Alcohol Metabolism

Alcohol

- Chemically known as ETHANOL
- Considered a food, because it contributes energy to the diet (7 kcals/gram)
- Not considered a nutrient, because is not needed
- In west used as social stimulant: removes inhibitions
- Has been used as an analgesic to treat aches and pains

Alcohol (Ethanol) Metabolism

- Person with 70kg wt with normal liver function metabolizes about 5-7 grams of alcohol per hr
- When intake of alcohol exceeds liver's ability to metabolize it, builds up in the bloodstream
- Major fraction of the alcohol is oxidized in liver.
- Small fraction excreted in urine, sweat, expired air (levels in expired air correspond with blood alcohol content → Breathalyzer test)

Absorption & Transport of Alcohol (Ethanol)

- Absorbed directly through the stomach mucosa and intestinal lining
- Once alcohol is in the bloodstream, it is carried to all organs of the body.
- In the majority of healthy people, blood circulates through the body in 90 seconds, - allowing alcohol to affect the brain and all other organs in a short amount of time.

Metabolim of Alcohol (Ethanol)

The effects of alcohol on the body will vary according to the individual:

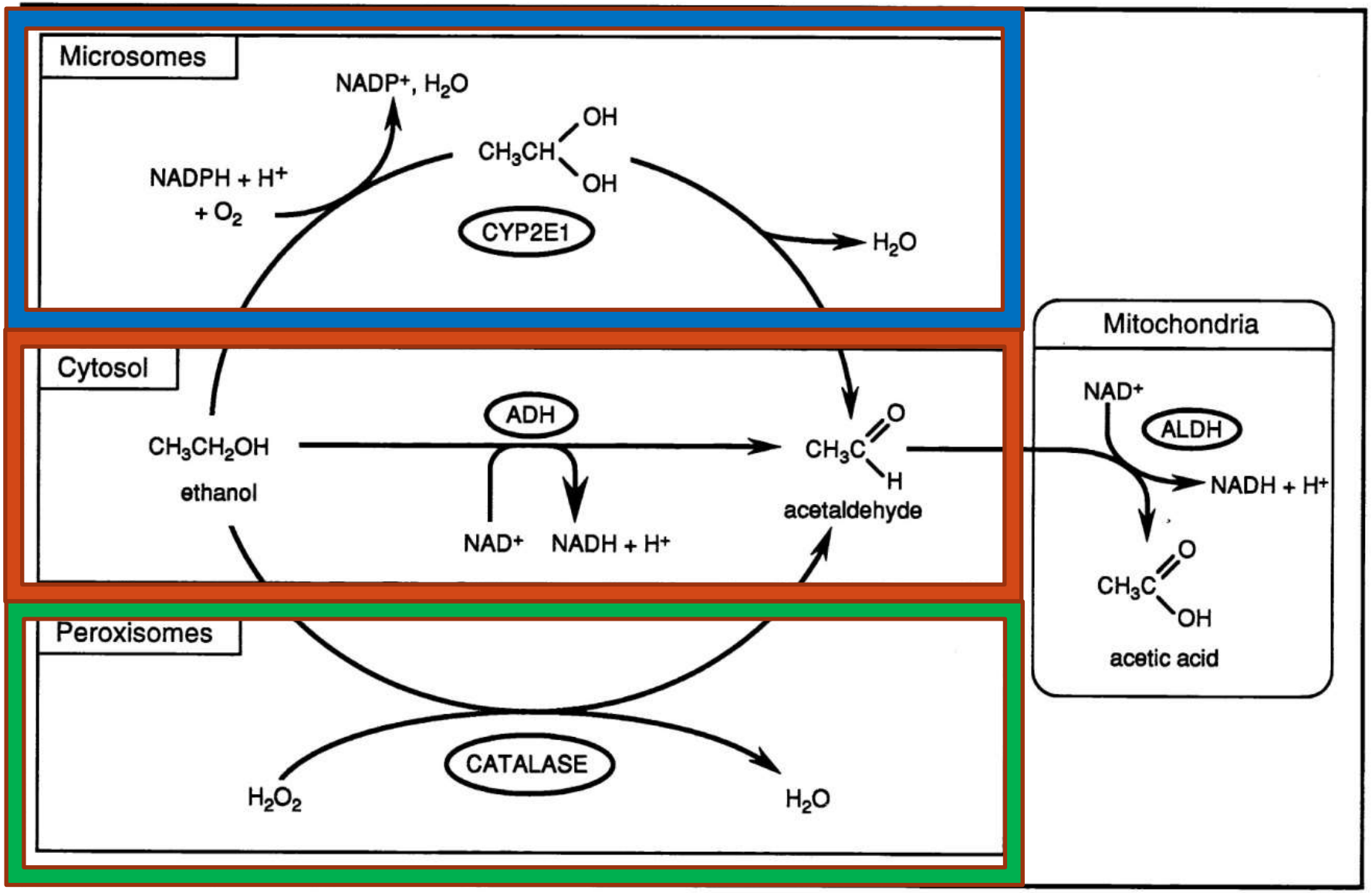
- sex,
- body composition,
- the amount of alcohol consumed,
- the presence of food, and
- the ability of the liver to produce the alcohol dehydrogenase enzymes.

➢ Nothing will speed up the rate of detoxification, but the effective metabolism of alcohol can be limited by medications and liver damage.

Women and Alcohol

- Women absorb and metabolize alcohol differently than men
- Have less activity of ADH
- Have less body water in which to dilute the alcohol than men do

