hepatic gluconeogenesis & excessive lipolytic factors, especially increased cortisol and growth hormone.

Central Nervous System

- Tolerance
- Physiological and psychological dependence
- Addiction: **dopamine, serotonin and opioids** are involved.
- Neurologic disturbances
- **Wernicke-Korsakoff syndrome**

Wernicke-Korsakoff syndrome

It is a combined manifestation of 2 disorders:

Wernicke's encephalopathy: characterized by

- ocular disturbances - unsteady gait
- changes in mental state as confusion, delirium, ataxia

Korsakoff's psychosis: impaired memory & cognitive and behavioral dysfunction.

Cause: thiamine (vitamin B1) deficiency due to:

- inadequate nutritional intake
- decreased uptake of thiamine from GIT
- decreased liver thiamine stores

Treated by: thiamine + dextrose-containing IV fluids.

Alcoholism Tolerance

Chronic consumption of alcohol leads to tolerance That develops due to:

Metabolic tolerance (pharmacokinetic): due to induction of liver microsomal enzymes.

Functional tolerance (Pharmacodynamic): due to change in CNS sensitivity.

Alcoholism withdrawal symptoms

- Autonomic hyperactivity & craving for alcohol
- Vomiting, thirst
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Delirium, tremors, anxiety, agitation, insomnia
- transient visual/ auditory illusions, violent behavior, hallucinations.
- Grand mal **seizures** (after 7-48 hr alcohol cessation)
- Due to super-sensitivity of glutamate receptors & hypoactivity of GABA receptors are possibly involved.

Management of alcoholism withdrawal

- Substituting alcohol with a long-acting sedative hypnotic drug then tapering the dose.
- **Benzodiazepines** as (chlordiazepoxide, diazepam) or lorazepam that is preferable (shorter duration of action).
- **Efficacy:** IV/ po
- Manage withdrawal symptoms & prevent irritability, insomnia, agitation & seizures.
- Dose of BDZs should be carefully adjusted to provide efficacy & avoid excessive dose that causes respiratory depression & hypotension.

Management of alcoholism withdrawal

- **Fluoxetine**

- **Clonidine & Propranolol**: inhibits the action of exaggerated sympathetic activity.

- **Acamprosate:** a weak NMDA receptor antagonist & GABA activator, reduce psychic craving.

To prevent alcohol relapse:

Disulfiram therapy: 250 mg daily

- Inhibits hepatic **aldehyde dehydrogenase**, this will increase blood level of **acetaldehyde.**
- Acetaldehyde produces extreme discomfort, vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache.
- Disulfiram-induced symptoms that render alcoholics afraid from alcohol drinking.

Alcohol and drug interactions

- **Acute alcohol use** causes inhibition of liver microsomal enzymes thus decreases metabolism of some drugs and increases their toxicities e.g. bleeding with **warfarin**
- **Chronic alcohol use** induces liver microsomal enzymes and increases metabolism of drugs such as **warfarin, propranolol** and etc.

- **Acetaminophen + alcohol** (chronic use)**:** risk of hepatotoxicity due to increased production of free radical metabolite of acetaminophen.

- **NSAIDs + alcohol:** Increase in the risk of developing a major GIT bleeding or ulcers.
- **Narcotic drugs (codeine and methadone) + alcohol**: risk of respiratory and CNS depression.
- Alcohol suppresses gluconeogenesis, which may increase risk for hypoglycemia in diabetic patients.