Effects of tobacco.
Injury by drugs and drugs of abuse.
Effects of alcohol.
Obesity.

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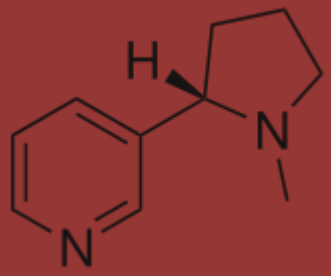
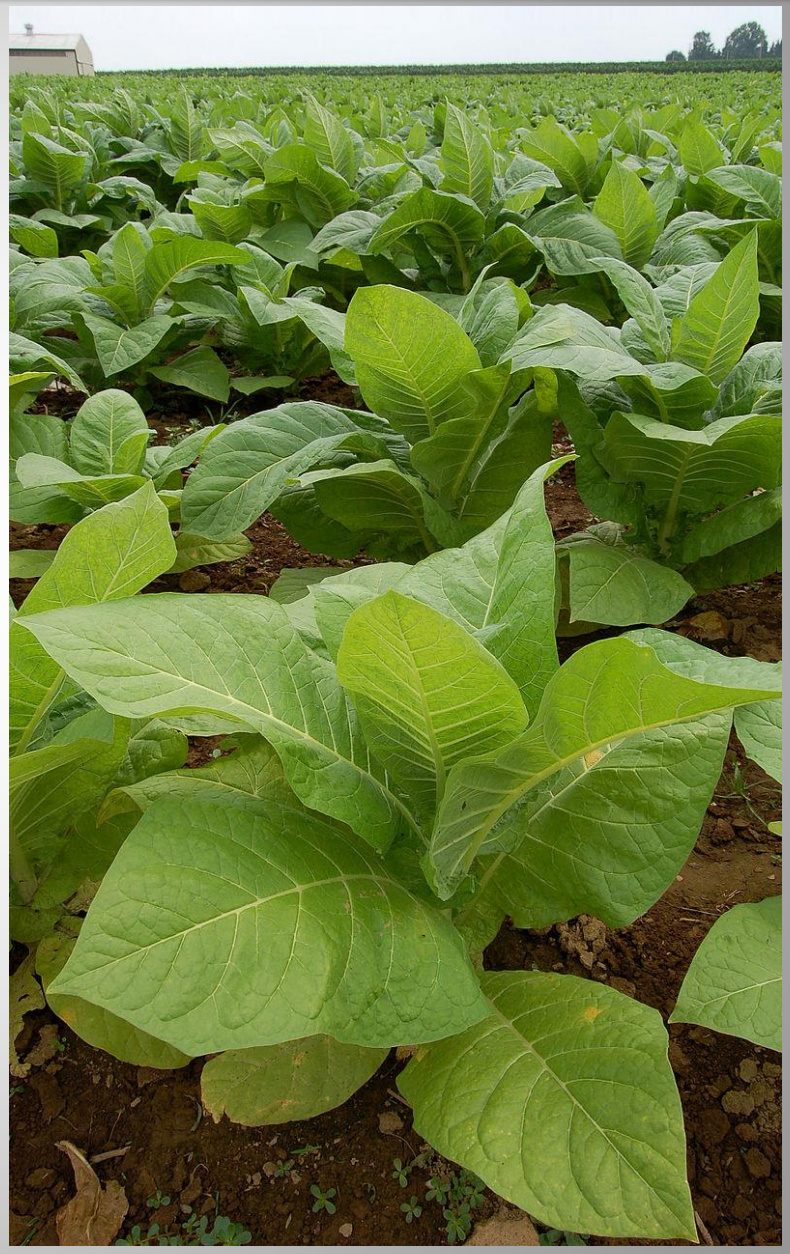
Effects of Tobacco

- **Tobacco**
  - *Nicotiana tabacum*
  - Alkaloid nicotine: parasymathomimetic stimulant
  - Dried tobacco leaves are mainly used for smoking in
    - Cigarettes
    - Cigars
    - Pipe
    - Flavored shisha tobacco
  - Not smoking consumed by using
    - Snuff
    - Snus
    - Chewing tobacco
    - Dipping tobacco



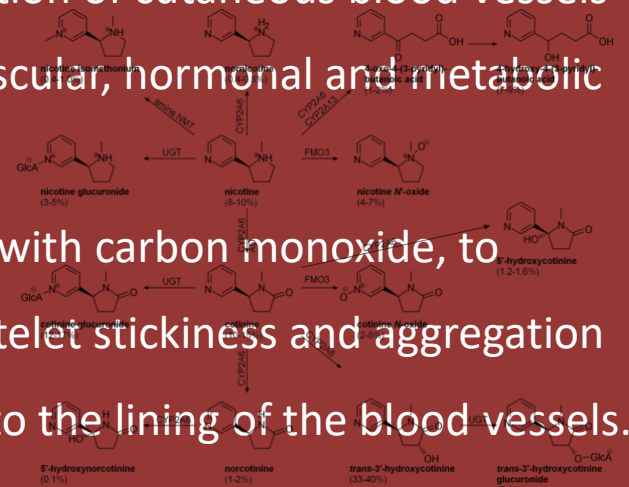


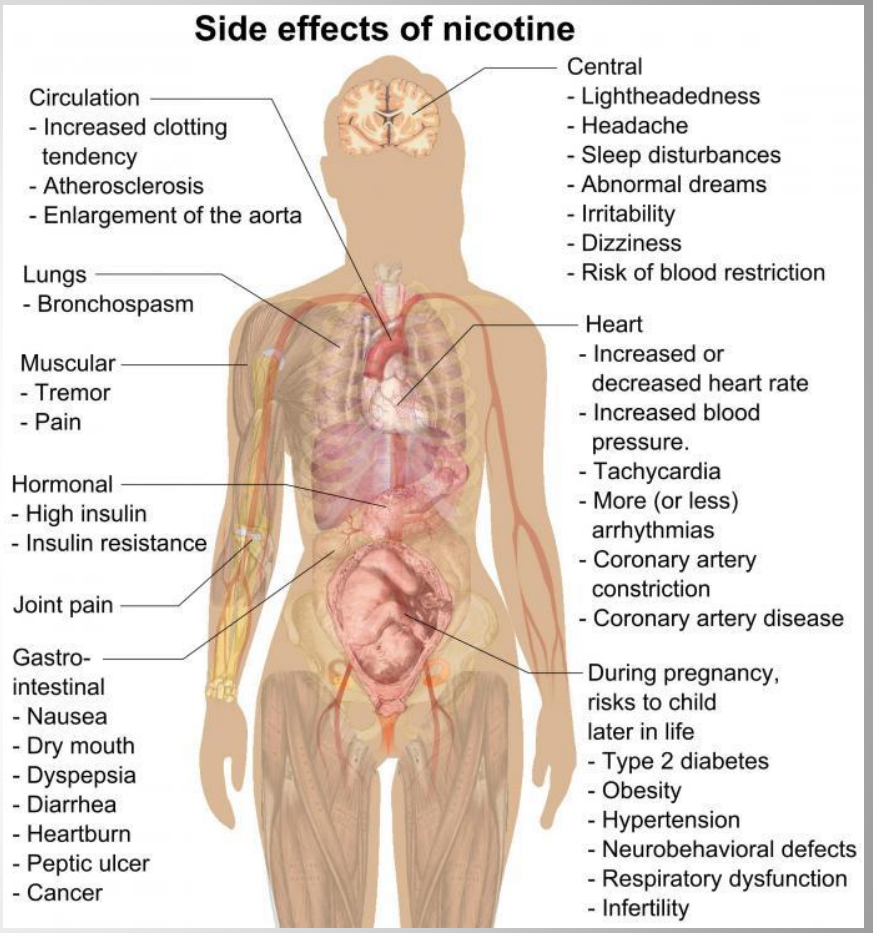
Effects of Tobacco

- **Using tobacco**
  - Smoking is the most common method of consuming tobacco
  - Tobacco is the most common substance smoked.
  - Tobacco smoking is the practice of burning tobacco and inhaling the smoke.
  - The resulting smoke is then inhaled and the active substances absorbed through the alveoli in the lungs or the oral mucosa.
  - Tobacco pipe and cigars: taking tobacco smoke into the mouth, and then releasing it without inhaling.

