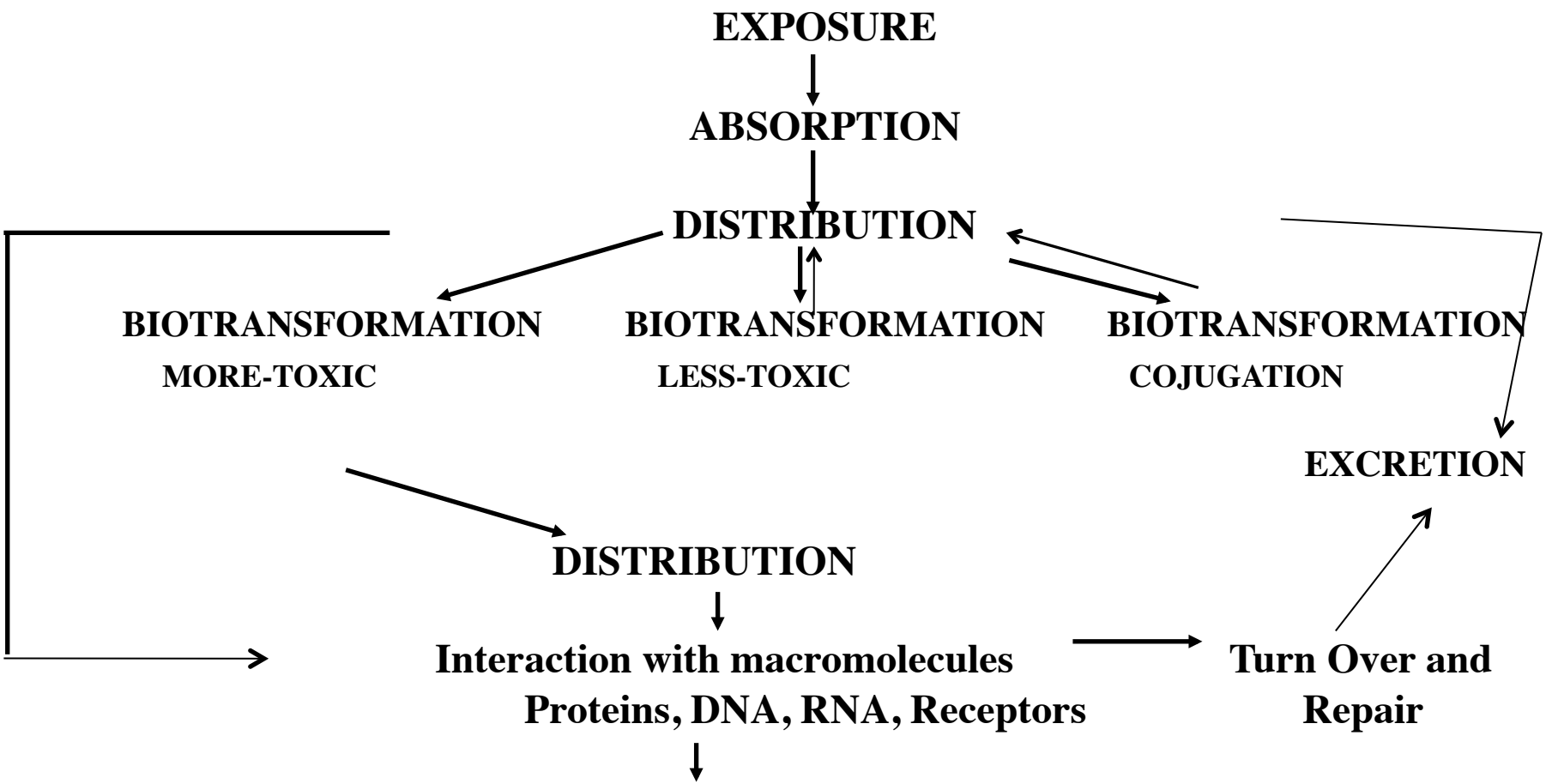
Environmental Pathology

Humans are surrounded by, contact, breathe in and consume many chemicals that are added to, or appear as contaminants in food, water and air or derive from bad behaviors.

Often, the effects of the chemical compouds are mostly dependent on the metabolites produced by the original substance.



- **Metabolites may ineract with target macromolecules triggering a toxic effect**
- **The place of the effect is often different from the place of biotransformation or where the metabolites are excreted**
- **The given dose (initial dose) may be different by the dose reaching the target (biologic effective dose)**

WHAT IS ALCOHOLISM ?

"***Alcoholism has been defined as both a chronic disease and a disorder of behaviour, characterized in either context by drinking of alcohol to an extent that surpasses the social drinking customs of the community and that interferes with the drinker's health, interpersonal relations, or means of livelihood."***

(according to WHO)

Alcohol Absorption:

By Mouth and Esophagus ⟶ in small quantities

By Stomach and Intestine ⟶ in moderate quantity

By proximal Ileum ⟶ **in large amount**.

<u>The absorbed quantity increases depending on:</u>

- the empty stomach and the small intestine
- the absence of proteins, fatty foods and carbohydrates that generally impede alcohol absorption
- the absence of similar compounds
- the water content that facilates its absoption (maximum 20% diluted)
- the carbon dioxide presence (Soda, Perle wine)

Comsumption of Alcohol and Nutrition value

1gr of alcohol contains 7kcal, with little nutrional value as: minerals, proteins and vitamins