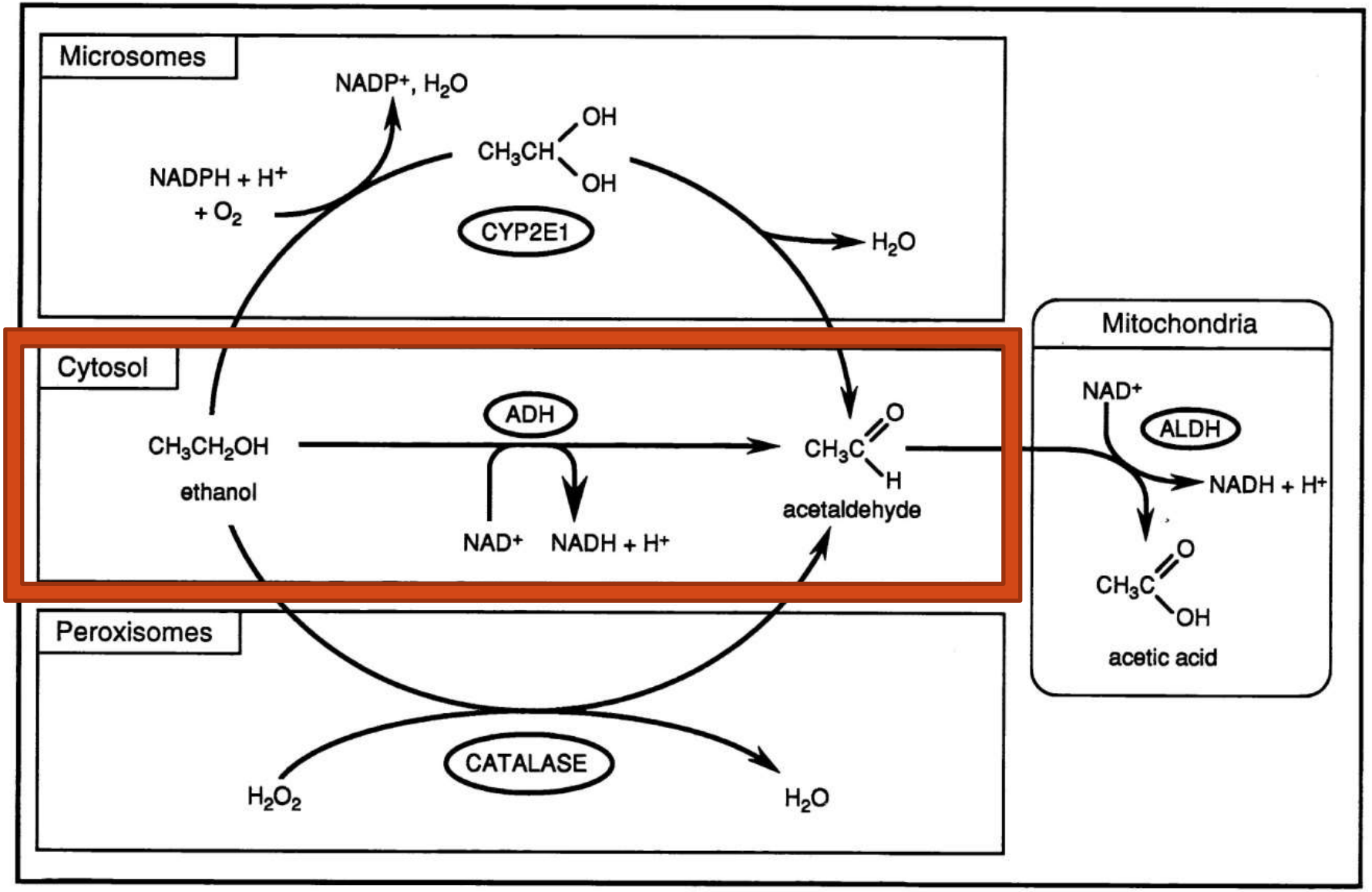
Oxidative pathways of alcohol metabolism – 3 ways

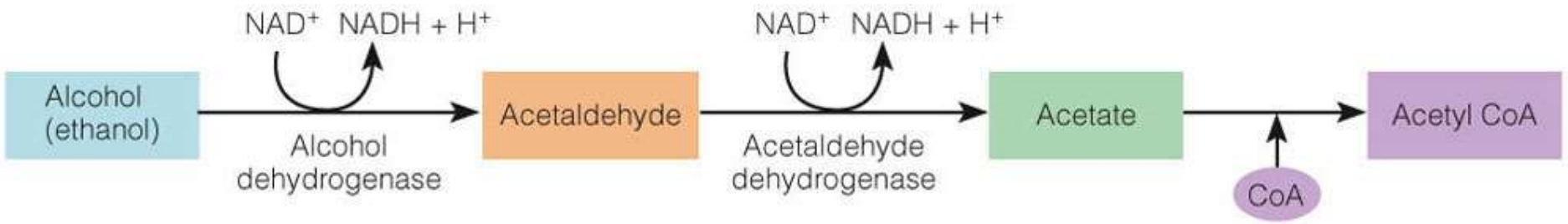


Meatbolism of Alcohol

- Stomach and Small intestine – rapid absorption with/without food
- Liver – major site of metabolism
  - 70-80% via ADH
  - 10-20% MEOS (microsomal ethanol oxidizing system)
  - 15-25% by Catalase (peroxisomal enzyme system)
  - Small amount excreted unchanged
- Alcohol is also metabolized in the brain
- Excess energy from alcohol is converted to fatty acids and stored as triglycerides

Oxidative pathways of alcohol metabolism





The conversion of alcohol to acetyl CoA requires the B vitamin niacin in its role as the coenzyme NAD. When the enzymes oxidize alcohol, they remove H atoms and attach them to NAD. Thus NAD is used up and NADH accumulates. (Note: More accurately, NAD+ is converted to NADH + H^+.)

Elevated acetaldehyde cause increased flushing, tachycardia (elevated heart rate), nausea, vomiting & hyperventilation.

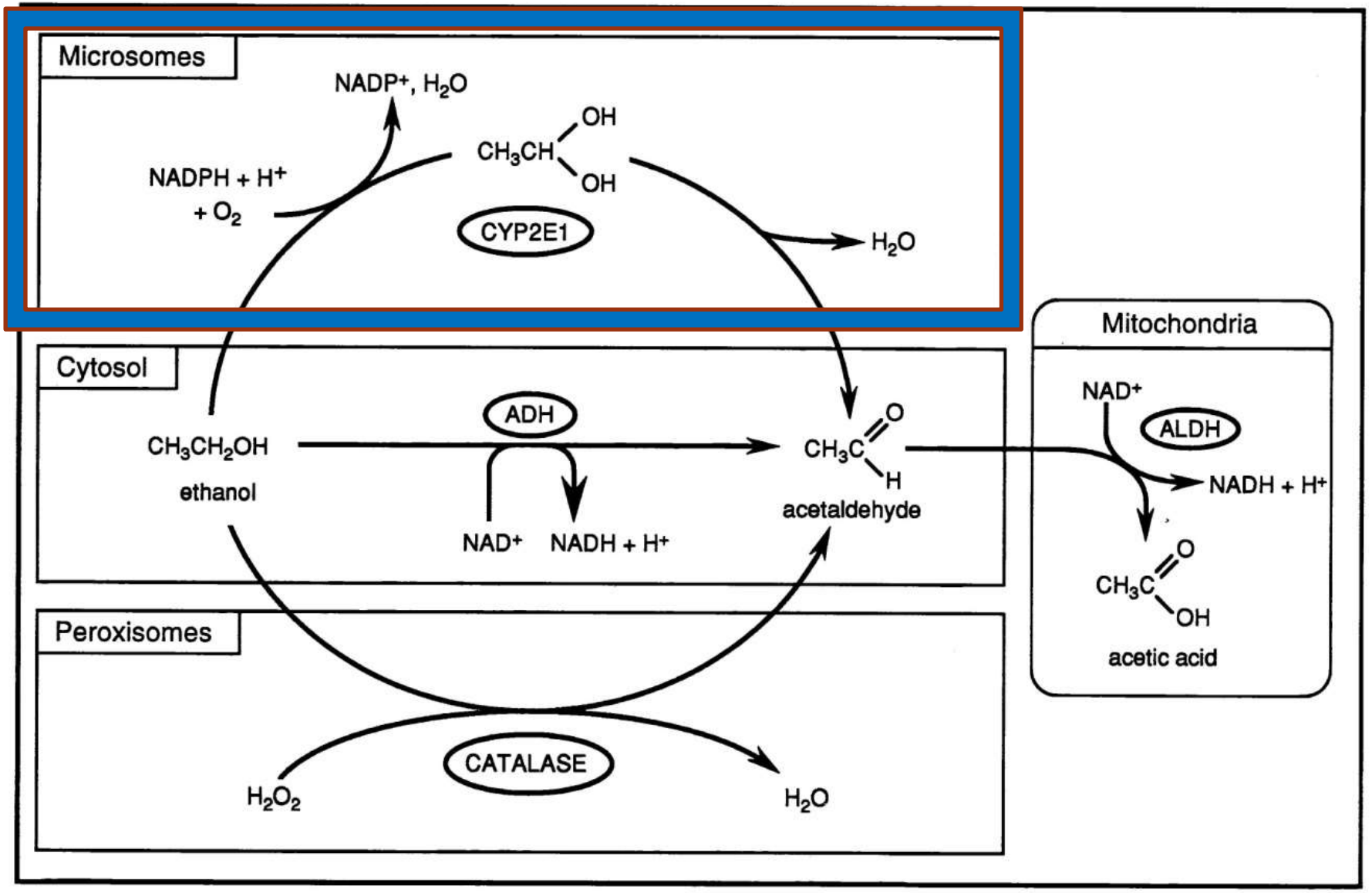
Genetic Variation in ALDH

Acetaldehyde Dehydrogenase (ALDH) varies in Caucasians, Blacks and Asians.