Effects of Tobacco

- **Nicotine**
- Acute-acting pharmacological agent
- Causes addiction among smokers.
- Immediate physiological effects
  - increased heart rate and blood pressure
  - constriction of cutaneous blood vessels
  - and muscular, hormonal and metabolic effects.
- Combination with carbon monoxide, to increased platelet stickiness and aggregation and damage to the lining of the blood vessels.
- No direct carcinogenic activity itself, it enables the formation of tobacco-specific nitrosamines, which are potent carcinogens



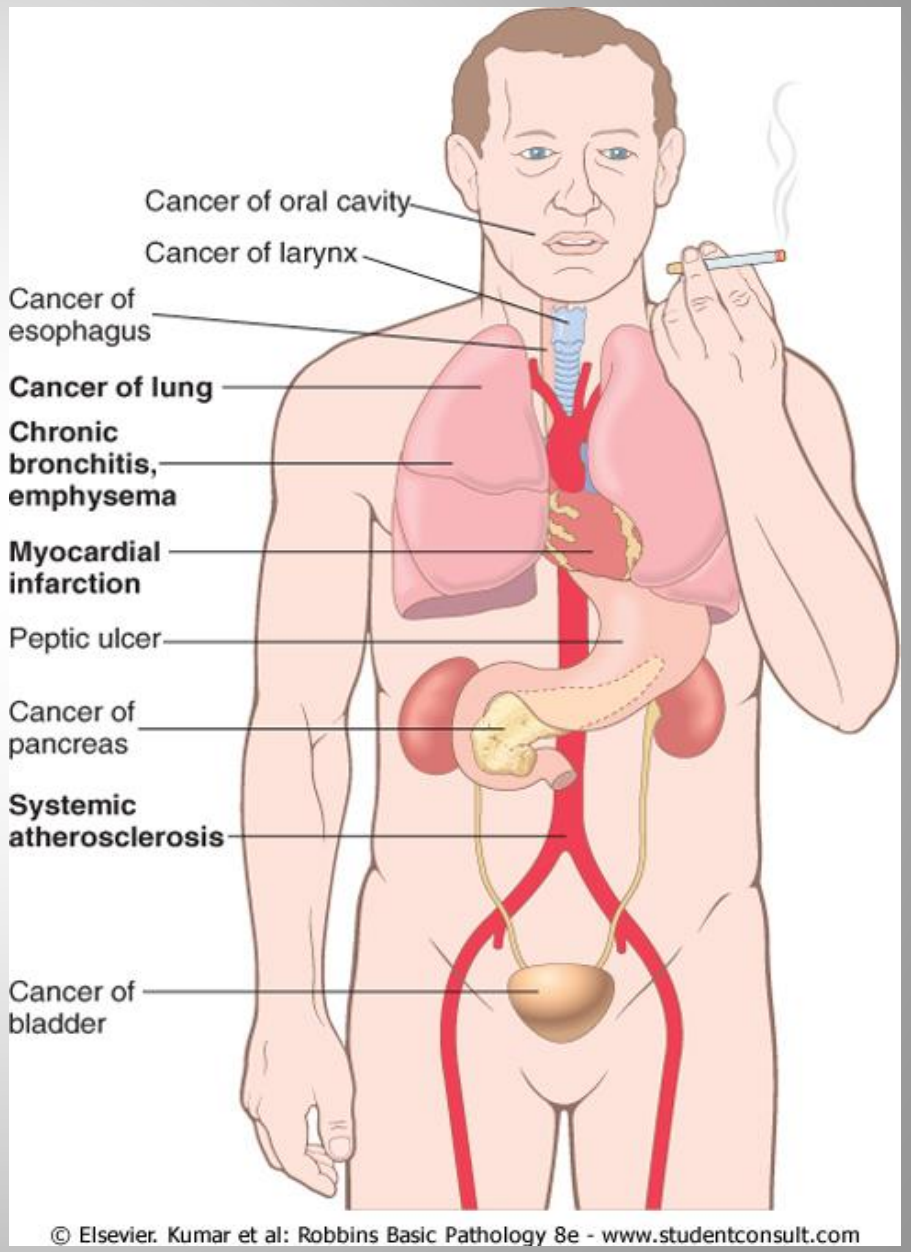


Effects of Tobacco

- **Tobacco smoke**
  - Potentially noxious chemicals in tobacco smoke are more than 4000.
    - Toxic to cilia and irritative to mucosa
      - Formaldehyde
      - Oxides of nitrogen
      - Hydrogen cyanide
    - Impared oxigen transport
      - CO
    - Carcinogenesis
      - Tar, PAH, Benzopyrene, Nitrosamine, Metals-niccel, arsenic, cadmium, chromium, lead
    - Tumor promotion
      - Phenol

Effects of Tobacco

- **Tobacco induced diseases**
  - Direct irritant effect on the tracheobronchial mucosa
  - Carcinogenesis
  - Atherosclerosis and its major complication, myocardial infarction
  - Maternal smoking increases the risk of spontaneous abortions and preterm births and results in intrauterine growth retardation
  - Passive smoke inhalation