⬇

EMPTY CALORIES

Moderate consumption

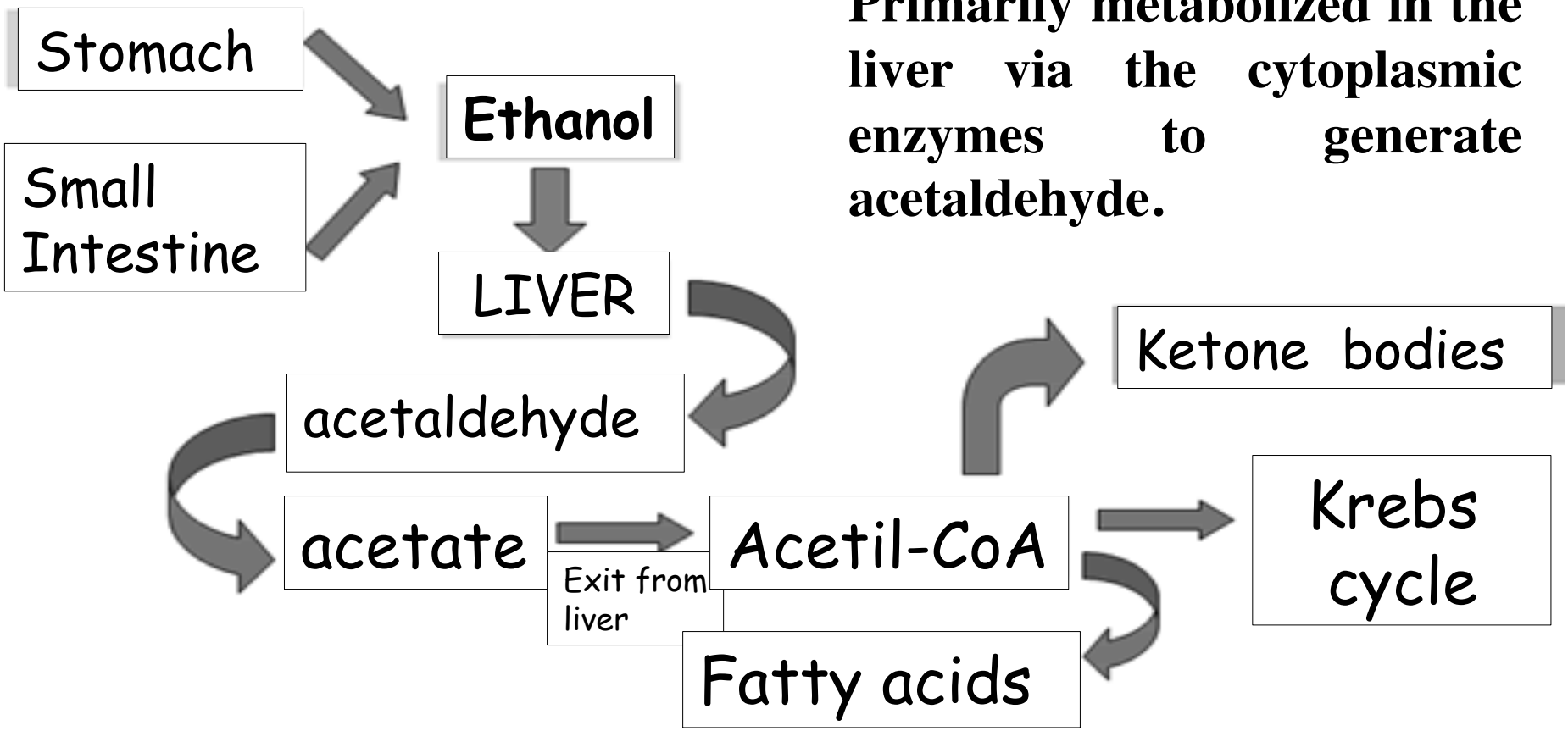
Lower risk of coronaric pathologies by reducing platelet aggregation and increasing circulating HDL, possibly through two mechanisms:
-Reduction of Hepatic lipase activity
-Alteration of the proteic part of HDL particles.
Increased peripheral vasodilatation.

Excessive consumption

-deficit of all the vitamins absorbed by tenue. Including folate (folic acid), piridoxin (B6), thiamine (B1), nicotin acid o niacin (B3) and vitamin A.
-Low plasma levels of kalium, magnesium, calcium, zync and phosphorus.

Ethanol Metabolism

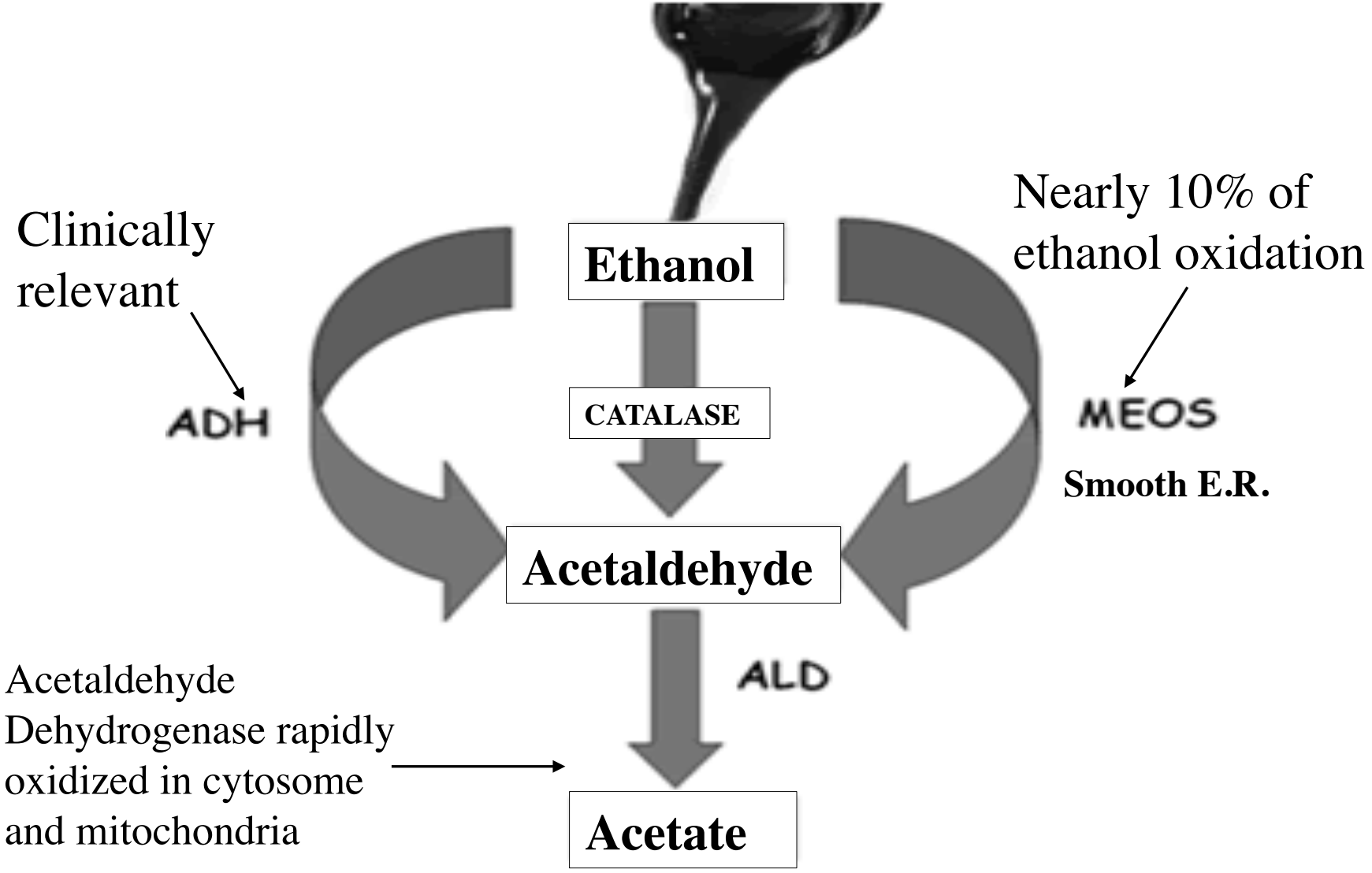
Ethanol is eliminated chiefly by oxydation to carbon dioxide, less than 10%, being excreted chemically unchanged in the urine, sweat and breath with a range from 2% to 10%.