50% of Asians have inactive ALDH

- **Alcoholism Treatment with Disulfiram**
- **Inhibits acetaldehyde dehydrogenase (ALDH)**
- **Elevated acetaldehyde cause increased flushing, tachycardia (elevated heart rate), nausea, vomiting & hyperventilation.**

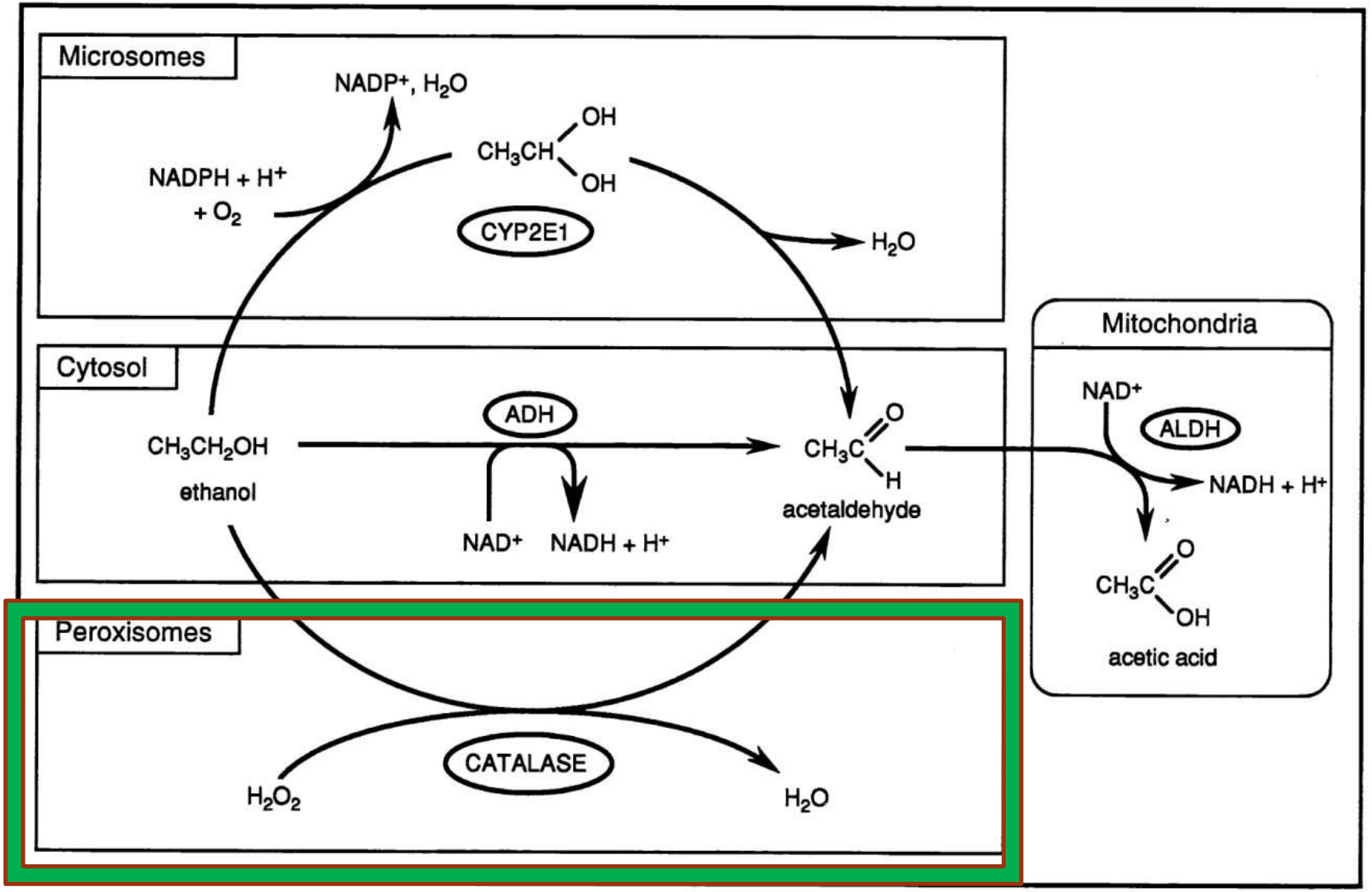
Oxidative pathways of alcohol metabolism



Microsomal Ethanol Oxidising System(MEOS)

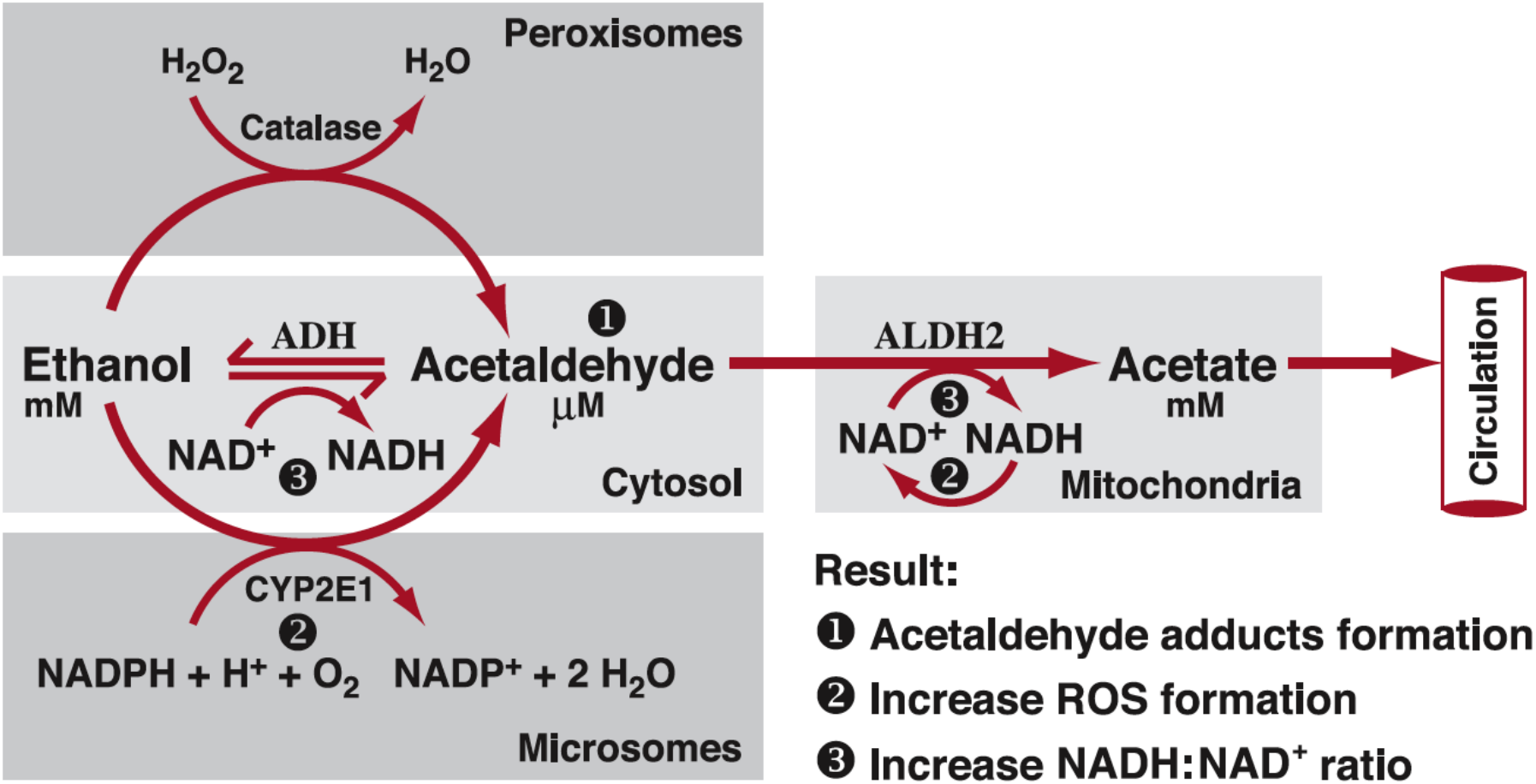
- 10 to 20% ingested Ethanol is oxidised through MEOS.
- Which also oxidises Ethanol to acetaldehyde.
- MEOS is part of the superfamily of cytochrome P450, all of which catalyze similar reactions.
- The isoenzyme with highest activity towards ethanol is designated CYP2E1
- It uses NADPH and molecule O_2 forming water and acetaldehyde.