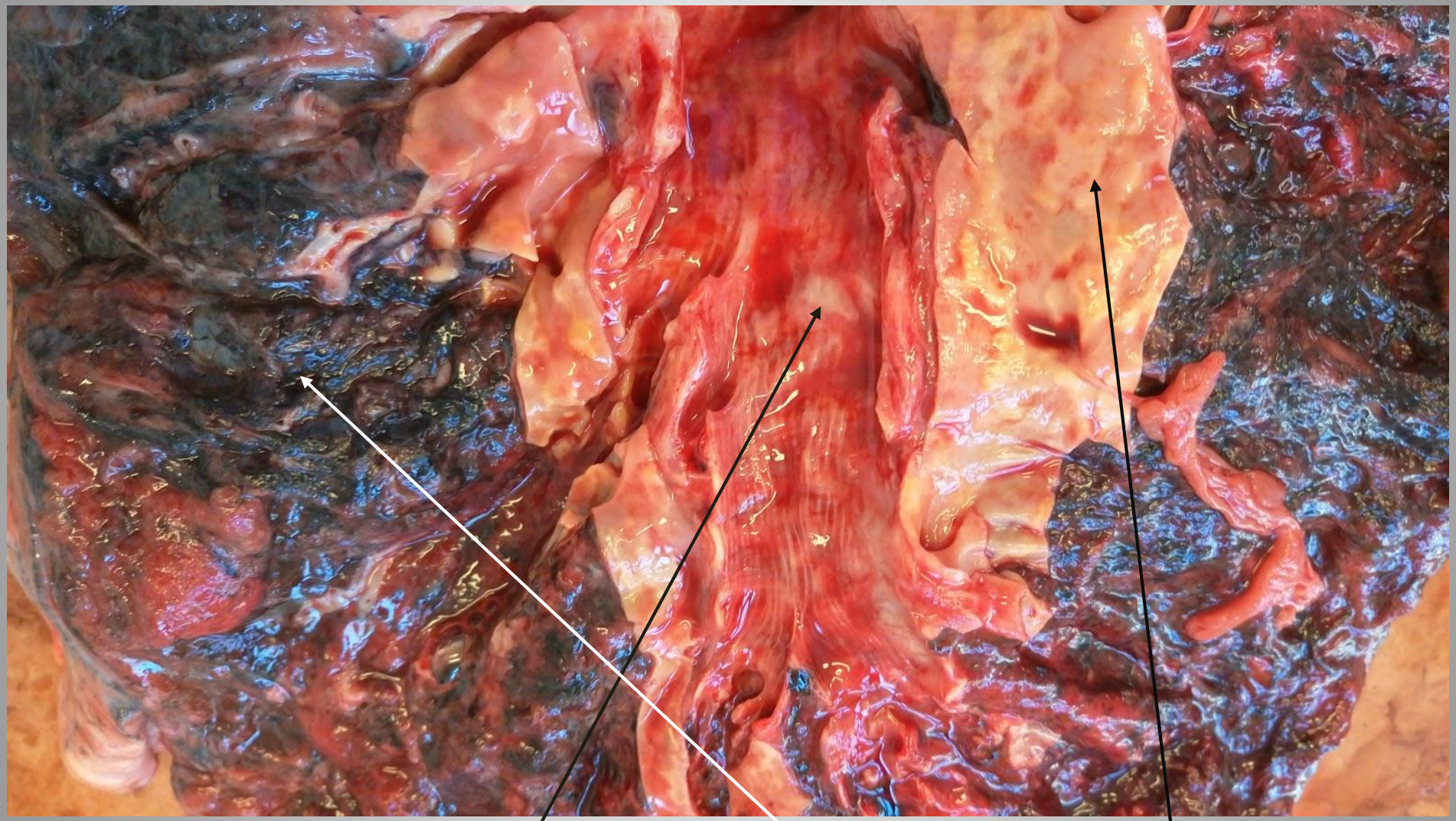
Effects of Tobacco

Non-smoker adult lungs

Effects of ALCOHOL

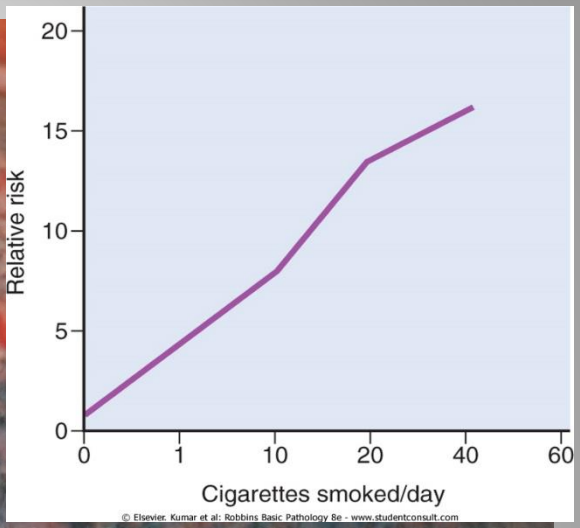
Heavy smoker’s lung

Effects of Tobacco



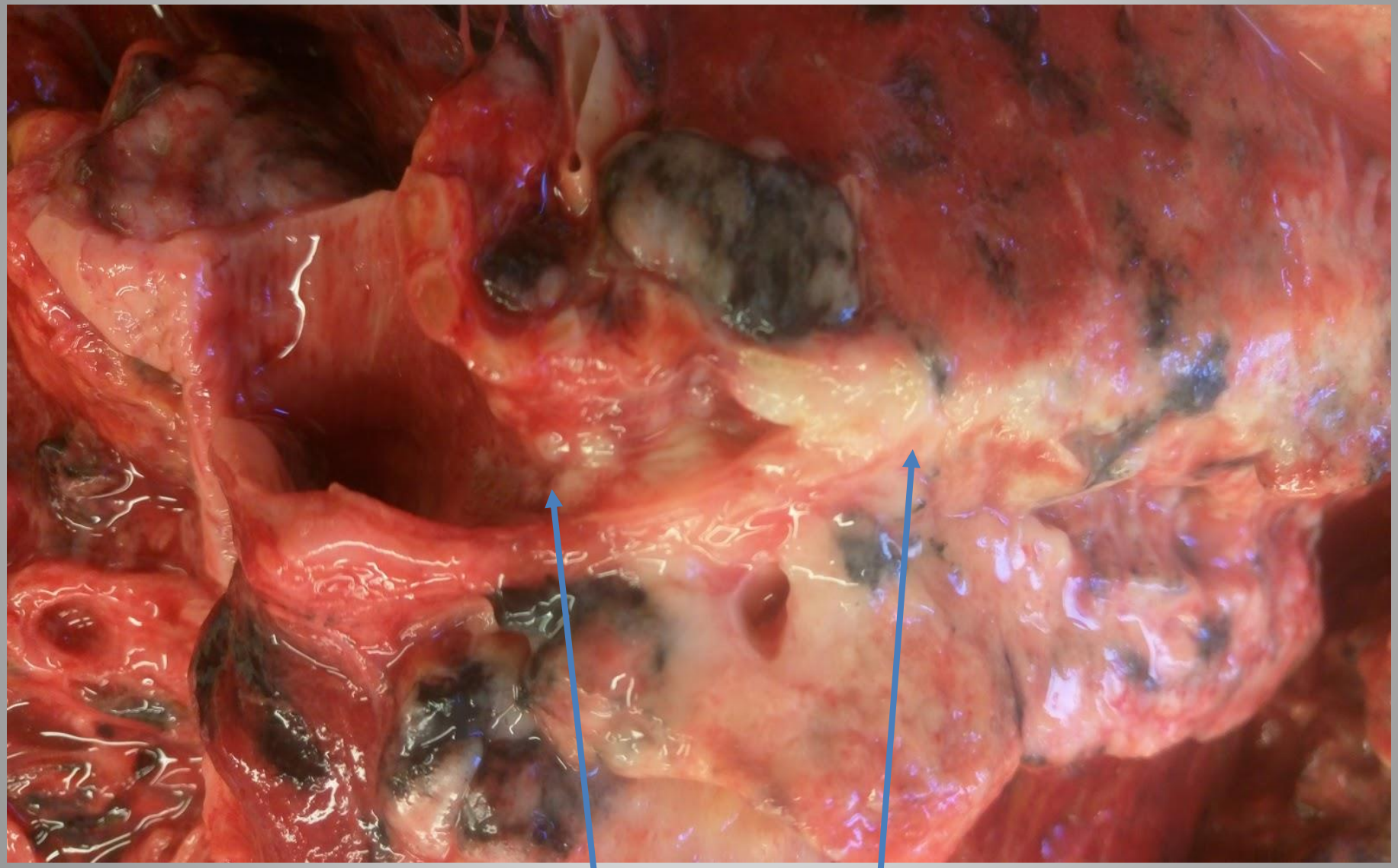
Chronic bronchitis with acute exacerbation, anthracofibrosis and pulmonary sclerosis