Primarily metabolized in the liver via the cytoplasmic enzymes to generate acetaldehyde.

Ethanol Metabolism

In Hepatocytes, ethanol is metabolized through three metabolic pathways each with a different value.

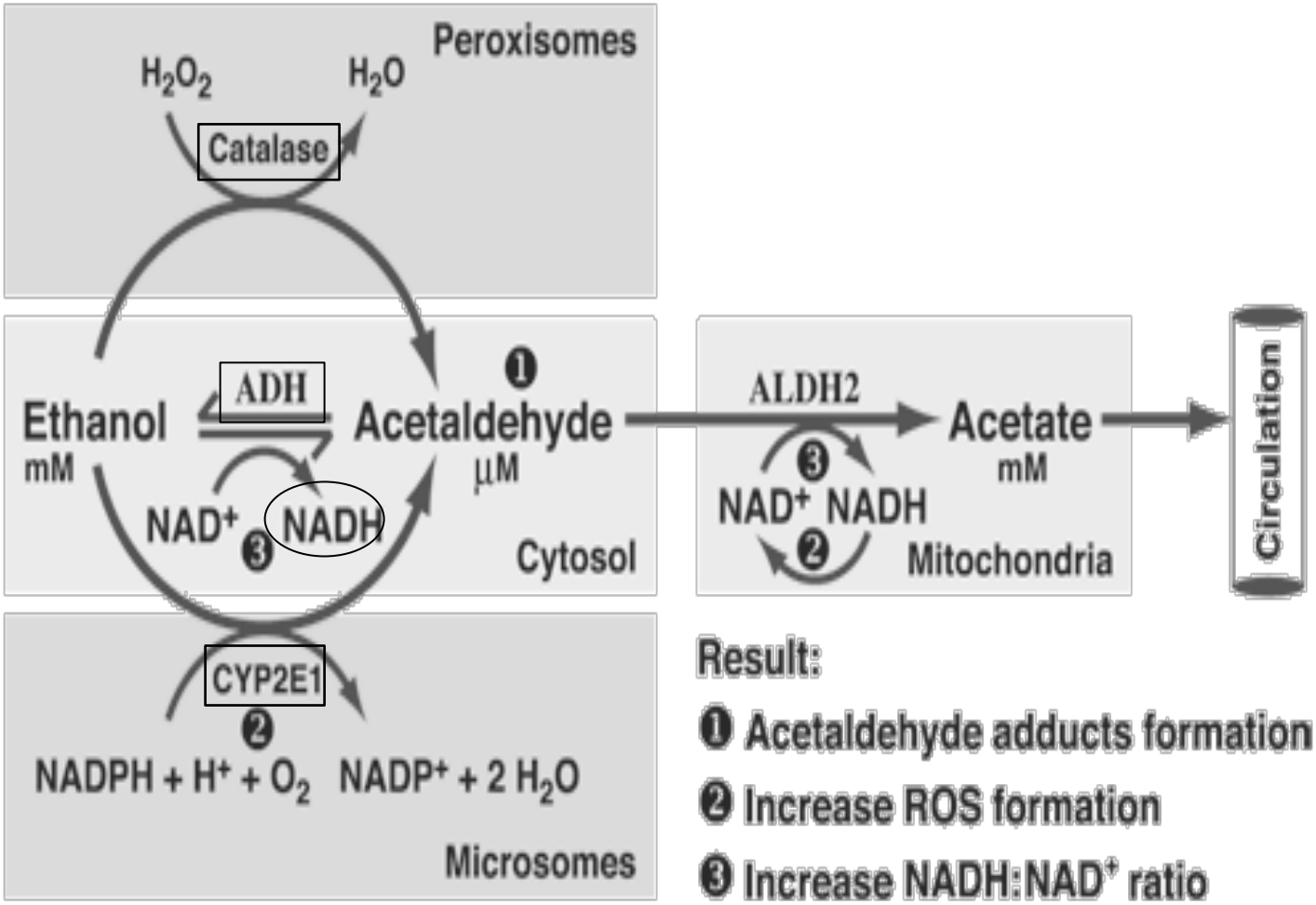


Cellular Metabolism of Alcohol

CATALASE dual function:
-oxidizes ethanol