Oxidative pathways of alcohol metabolism



Catalase, peroxisomal enzyme

- Catalase, peroxisomal enzyme, uses H_2O_2 to oxidize substrates, including phenols, formic acid, formaldehyde, and alcohol, by means of the peroxidation reaction.
- This reaction is important in liver and kidney cells, where the peroxisomes detoxify various toxic substances that enter the blood.



Result:

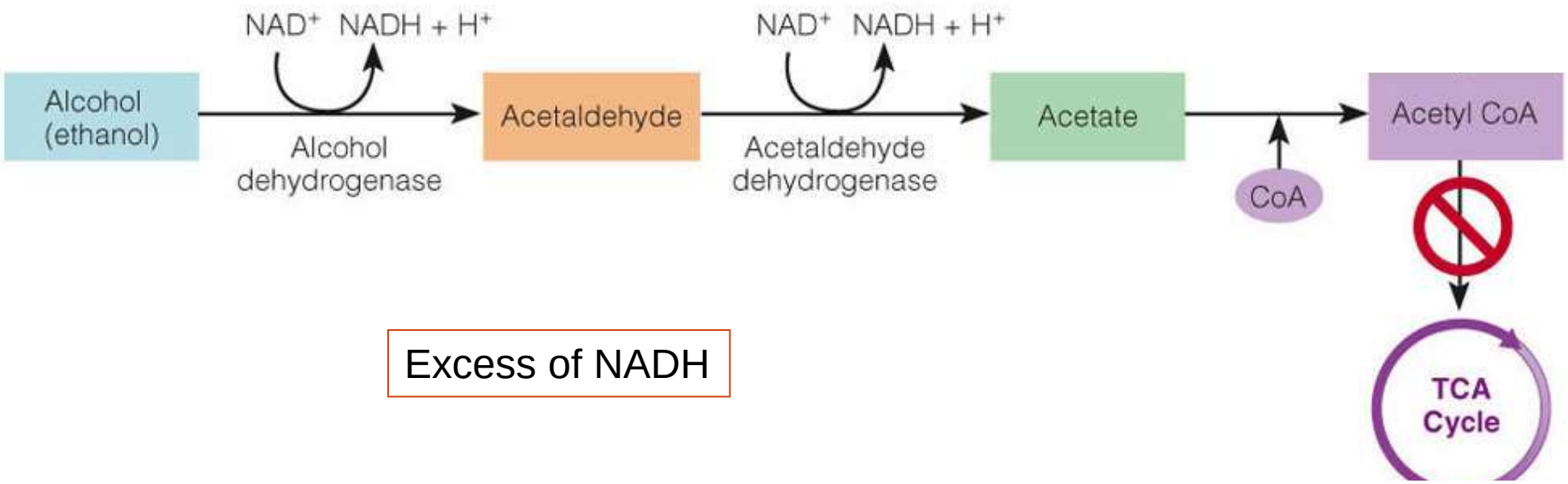
❶ Acetaldehyde adducts formation

❷ Increase ROS formation

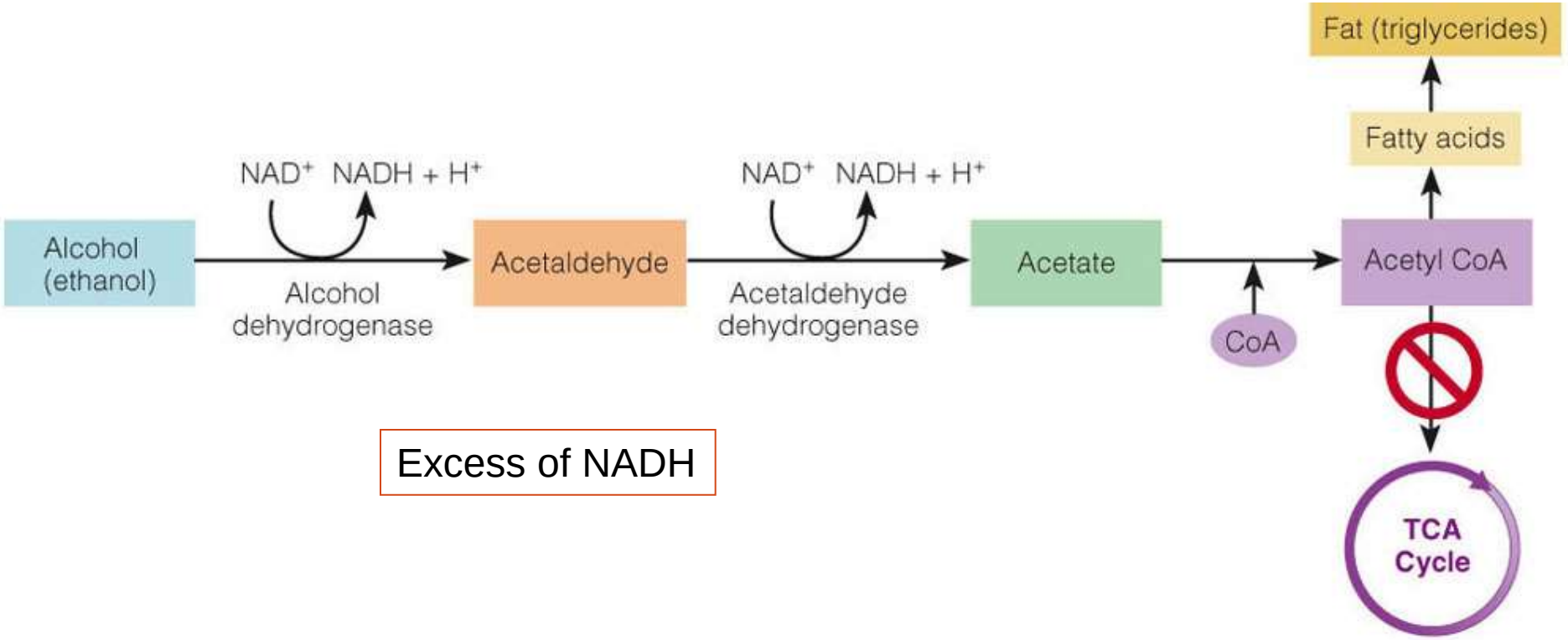
❸ Increase NADH:NAD^+ ratio

Alcohol Disrupts the Liver – **chronic effects**

- Eliminates liver production of glucose creating hypoglycemia
- Development of a fatty liver is the first stage of liver deterioration.
- Fibrosis is the second stage.
- Cirrhosis is the most advanced stage of liver deterioration.



- The resulting backup of acetate shifts the reaction equilibrium back towards acetaldehyde.
- **Acetaldehyde subsequently accumulates and begins to form covalent bonds with cellular macromolecules, forming toxic adducts**