Effects of Tobacco



Lung cancer and pleural infiltration

Effects of Tobacco

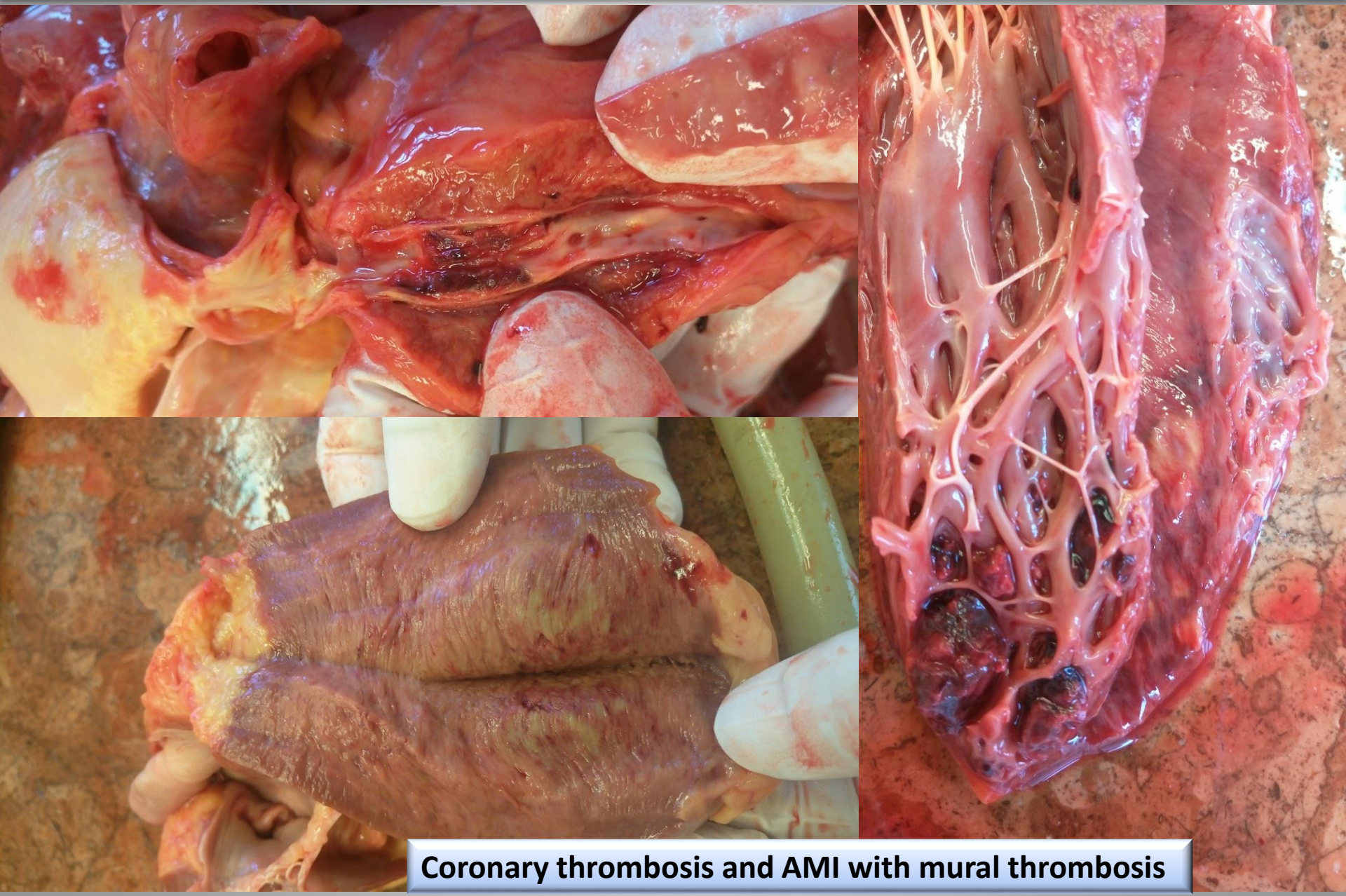


Bronchial cancer origin and its local infiltration

Effects of Tobacco

Severe general atherosclerosis

Effects of Tobacco

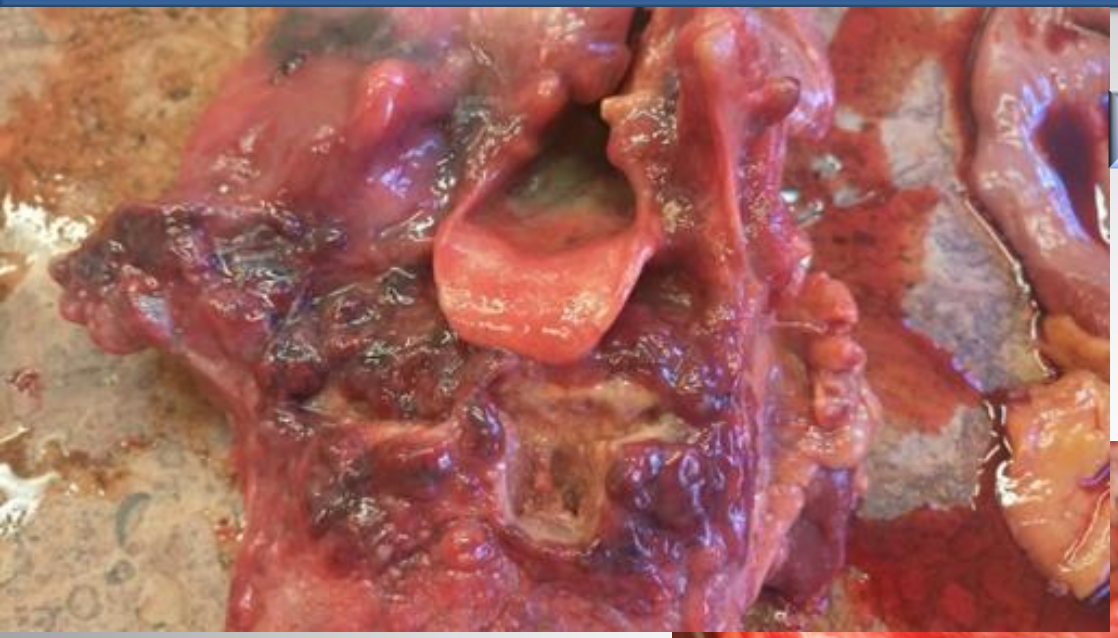


Coronary thrombosis and AMI with mural thrombosis

Effects of Tobacco

Lip cancer

Effects of Tobacco



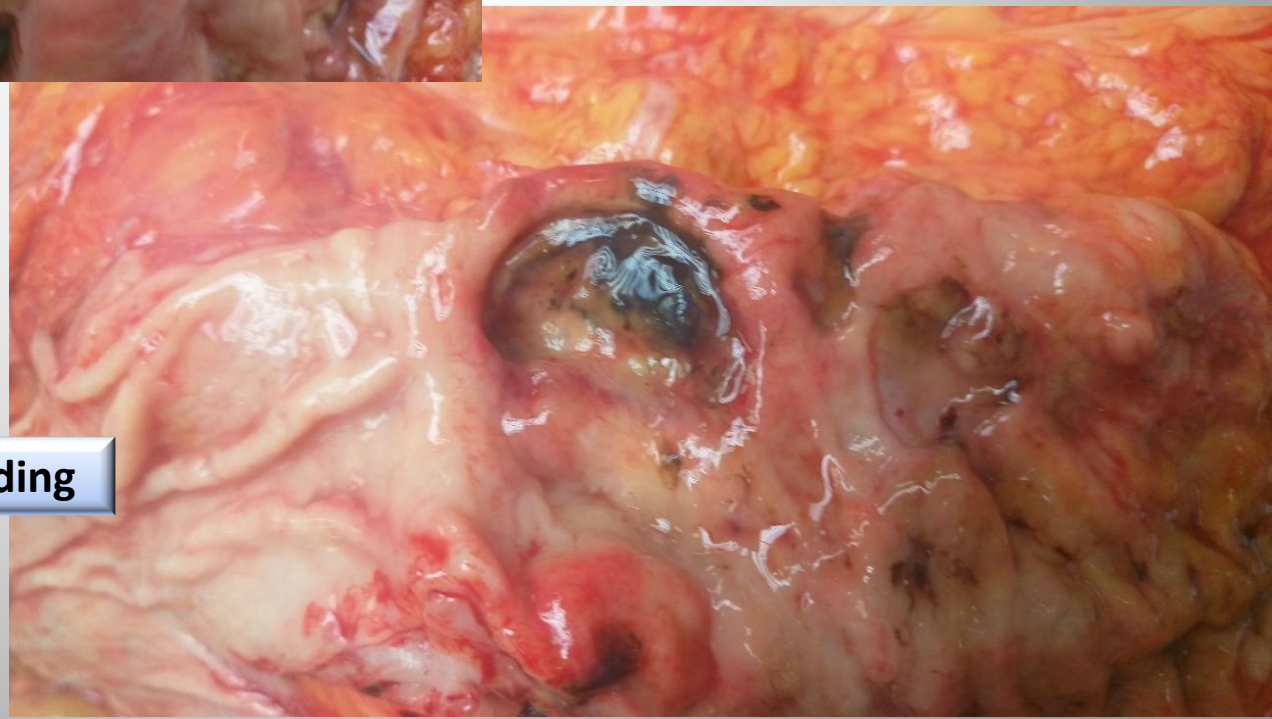
Oral cavity cancer

Esophagus cancer

Effects of Tobacco

Effects of Tobacco

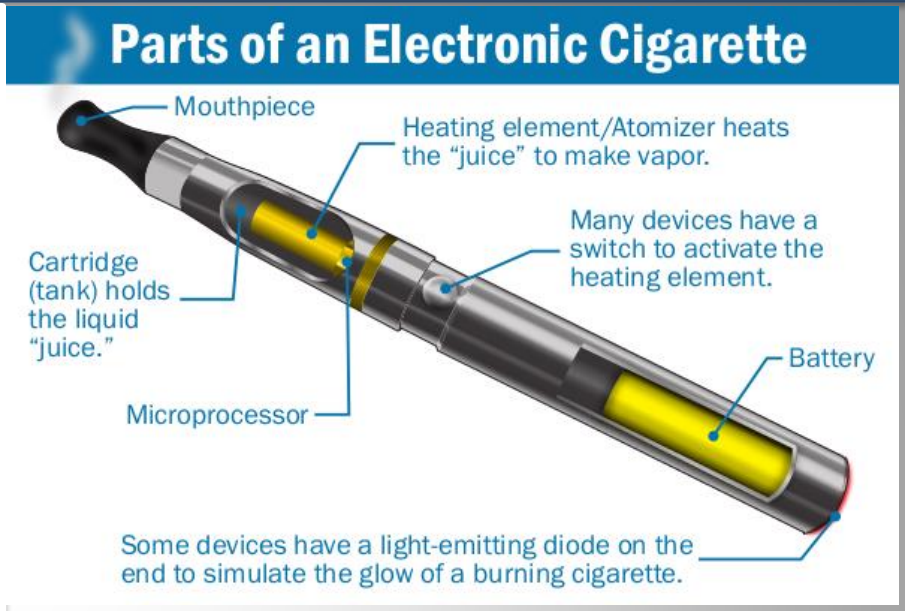
Chronic peptic gastric ulcer



Chronic gastric ulcer with bleeding

Effects of Tobacco

- **Electronic cigarette**
  - Electronic device that tries to create the feeling of tobacco smokeing
  - Heating a liquid to generate an aerosol, commonly called a "vapor", that the user inhales.
  - The liquid made of **nicotine, propylene glicol, glycerine** and **flavorings**.
  - Can lead to nicotine addiction
  - The aerosol can contain toxicants and traces of heavy metals
  - Health risks are uncertain, but safer than tabacco cigarettes



Effects of Tobacco

- **Waterpipe (WP) Figure 1.**
  - Not a safe alternative to cigarette smoking
  - A typical 1-hour long WP smoking session inhaling 100-200 times the volume of smoke inhaled with a single cigarette
  - Contains high level of toxic compounds, including carbon monoxide, heavy metals and cancer-causing chemicals
  - Sharing a WP mounthpiece is a risk of transmission of tuberculosis or hepatitis
  - No proof that any device or accessory can make WP smoking safer

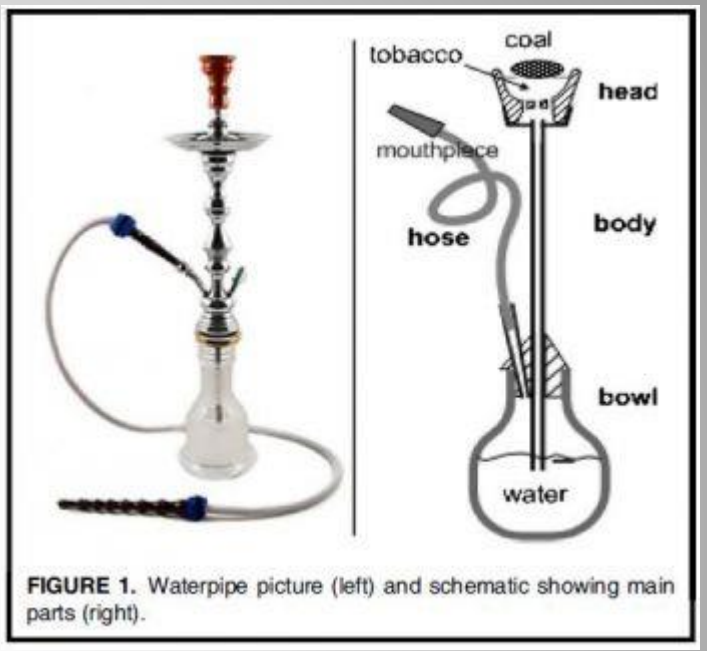
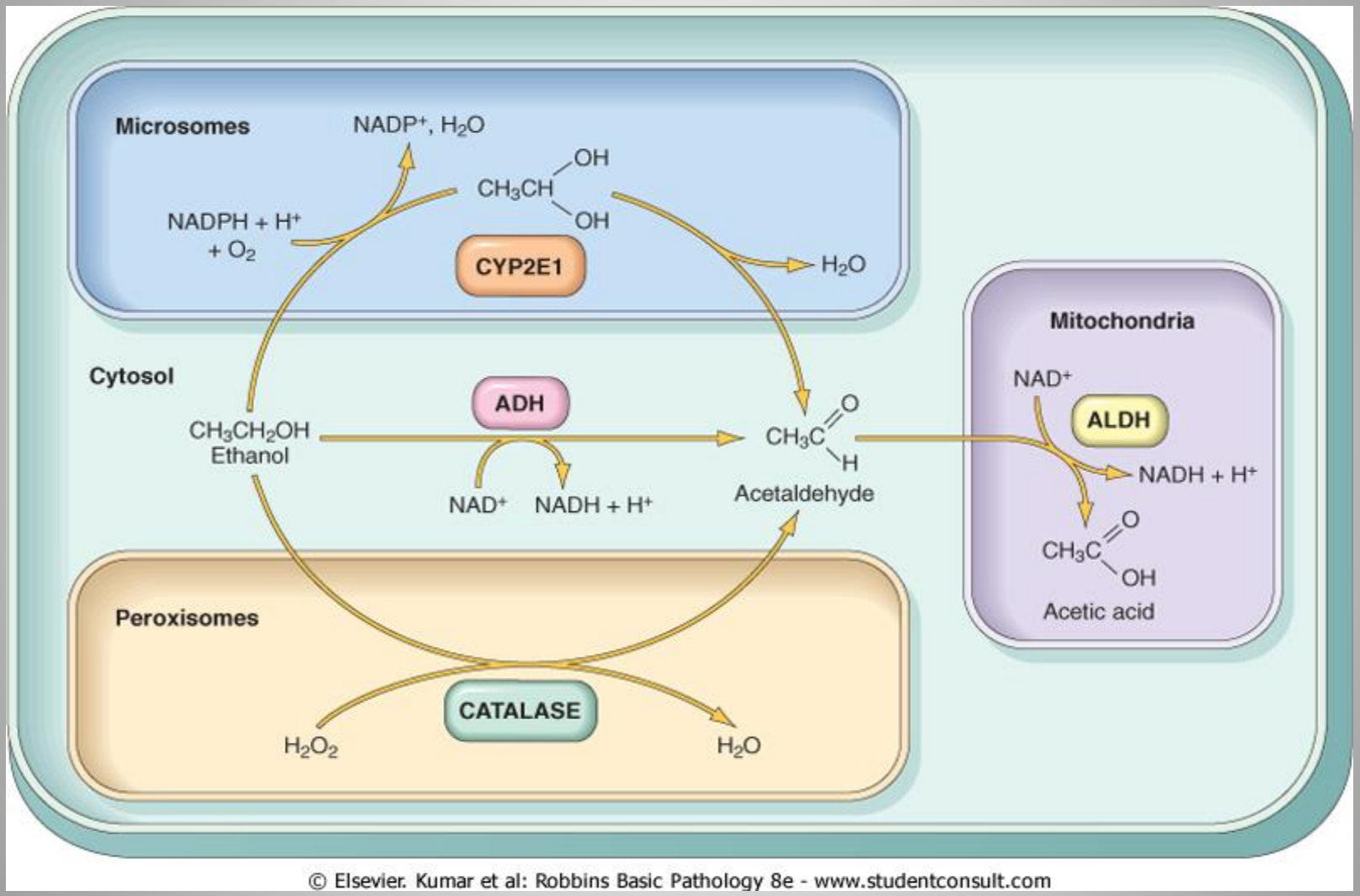