-reduces peroxides

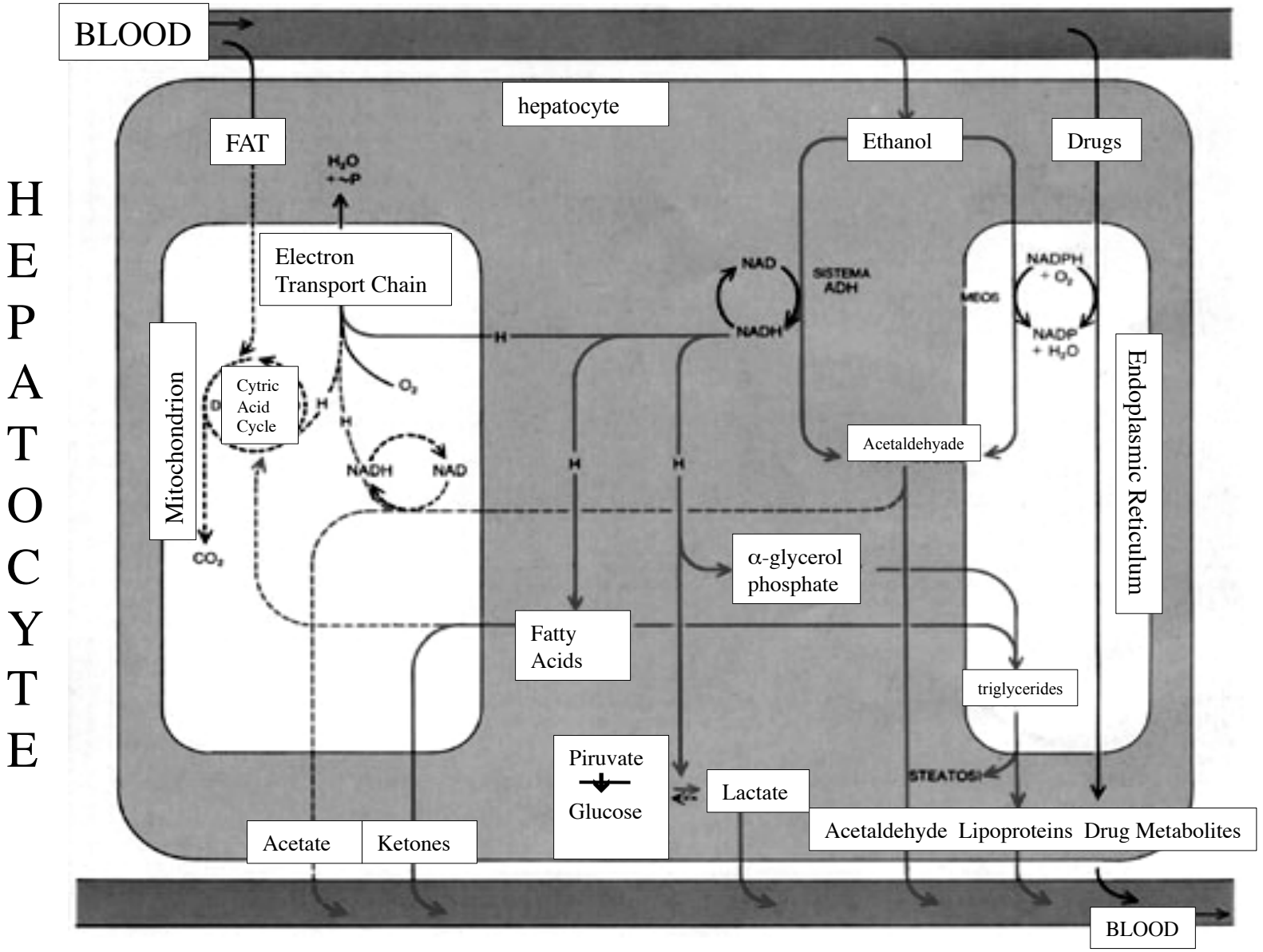
ALCOHOL DEYDROGENASE:
-principal enzyme of the gastric mucosa and liver
-metabolizes 90% of absorbed ethanol

The inducible MEOS system: CYP2E1 metabolizes ethyl alcohol and drugs



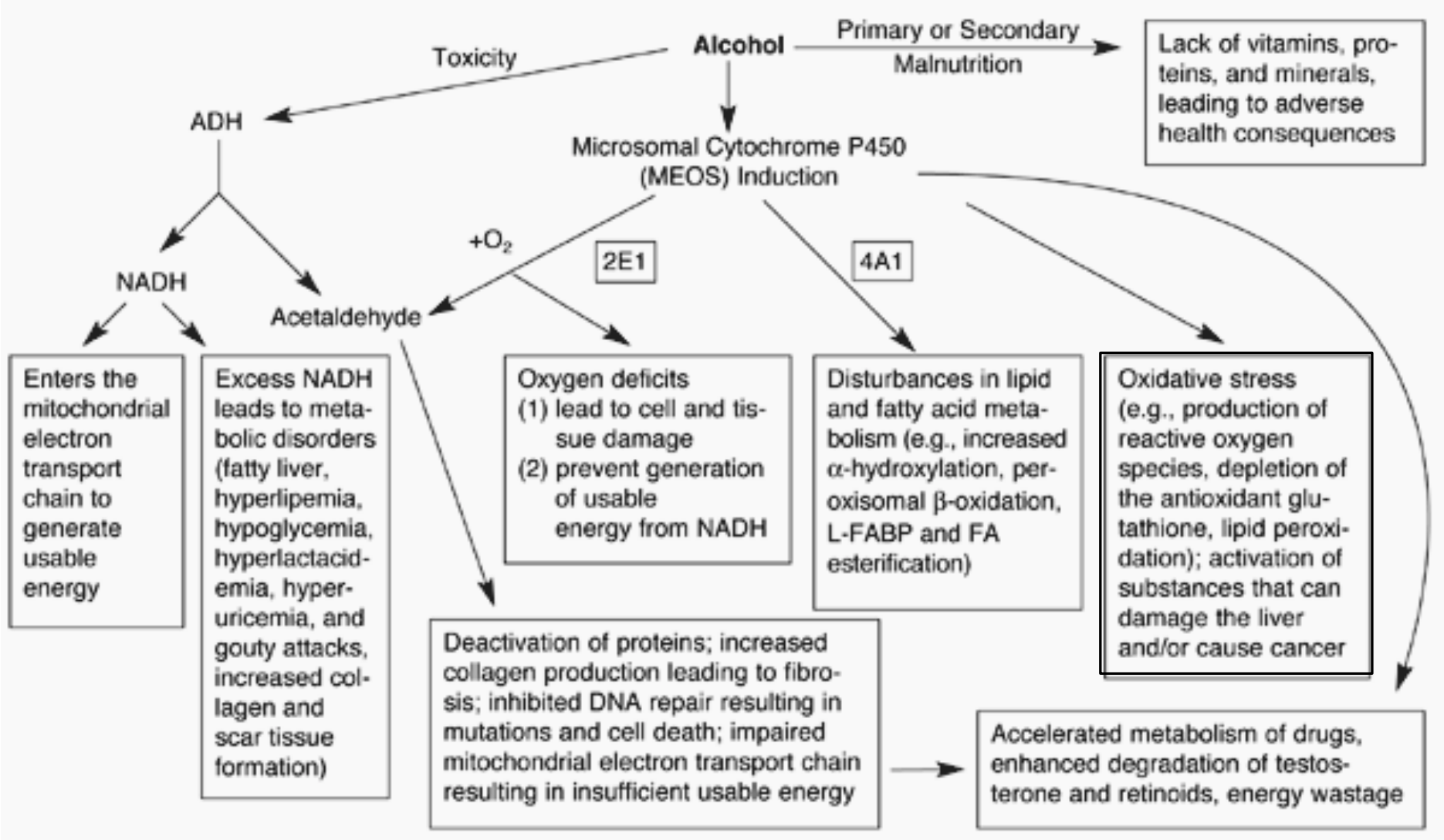
Over production of H^+ and unbalanced NADH/NAD^+