- Eventually, lead to cell dysfunction and death of the cell.



Excess of NADH

Acetyl CoA molecules are blocked from getting into the TCA cycle by the high level of NADH. Instead of being used for energy, the acetyl CoA molecules become building blocks for fatty acids.

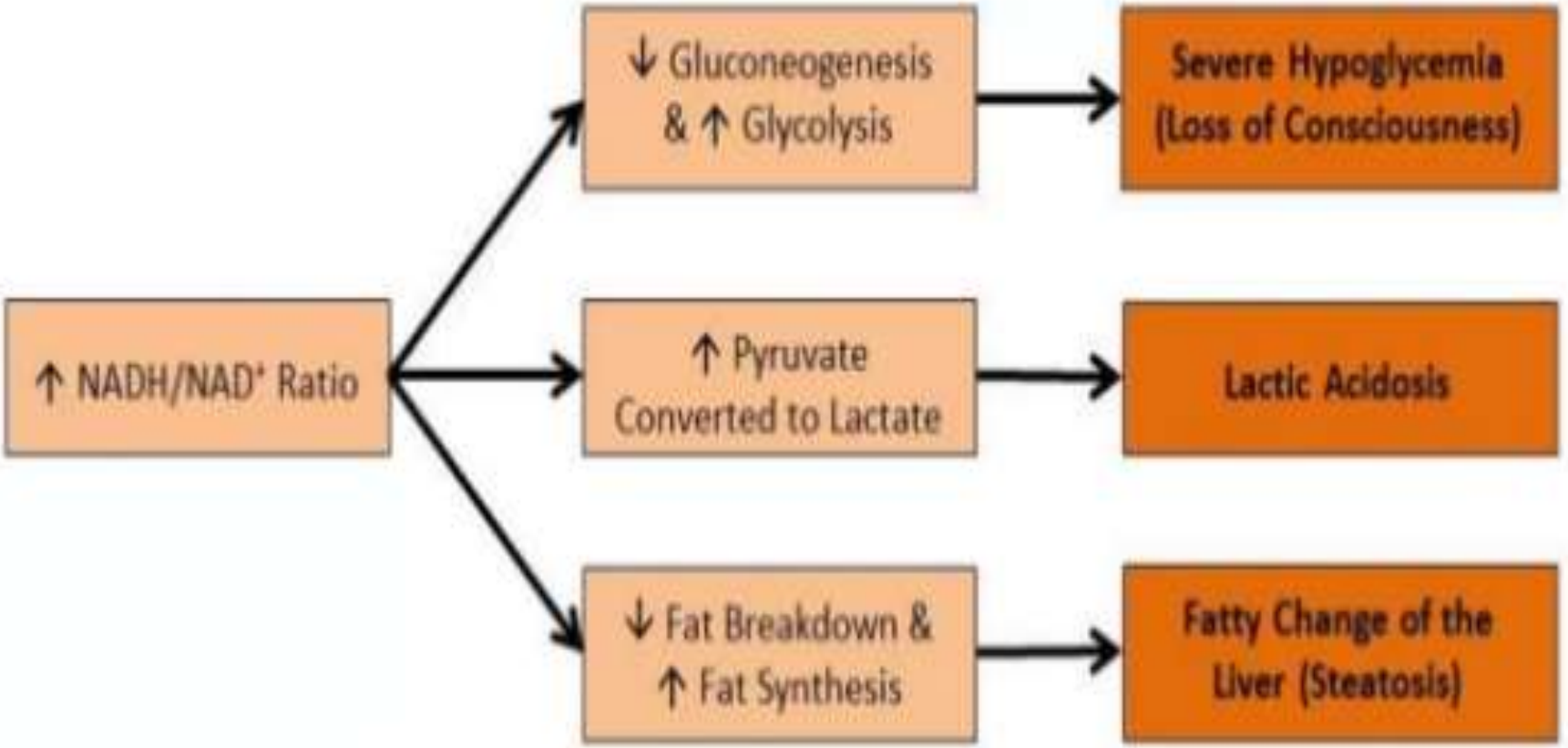
Alcoholism and Hypoglycemia

- Alcoholics are very susceptible to hypoglycemia.
- In addition to poor nutrition and the fact that alcohol is metabolized to acetate (acetyl-CoA), the high amounts of cytoplasmic NADH formed by alcohol dehydrogenase and acetaldehyde dehydrogenase interfere with gluconeogenesis.

Alcoholism and Hypoglycemia

- High NADH favors the formation of:
  - Lactate from pyruvate
  - Malate from OAA in the cytoplasm
  - Glycerol 3-phosphate from DHAP

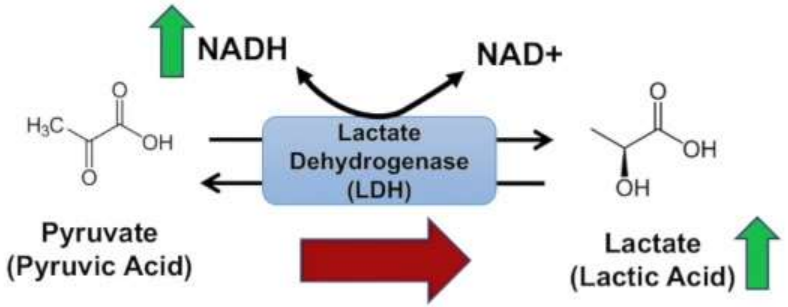
Effects of NAD^+/NADH Ratio Fluctuation



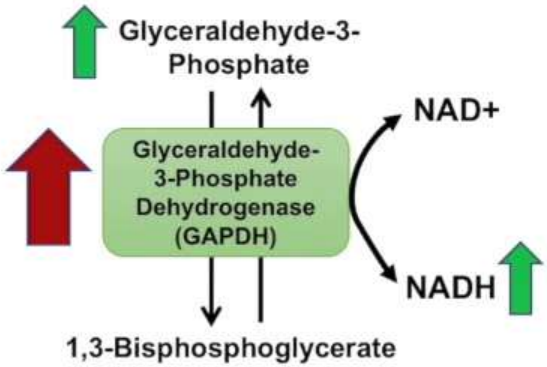
Consequences of ↑ NADH, ↓ NAD+/NADH, ↑ Acetyl CoA