FIGURE 1. Waterpipe picture (left) and schematic showing main parts (right).

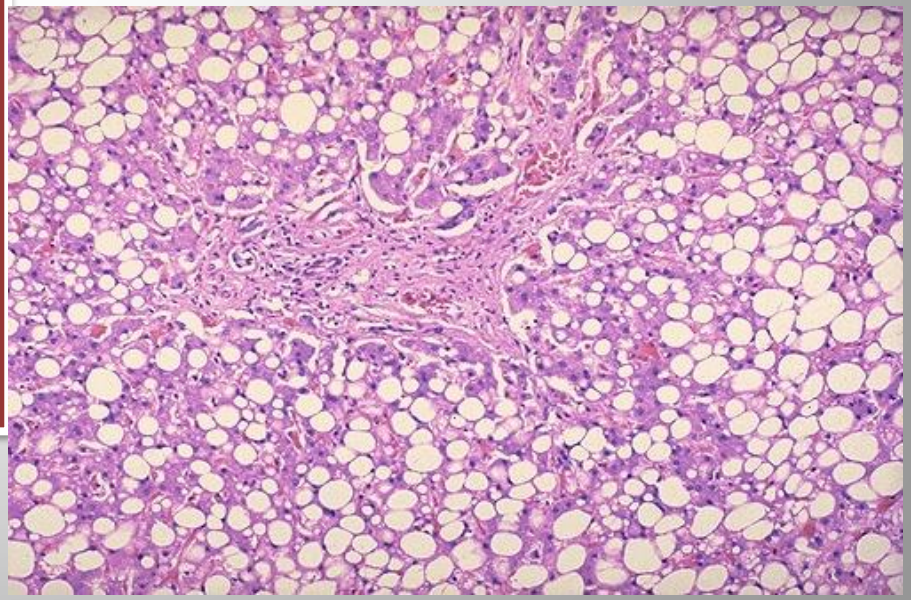
Effects of ALCOHOL



Effects of ALCOHOL

- **Toxic effects result from ethanol metabolism**
  - decrease in nicotinamide adenine dinucleotide (NAD+) and an increase in NADH
  - NAD+ is required for fatty acid oxidation in the liver. Its deficiency is a main cause of **fat accumulation** in the liver of alcoholics.
  - **Acetaldehyde toxicity**
    - Acute effects of alcohol
  - **Endotoxin release from GI bacteria**
    - Stimulates TNF release of Kuppfer cells
  - **ROS generation**
    - Lipid peroxidation of membrabnes

Fatty change of liver



Effects of ALCOHOL

Chronic alcoholism

- **Liver**
  - Fatty change
  - Alcoholic hepatitis
  - Fibrosis
  - Cirrhosis
  - Hepatocellular carcinoma (HCC)
- **GI**
  - Gastritis
  - Bleeding
    - Gastric ulcer
    - Esophageal varices
- **Pancreas**
  - Acute pancreatitis
  - Chronic pancreatitis

Chronic alcoholism

- **Cardiovascular effects**
  - Alcoholoic cardiomyopathy (DCM)
  - Decreased levels of HDL
  - Hypertension
- **Neurologic effects**
  - Thiamine deficiency
  - Peripheral neuropathies
  - Wernicke-Korsakoff syndrome
- **Malnutrition**
  - Ethanol=empty calories
  - Deficiencies, B vitamins.
- **Effects on fetus**
  - Fetal alcohol syndrome
- **Carcinogenesis**
  - Oral cavity, esophagus, liver, brest