Oxidation of Ethanol in the Hepatocyte



Acetate is the final product of ethanol metabolism. It will be futher metabolized to acetyl CoA, released in venous circulation and then distributed to peripheral organs to be metabolized (heart, muscle)

METABOLIC ALTERATIONS INDUCED BY ETHANOL



Alcohol Effects

General Effect
(< 50mg/dl)

Impairment begins. Depressive on CNS.
Dose-dependent inhibitory effect on information processing.

Legally intoxicated
(80-100mg/dl)

-Driving skills significantly affected,
-Altered information processing.
-Reaction time slowered,
-Loss of balance,
-Impaired movement,
-Slurred speech

Damage by alcohol
(< 300mg/dl)

-Brain injuries (Korsakoff syndrome)
-Cardiovascular disease
-Alcoholic cerebellar degeneration
-Cirrhosis
-Pancreatitis
-Fetal alcohol syndrome

Chronic alcoholism: pathologies induced by ethanol

a) Direct toxic damage

Alcoholic Hepatopathies:

*Steatosis
*Alcoholic Hepatitis
*Cirrhosis
*Hepatocarcinoma

Encephalopathies:

*Wernicke-Korsakoff Syndrome
*Alcoholic Dementia

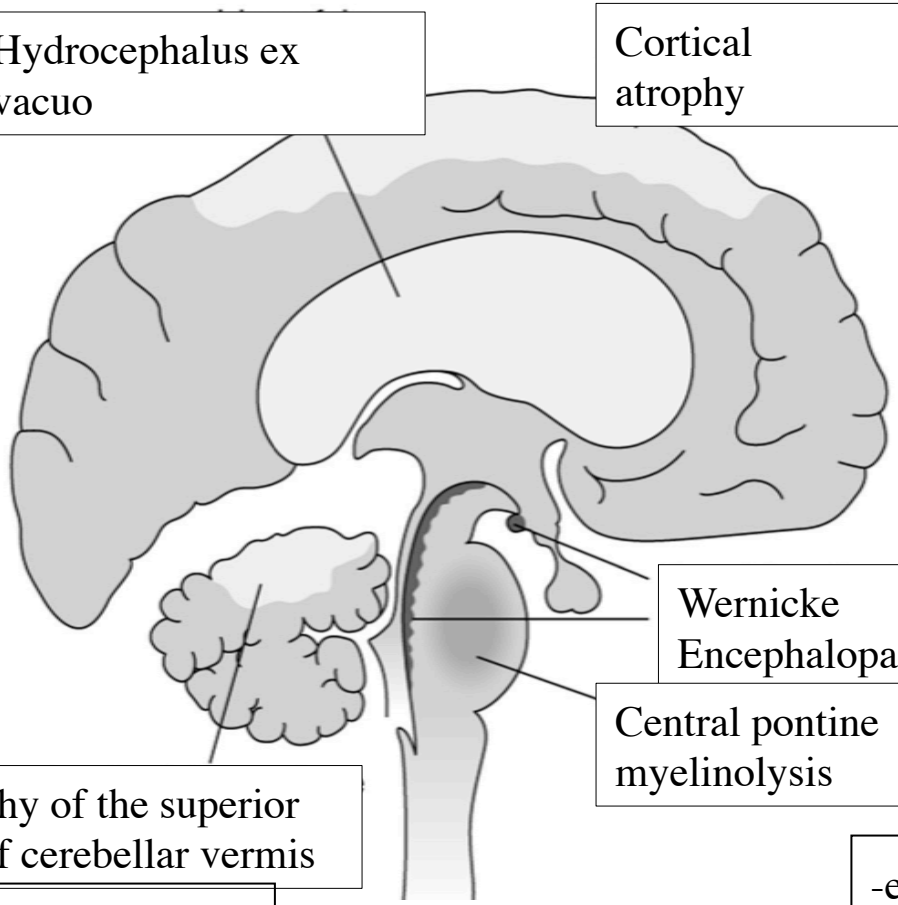
Other pathologies:

*Peripheral Neuropathy
*Alcoholic Cardiomiopathy
*Alcoholic Miopathy
*Anemia
*Platelet deprivation or Thrombocytopenia

Neural System

Frequent in chronic alcohohlics is a general atrophy of cerebral cortex which represents a direct damage.