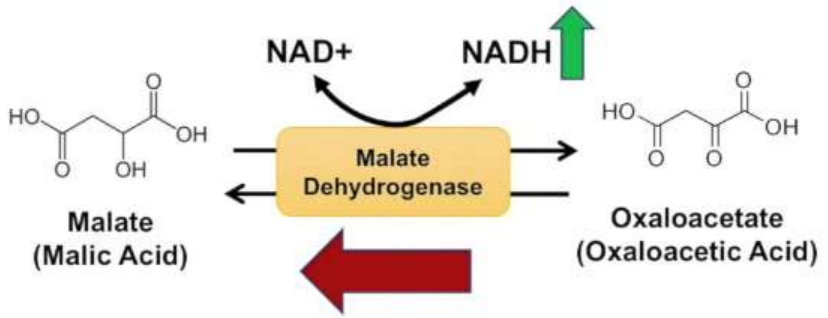
1. Glycolysis and Lactic Acidosis

2. TCA Cycle



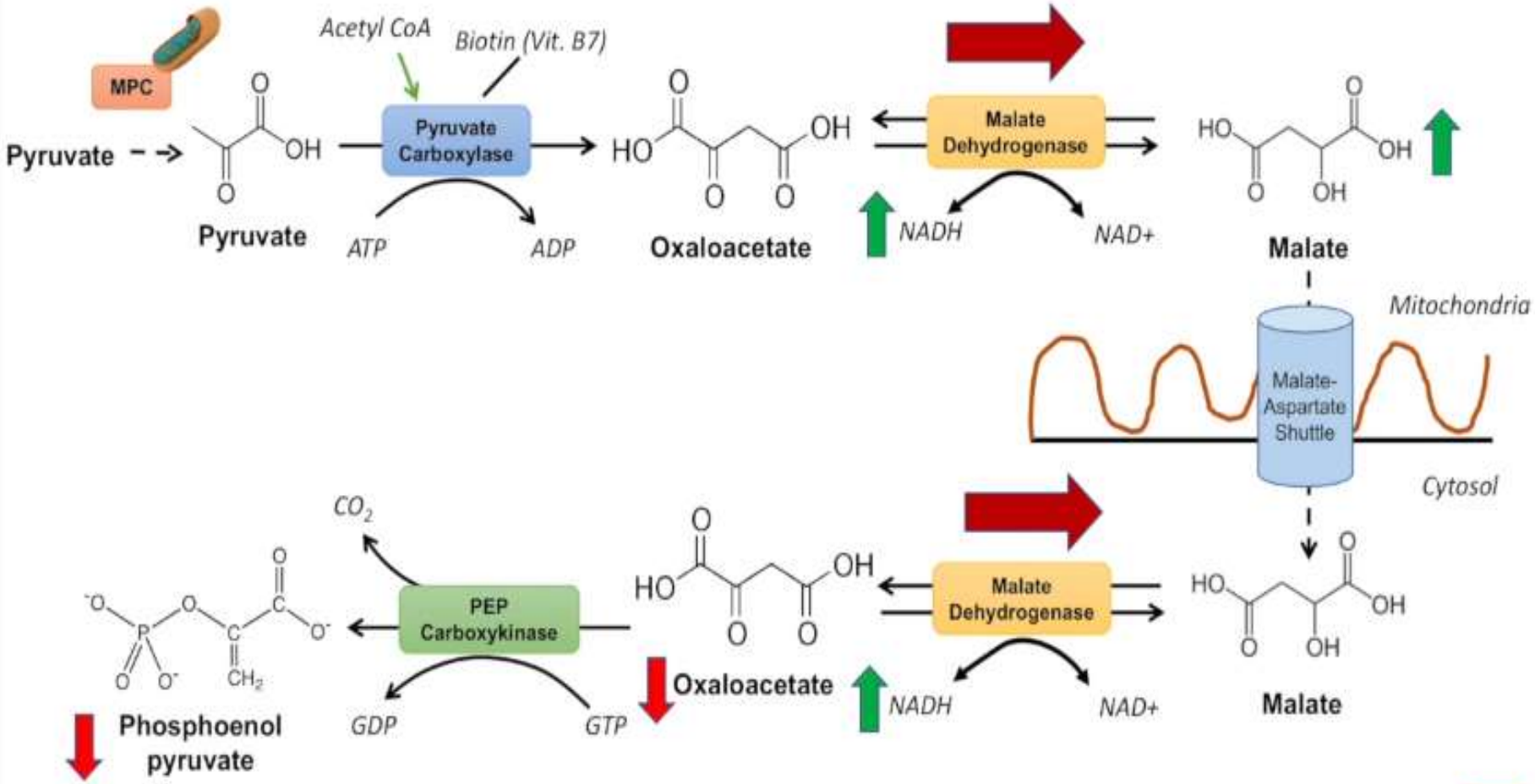
Lactic Acidosis





Consequences of ↑ NADH, ↓ NAD+/NADH, ↑ Acetyl CoA

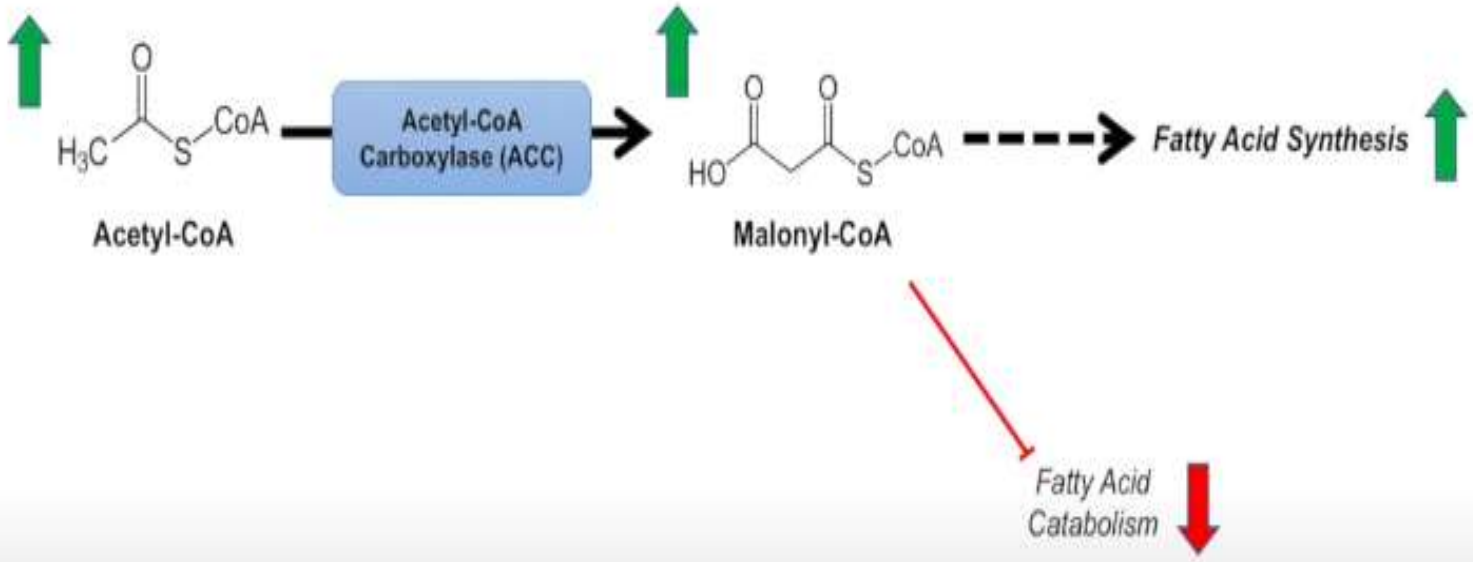
3. Gluconeogenesis



Hypoglycemia

Consequences of ↑ NADH, ↓ NAD+/NADH, ↑ Acetyl CoA

4. Fatty Acid Synthesis