Effects of ALCOHOL

Micronodular liver cirrrhois in chronic alcololic patient

Effects of ALCOHOL

Micronodular liver cirrrhois and liver atrophy in chronic alcololic patient

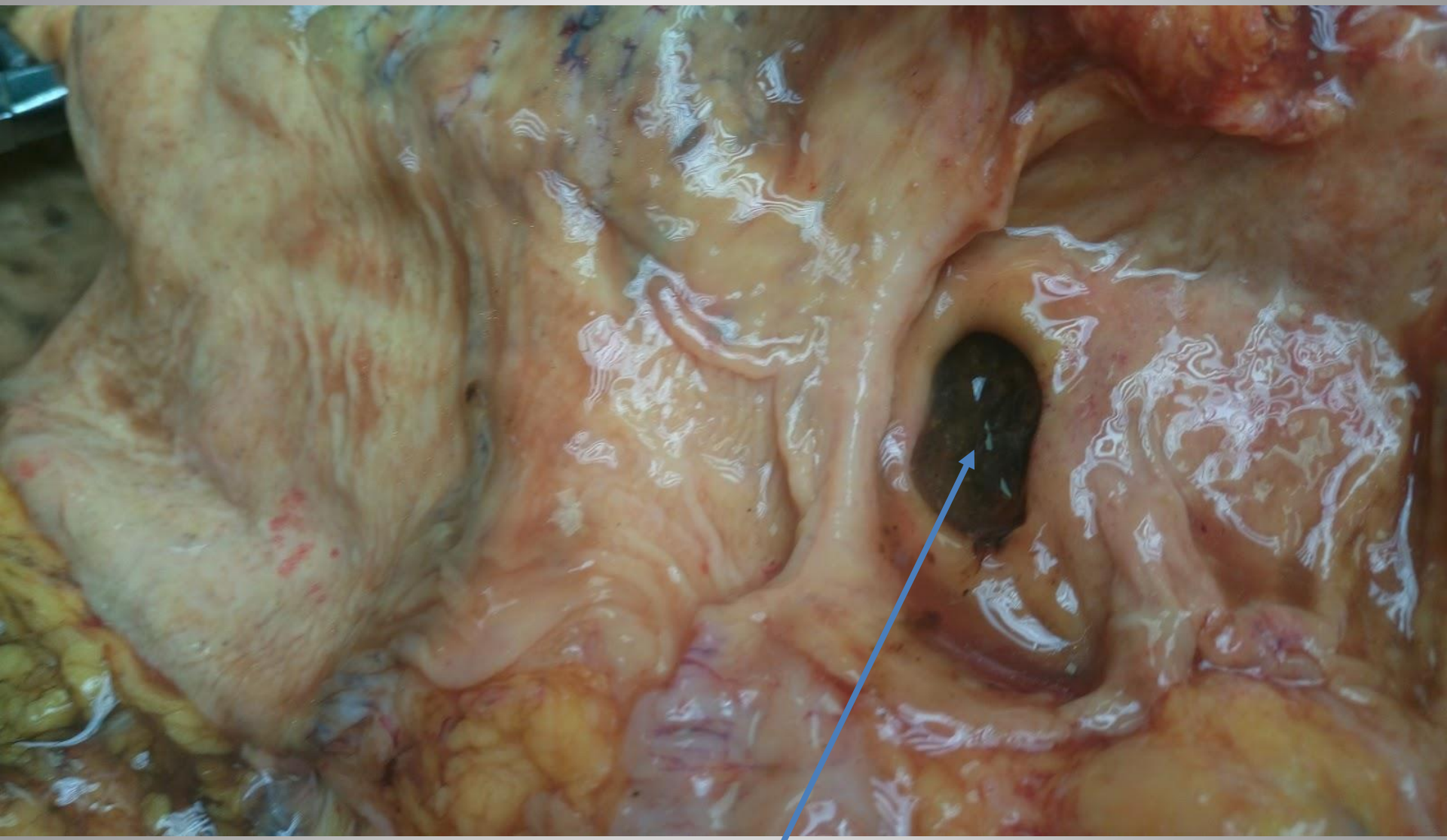
Effects of ALCOHOL

Chronic gastric ulcer

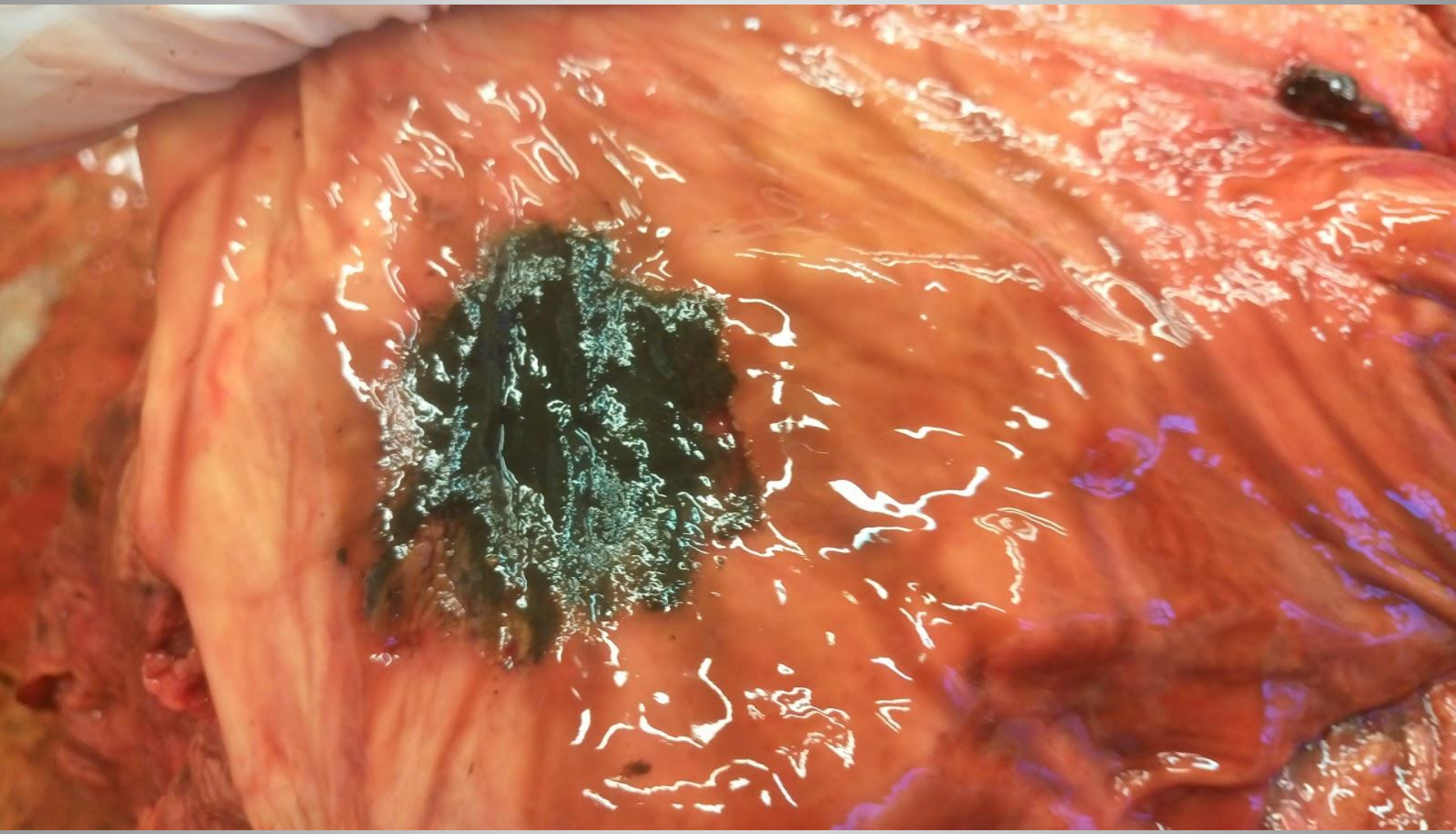
Effects of ALCOHOL

Chronic gastric ulcer's penetration

Effects of ALCOHOL

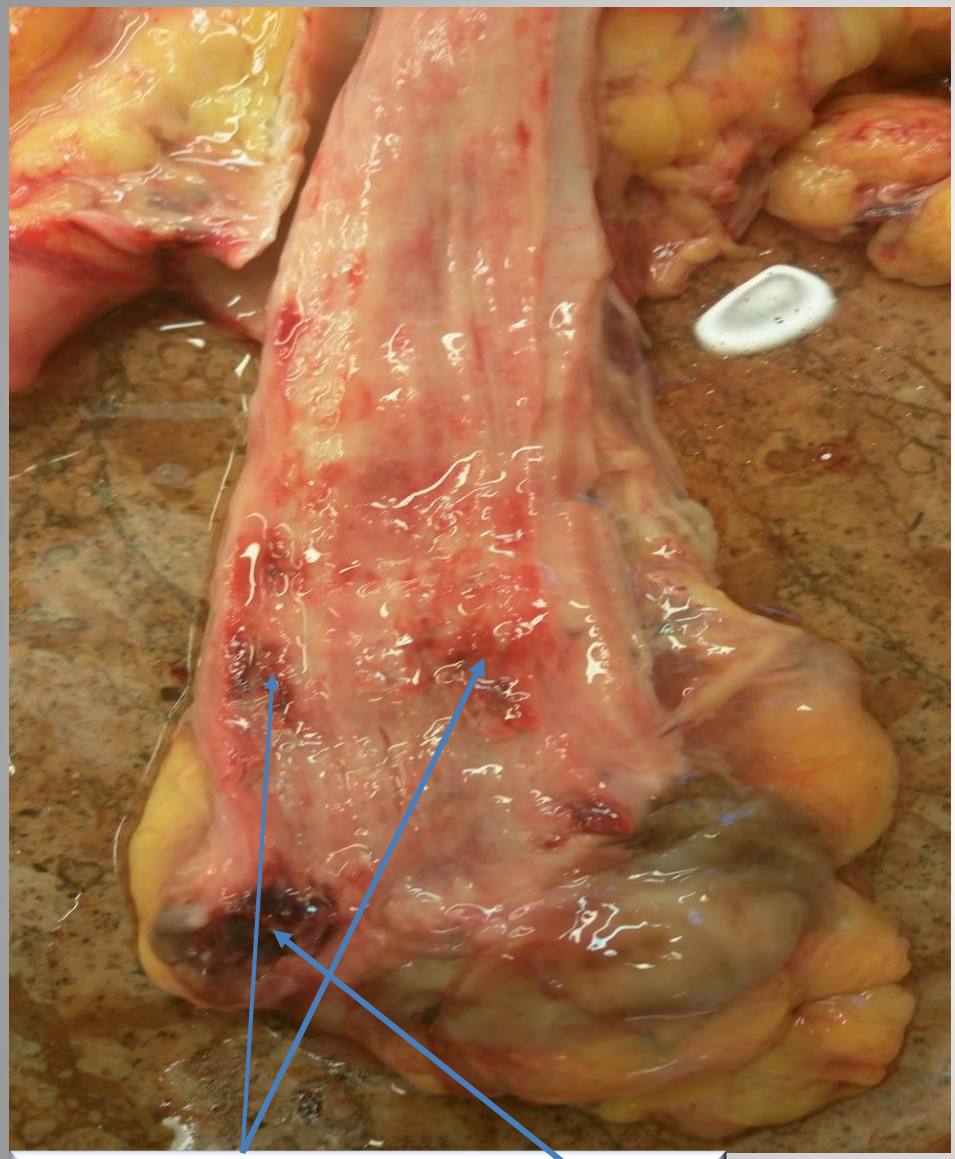


Effects of ALCOHOL



Gastric mucosal bleeding in liver failure patient

Effects of ALCOHOL



Esophageal varices and rupture

GI tract, digested bleeding called „melena”