Several other pathologies are derived by nutritional deficit



Hydrocephalus ex vacuo

Cortical atrophy

-thiamine deficiency (B1)
-mental confusion, ataxia, eye movements and polyneuropathy
- Korsakoff psychosis: retrograde amnesia and confabulation

Wernicke Encephalopath

Central pontine myelinolysis

Atrophy of the superior part of cerebellar vermis

-Toxicity and malnutrition
-inability of a standing position and to walk
-moderate nystagmus

From Rubin

-electolytic disequilibrium
-after an excessive dose of alcohol or after withdrawal
-respiratory depression

Nervous System
Other Pathologies by Malnutrition

Amblyopia or Optic Neuropathy
-altered vision with poor light(night blindness)
-ethanol-dipendent reduction of Vit.A: by reduced absorption and hepatic storage
-other vitamins defcit
-seldomly affecting alcoholics

Polyneuropathy
-common in chronic alcoholics
- deficit of thiamine (B1) and others of B group
-a direct damage by ethanol and acetaldehyde
-bilateral torpidity of limbs, tinglings and parasthesia associated to light or moderate pain, weakness and ataxia

Gastrointestinal System

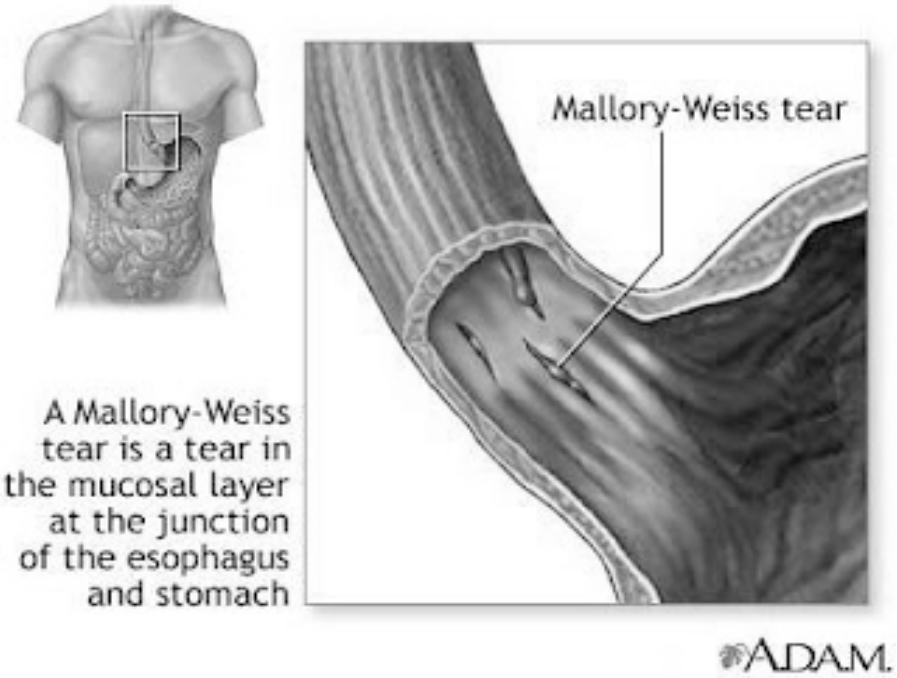
-Excessive concentration of Ethanol have a direct toxic effect on the mucosa of **Esophagus and Stomach**.

-Enhancement of gastric secretion by ethanol
-ESOPHAGUS and STOMACH inflammation causing frequent gastrointestinal hemorrhage

Esophageal reflux disease painful and frequent, with peptic ulcers

Mallory-Weiss Syndrome characterized by lacerations of the mucosa at or just below the gastresophageal junction after forceful vomiting caused by chronic ingestion of high doses of alcohol.

Reversible most of the alterations. Irreversible esophagus varices after cirrhosis and gastric atrophy.



Gastrointestinal system

SMALL INTESTINE (*INTESTINUM TENUE*)
-Mucosa alterations (structural) and hemorrhagic lesions of duodenal villi.
-Increased intestinum tenue motility (secondary diarrhoea) with reduced water and electrolyte assorbption.

Ethanol primarily absorbed in the first part of small intestine, where interferes with B group vitamins and other nutrients absorption: Including folate, piridoxine (B6), thiamine (B1), nicotinic acid or niacin (B3) and vitamin A.

Modulation of intestinal bacterial flora (Vitamin K).

PANCREAS
Acute and chronic pancreatitis with destruction of acinus and of pancreatic islets contributing to nutritional deficit.

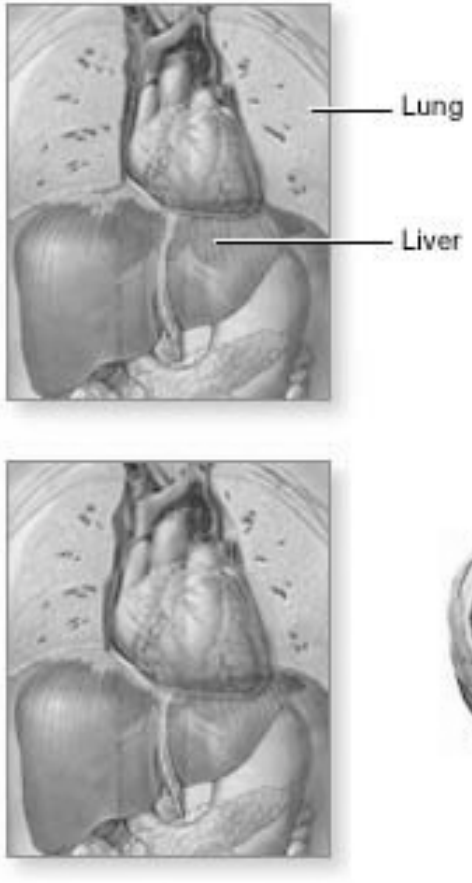
Chronic pancreatitis give rise to calcification associated to strong pain, pancreatic insufficiency and stones generation in pancreatic ducts .

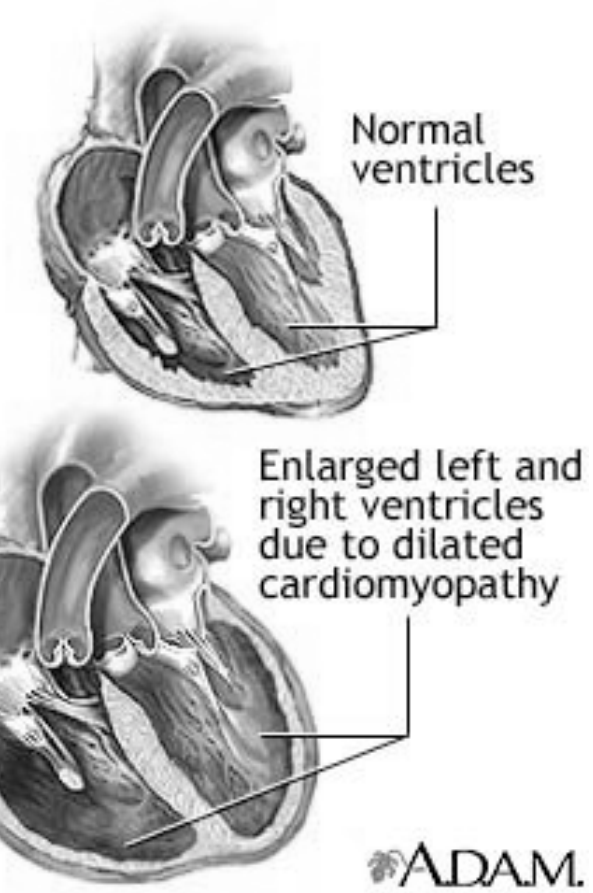
Cardiovascular Apparatus

Alcohol myopathy a degenerative disease of the heart muscle resulting in dilatation of the heart,probably due to a direct toxicity.