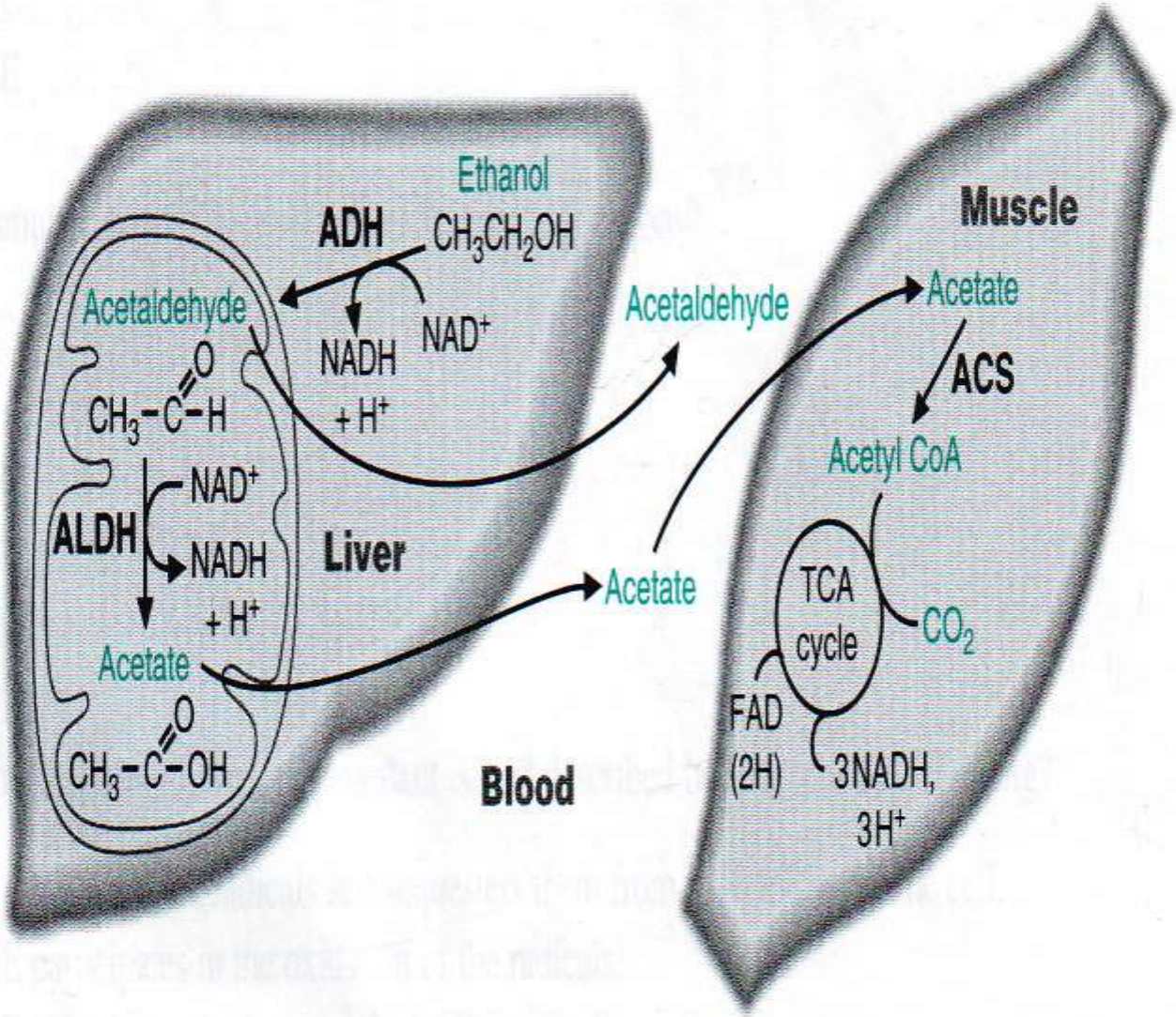


Fig. 25.1. The major route for metabolism of ethanol and use of acetate by the muscle. (ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; ACS, acetyl-CoA synthetase).

ALCOHOL'S EFFECT ON THE KIDNEYS

- INCREASED URINE OUTPUT
  - Consuming large quantities of liquid
  - Alcohol suppresses antidiuretic hormone (ADH) resulting in the loss of body water.