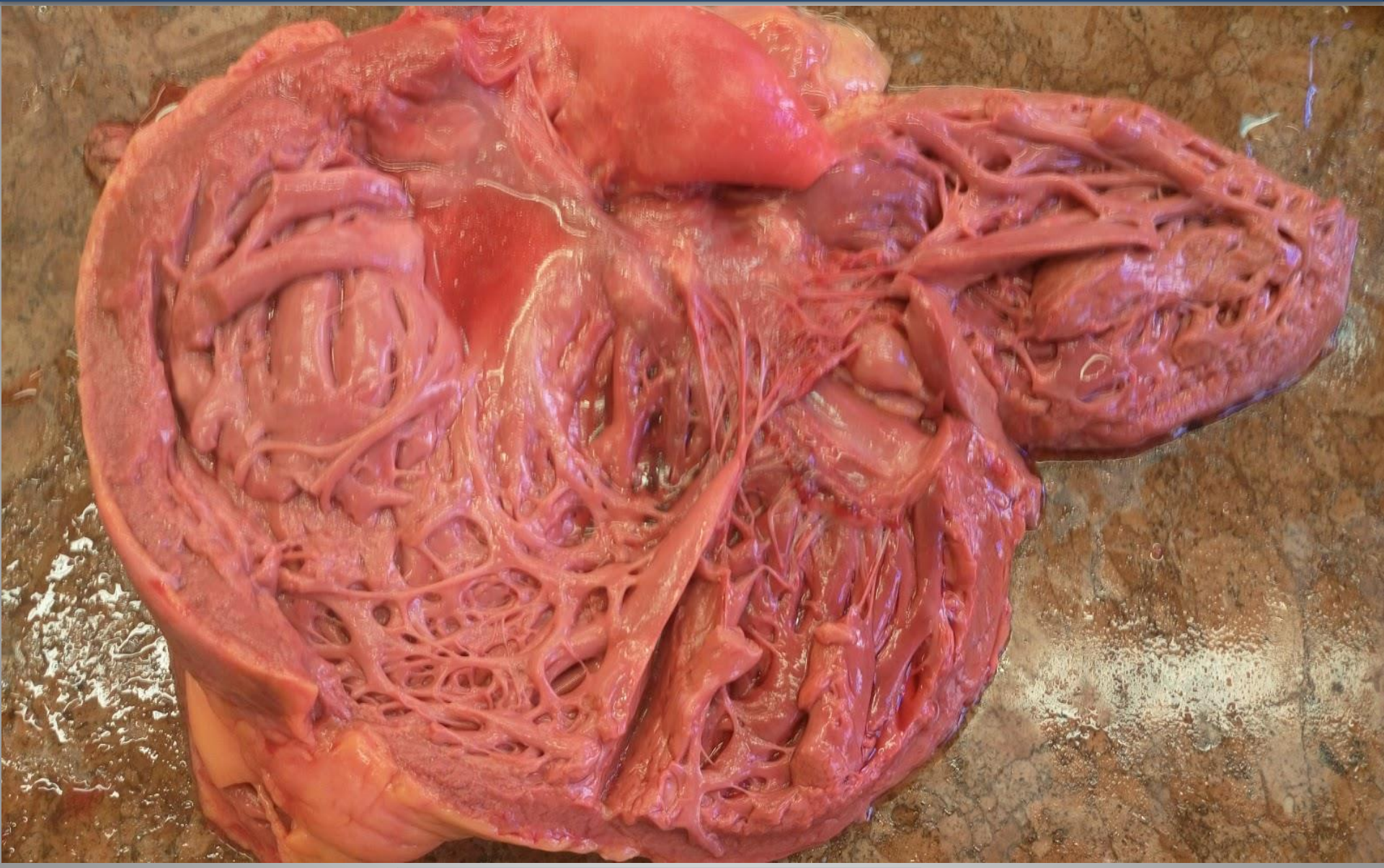
Effects of ALCOHOL

Spontaneous bacterial peritonitis (**SBP**) in chronic alcololic and liver cirhhosis patient

Effects of ALCOHOL

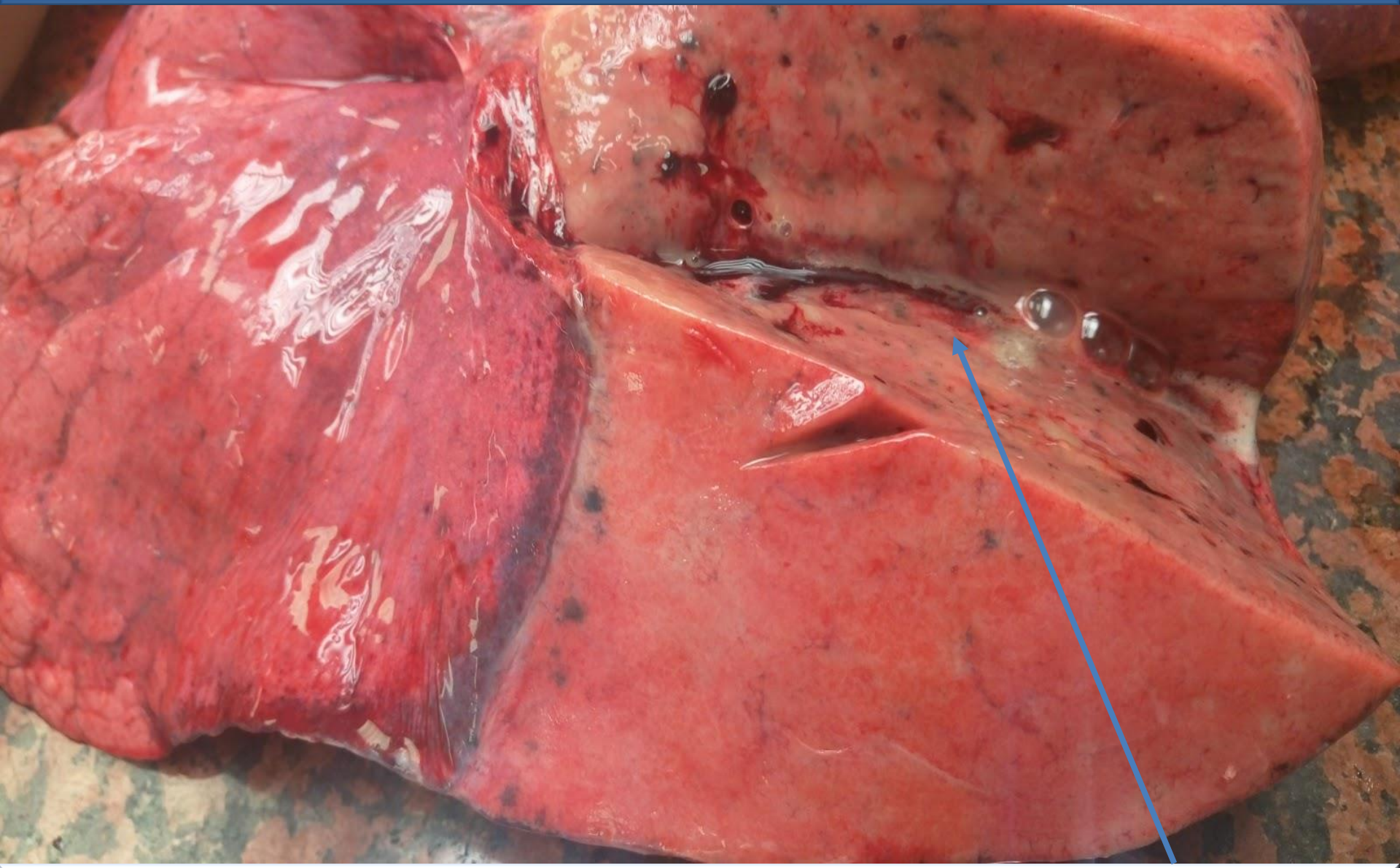
Jaundice (icterus): one typical gross findings of liver failure

Effects of ALCOHOL



Secunder diltative cardiomyopathy

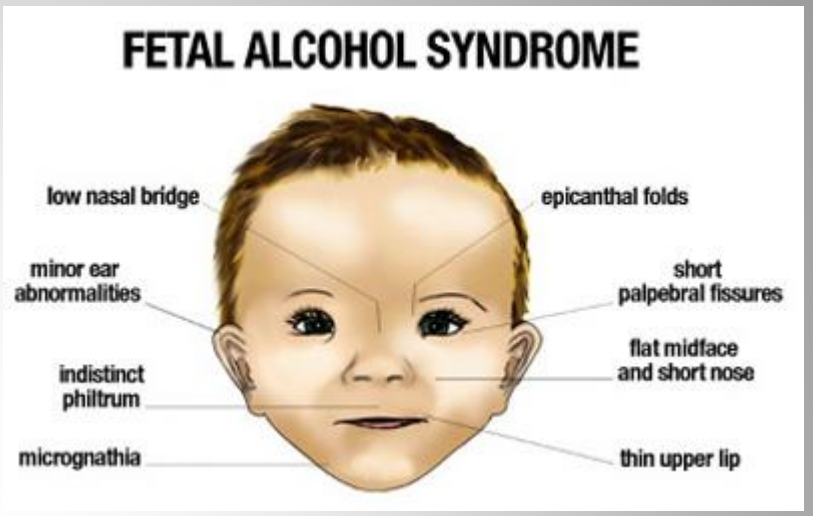
Effects of ALCOHOL



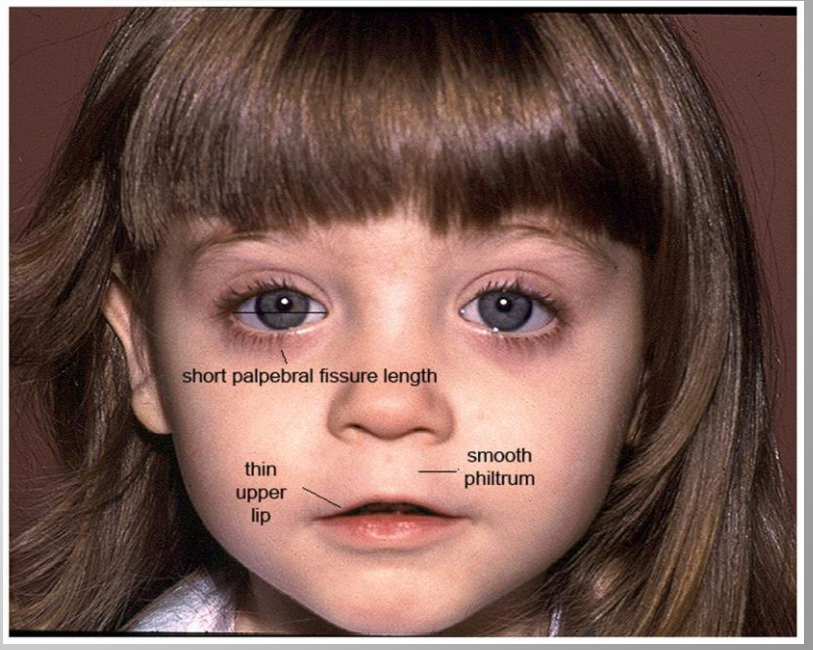
Common intercurrent infection and cause of death in chronic alcololic patient: lobar pneumonia