Heart arrhythmia until heart failure and myocardial hypocontraction.

Hypertension, secondary to vasopressor effects of ethanol. Daily high alcohol consuption determines a dose-dependent increased pression.





Strict relationship between alcoholism and cerebrovascular accident (frequent in the 24h after alcohol abuse).

Fatal and sudden heart arrhythmia the main causes of death.

Hematopoietic system

Acute and reversible or chronic effects on whole blood cells.

- Megaloblastic Anemia secondary to folic acid deficiency, frequent in alcoholics suffering for malnutrition. Weak antagonistic effect of ethanol on folic acid.

-Increased Erythrocyte Mean Corpuscular volume (MCV) by ethanol intoxication

-Reduced production of white blood cells, motility and adhesion to granulocytes thus impairing immune response.

-Temporary acute Thrombocytopenia giving rise to hemorrhage.

Bones

Increased risk of Osteoporosis in women menopause

Increased incidence of necrosis of femoral head in men.

CHRONIC ALCOHOLISM:
Pathologies induced by ethanol

b) Indirect damages:

- **Prone to Airway diseases**
- **Prone to esophagus tumors and of airway**
- **Prone to Peptic ulcer disease**

c)F.A.S.: fetal alcohol syndrome o fetopatia alcolica

Fetal alcohol syndrome

A baby with fetal alcohol syndrome may have the following symptoms:

° Poor growth while the baby is in the womb and after birth

°Decreased muscle tone and poor coordination

°Delayed development and problems in three or more major areas: thinking, speech, movement, or social skills

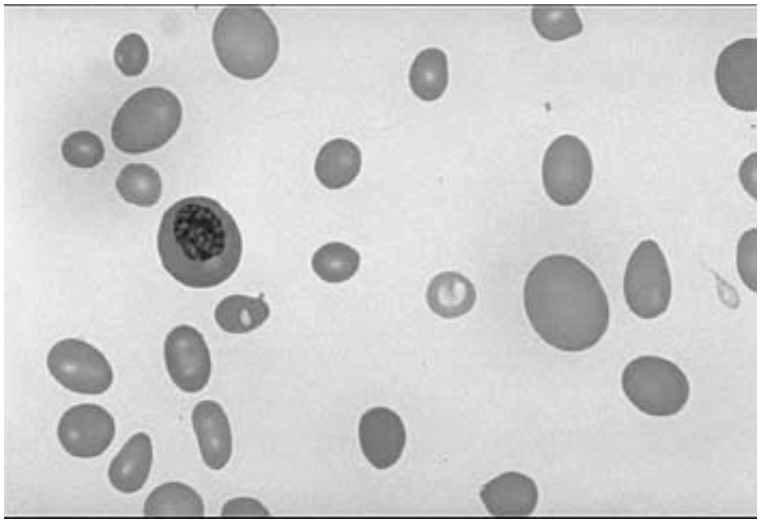
°Heart defects such as ventricular septal defect (VSD) or atrial septal defect (ASD)

Problems with the face, including:

- o Narrow, small eyes with large epicanthal folds
- o Small head
- o Small upper jaw
- o Smooth groove in upper lip
- o Smooth and thin upper lip

Laboratory Tests:

- MCV normal or slightly increased
- γ-glutamil trasferase serum values (GGT)
- Blood uric acid levels range (> 416 mmol/L; 7mg/dl)
- The Triglyceride level (2mmol/L; 180mg/dl)



Clinical Conditions:

- Hypertension
- Recurrant infectious episodes
- Carcinoma

Environmental Exposure

- Metals are an important group of chemical compounds that are disease agents.
- We are exposed to these agents for occupational reasons or for outdoor pollution.
- Metals are chemicals with a high toxicity: acute and chronic.
- Metals make up a substantial portion of known human carcinogens.
- The most common heavy metals with harmful effects in humans are: lead, mercury, arsenic and cadmium.

Mercury

Humans may be exposed to inorganic and/or organic mercury compounds, both toxic. (Mercurialism or Hydrargyria)

Inorganic

Natural mercury (thermometer, sphygmomanometer, dental amalgams) is a gas easily absorbed by lungs, it crosses the placenta and the hematoencephalic barrier

Mineral salts compose several drugs and medications, plastic and food production. Toxicity occurs through gastrointestinal ingestion or skin contact.

Organic

Methylmercury is used to produce residential paints, cosmetics and drugs but is also contained in seeds and some foods.
Methylmercury is easily absorbed by intestine and skin and directly excreted with urine.
As a liposoluble molecule it crosses the placenta and the hematoencephalic barrier.

Biomethylation

Mercury can be methylated by aquatic microrganisms that are subsequently ingested by herbivorous fish.

$$Hg^{2+} \rightarrow CH_3Hg^{+} \rightarrow (CH_3)_2Hg$$

inorganic mercury methylmercury dimethylmercury

These will be ingested by the carnivorous fish, thus entering the Food Chain

Methylmercury and dimethylmercury are partially soluble in water and fast absorbed becaming stable.

For every trophic level excretion is lower than assumption. These represent an example of bioaccumulation of a toxic chemical compound.

Target organs of inorganic mercury toxicity in man

Acute poisononing by inorganic mercury can affect gastrointestinal system being corrosive on mucosa barrier thus causing: nausea, abdominal pain followed by tenesmus and intestinal mucosa necrosis.

Principal target of inorganic mercury toxicity is kidney.
Main consequences:

- **Acute tubular necrosis**
- **Renal failure**

Chronic poisonong causes nephrosic syndrome with proteinuria with hypoalbuminemia.