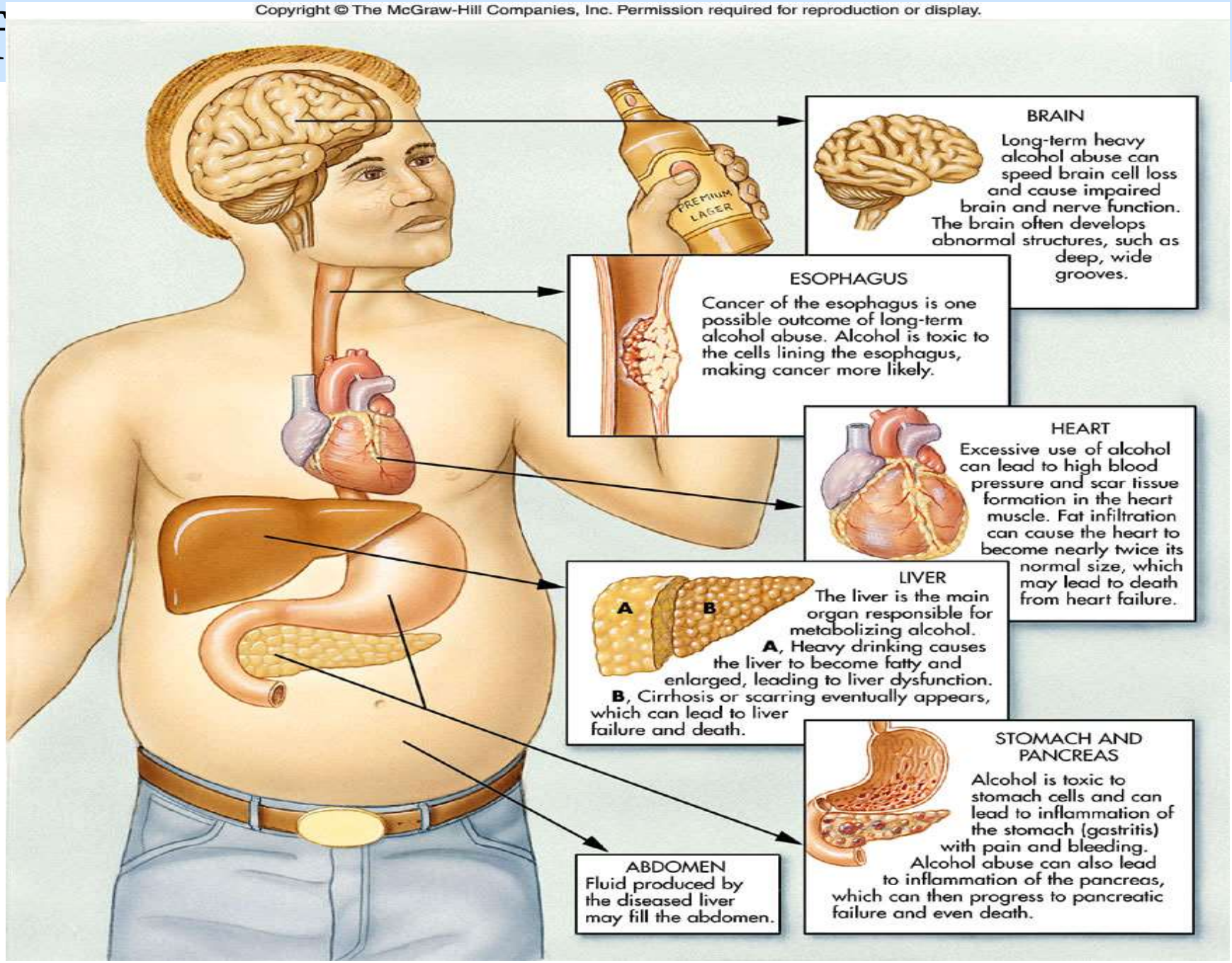
Alcohol and Malnutrition

- Poor and inadequate nutritional intakes and fat malabsorption and increased urinary losses.
- Impaired nutrient metabolism will result from chronic alcohol abuse.
- Vitamin B_6, folate, thiamin and Vit-C deficiencies
- Aldehyde inhibits pyridoxal phosphate; neuritis is very common in alcoholics.
- Wernicke-Korsakoff syndrome is seen in chronic alcoholism.

Alcohol's Long-Term Effects

- Arthritis
- Cancer
- Fetal alcohol syndrome
- Heart disease
- Hyperglycemia
- Hypoglycemia
- Liver disease
- Infertility
- Kidney disease
- Malnutrition
- Nervous disorders
- Obesity
- Psychological disturbances
- Affect hormonal status

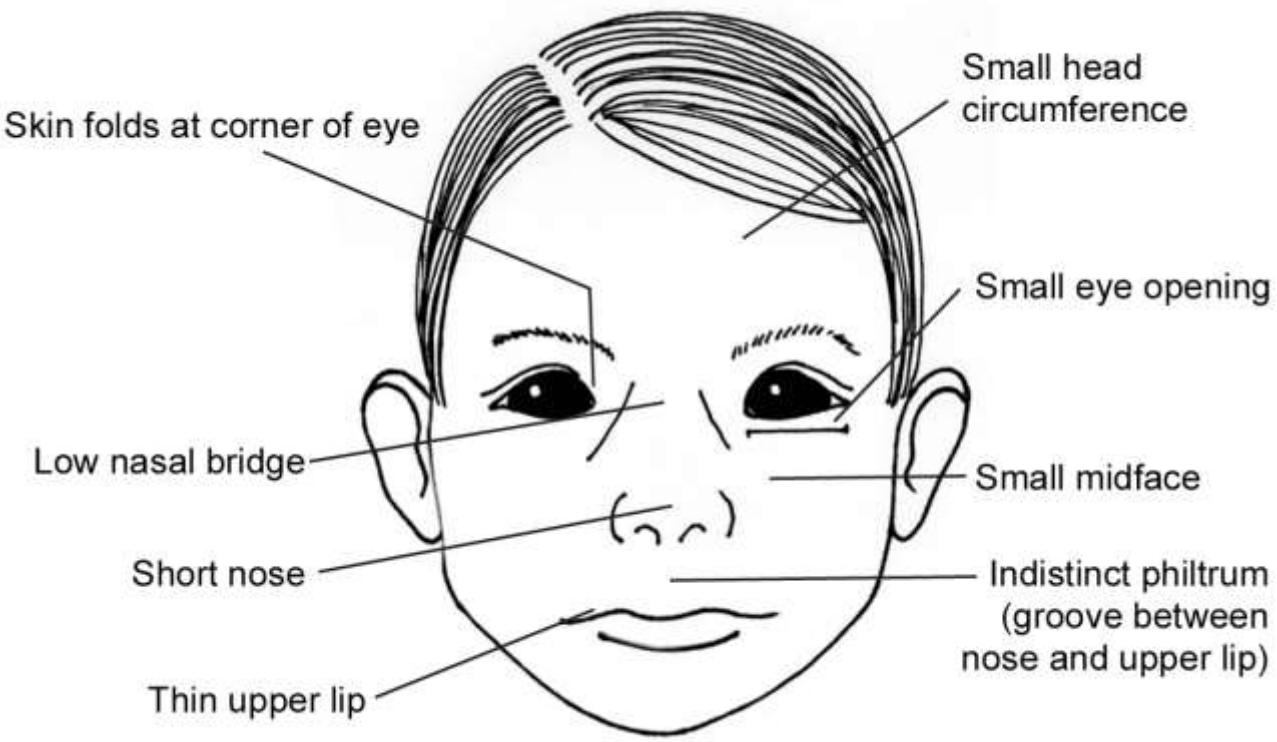
Ef



Fetal Alcohol Spectrum Disorders

- The most serious risk during pregnancy is fetal alcohol spectrum disorders (FASD).
- FASD is the leading known cause of mental retardation in the United States.

Fetal Alcohol Spectrum Disorders



Gut Fermentation Syndrome

(Auto-brewery Syndrome)

Endogenous Ethanol **Fermentation**, or Drunkenness Disease, is a condition characterized by the **fermentation** of ingested carbohydrates in the gastrointestinal tract of the body caused by bacteria or fungi.

How toxic is methanol (methyl alcohol)?

Methanol is extremely toxic. As little as 2 tablespoonfuls can be fatal to a child, and 2 to 8 oz. can be fatal for an adult.

Methanol more toxic than ethanol?

Yes,

because ethanol takes longer to metabolize then methanol and

because the aldehyde and organic acid formed from methanol are more toxic substances than those formed from ethanol.

Methanol to Formaldehyde to Formic acid

Formic acid is the primary toxin responsible for the metabolic acidosis, and for the visual disturbances, associated with methanol poisoning

Methanol more toxic than ethanol?

Fomepizole???

Methanol to Formaldehyde to Formic acid

Formic acid is the primary toxin responsible for the metabolic acidosis, and for the visual disturbances, associated with methanol poisoning

9 Possible Mechanisms How Alcohol Intake Increase Cancer Risk

According to Blot et al (1992)

1. Contain congeners and other contaminants that may be carcinogenic
2. Generated metabolites that are carcinogenic to humans
3. Act as solvent, increasing penetration of other carcinogens into target tissue
4. Reduce intake and bioavailability of nutrition
5. Inhibit the detoxification of carcinogenic compounds
6. Catalyze the metabolic activation of some compounds into carcinogens
7. Affect hormonal status
8. Increase cellular exposure to oxidants
9. Suppress immune function

Thanks for your attention!