Targets of the toxic effect of organic mercury

Acute and chronic poisoning cannot be distiguished.

Organic Mercury is neurotoxic.

An example: Minamata disease.

Characterized by parestesia, ataxia, dysartria, deafness and narrow visual field.

Dimethylmercury is more toxic than methylmercury leading to heavy neurotoxic effects, sometimes fatal.

Chromosomal abnormalities are associated to elevated blood levels of methylmercury.

<u>Prenatal</u>

Exposure during pregnancy causes neurotoxic effect on fetus.

(cerebral damage, mental retardation and intrauterine death)

<u>Postnatal</u>

Paresthesia, vision problems, uditive and of the speech, memory loss, ataxia, erethism.

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>3.5µg/dl Blood
>150µg/dl Urine

Review Article

Heavy Metal Poisoning and Cardiovascular Disease

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Evidence on the Human Health Effects of Low-Level Methylmercury Exposure

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Limit<0.05mg/Kg

Review

Fish, Mercury, Selenium and Cardiovascular Risk: Current Evidence and Unanswered Questions

Risk factor for Cardio Vascular Disease (CVD)

Food is an important pathway of Mercury intake throughout the lifespan.

High mercury concentrantions are reported in fish and seefood.

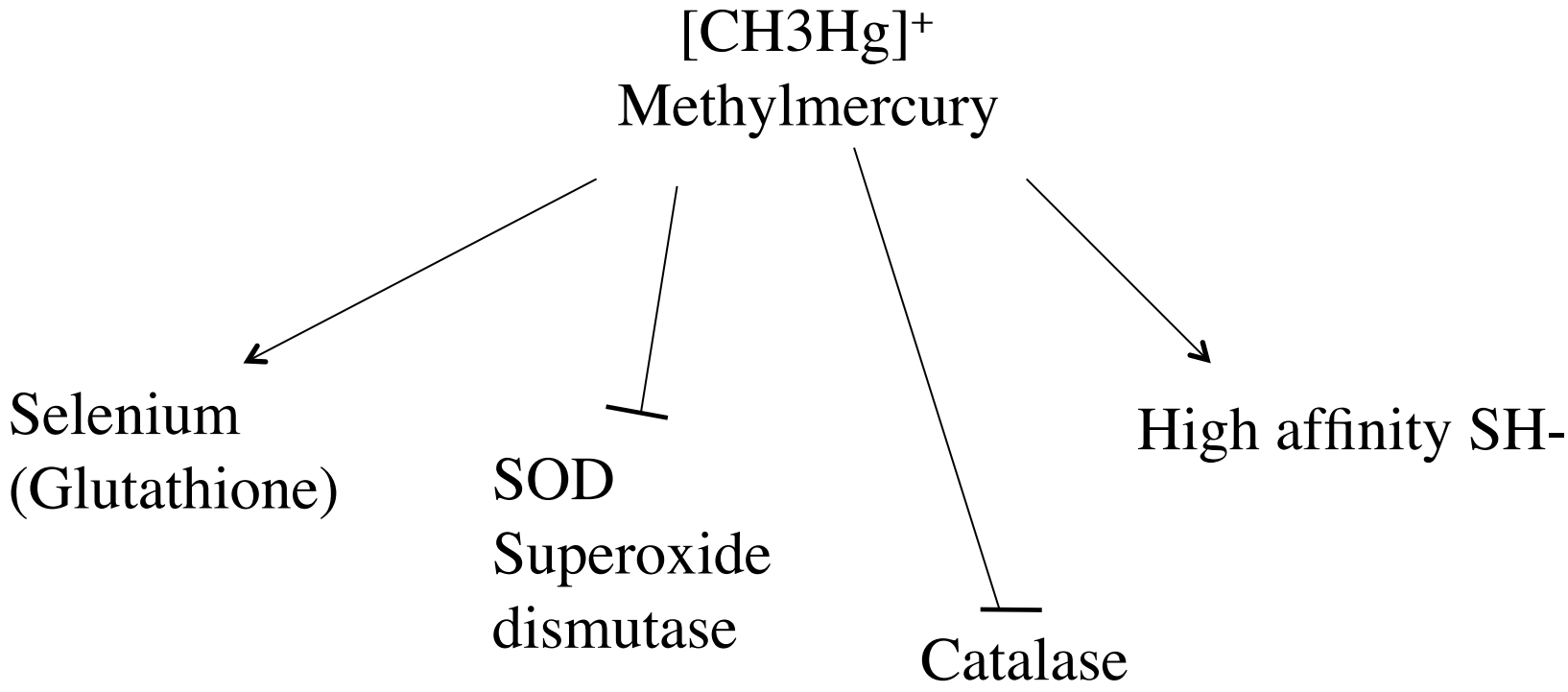
Dietary Methylmercury after absorption readily enters the blooodstream and is distributed to all tissues:

- 5% found in the blood mostly bound to erytrocytes
-10% found in the brain
-less than 1% is excreted/day

Methylmercury almost exclusively bound to the sulfur atom of thiol ligands, antioxidant able to prevent lipid peroxidation.

High mercury content in hair has been associated with increased progression of Atheroclerosis and risk of CVD.

Molecular targets of Methylmercury



Mercury effects

Table 1. Experimentally-observed effects of mercury which may increase CVD risk.

Systemic Effects
Promotion of free radicals and reactive oxygen species
Inhibition of antioxidant systems (glutathione peroxidase, catalase, superoxide dismutase)
Increased lipid (e.g., LDL cholesterol) peroxidation
Promotion of blood coagulation (clotting)
Inhibition of endothelial cell migration
Direct Cardiovascular Effects
Reduction in myocardial contractile force
Increased calcium release from myocardial sarcoplasmic reticulum
Reduction in left ventricular myosin ATPase activity
Decreased heart rate variability and increased blood pressure

Int. J. Environ. Res. Public Health ***2009, 6, 1894-1916; doi:10.3390/ijerph6061894***

Conclusions

Heavy metals are suspected of inducing pathophysiological changes relevant to atherogenic events including increased oxidative stress, inflammatory response, and coagulation activity.

Nevertheless, the combination with susceptible genetic background and dietary elements along with evironmental co-exposure to heavy metals may explain some aspects of their cardiovascular effects possibly contributing to the multifactorial CVD.