Effects of ALCOHOL

- Infansts show prenatal and postnatal growth retardation
- facial anomalies
  - microcephaly
  - short palpebral fissures
  - maxillary hypoplasia
  - psychomotor disturbances
  - reduction of mental functions

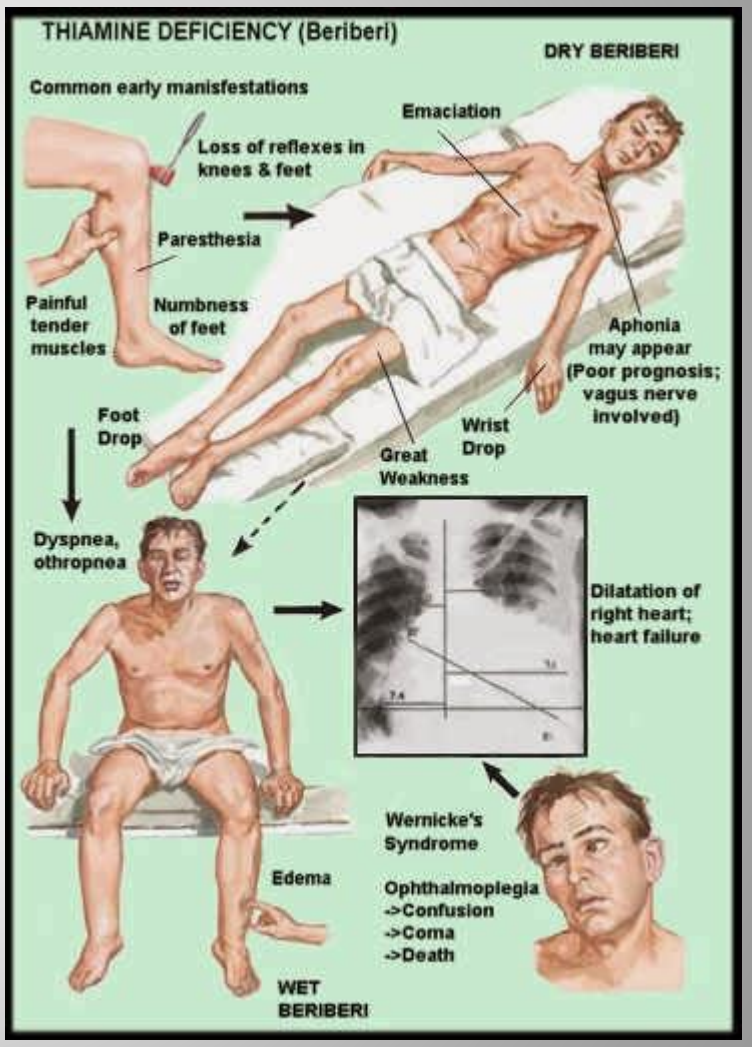


During the first trimester of pregnancy is particularly harmful!



Effects of ALCOHOL

- **Neurologic effect**
  - Thiamine deficiency
  - Wernicke-Korsakoff syndrome
    - Wernicke encephalopathy
      - confusion
      - abnormalities in eye movement
      - ataxia
    - Korsakoff syndrome
      - irreversible profound memory disturbance



INJURY BY THERAPEUTIC DRUGS

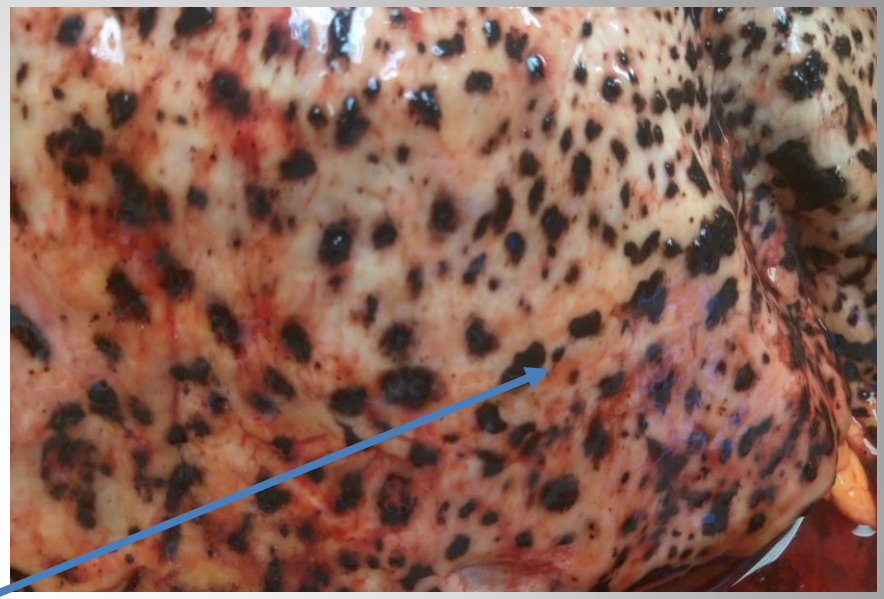
- **Adverse Drug Reaction**
  - 7% to 8% of patients
  - 10% of such reactions prove fatal

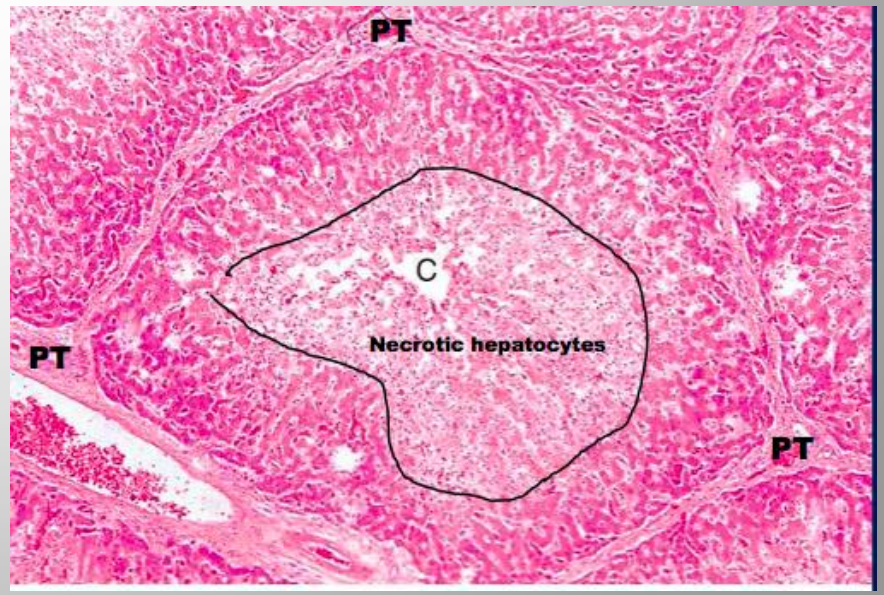
Reaction	Major Offenders
Blood Dyscrasias*	
Granulocytopenia, aplastic anemia, pancytopenia	Antineoplastic agents, immunosuppressives, and chloramphenicol
Hemolytic anemia, thrombocytopenia	Penicillin, methyldopa, quinidine
Cutaneous	
Urticaria, macules, papules, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, abnormal pigmentation	Antineoplastic agents, sulfonamides, hydantoins, some antibiotics, and many other agents
Cardiac	
Arrhythmias	Theophylline, hydantoins
Cardiomyopathy	Doxorubicin, daunorubicin
Renal	
Glomerulonephritis	Penicillamine
Acute tubular necrosis	Aminoglycoside antibiotics, cyclosporin, amphotericin B
Tubulointerstitial disease with papillary necrosis	Phenacetin, salicylates
Pulmonary	
Asthma	Salicylates
Acute pneumonitis	Nitrofurantoin
Interstitial fibrosis	Busulfan, nitrofurantoin, bleomycin
Hepatic	
Fatty change	Tetracycline
Diffuse hepatocellular damage	Halothane, isoniazid, acetominophen
Cholestasis	Chlorpromazine, estrogens, contraceptive agents
Systemic	
Anaphylaxis	Penicillin
Lupus erythematosus syndrome (drug-induced lupus)	Hydralazine, procainamide
Central Nervous System	
Tinnitus and dizziness	Salicylates
Acute dystonic reactions and parkinsonian syndrome	Phenothiazine antipsychotics
Respiratory depression	Sedatives

INJURY BY THERAPEUTIC DRUGS

- **Aspirin overdose**
  - Accidental or suicide
  - Resp.alkalosis and metabolic acidosis
  - Chronic toxicity (salicysm): >3 mg daily
  - headache, dizziness, ringing in the ears (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, and diarrhea and:
  - **acute erosive gastritis**

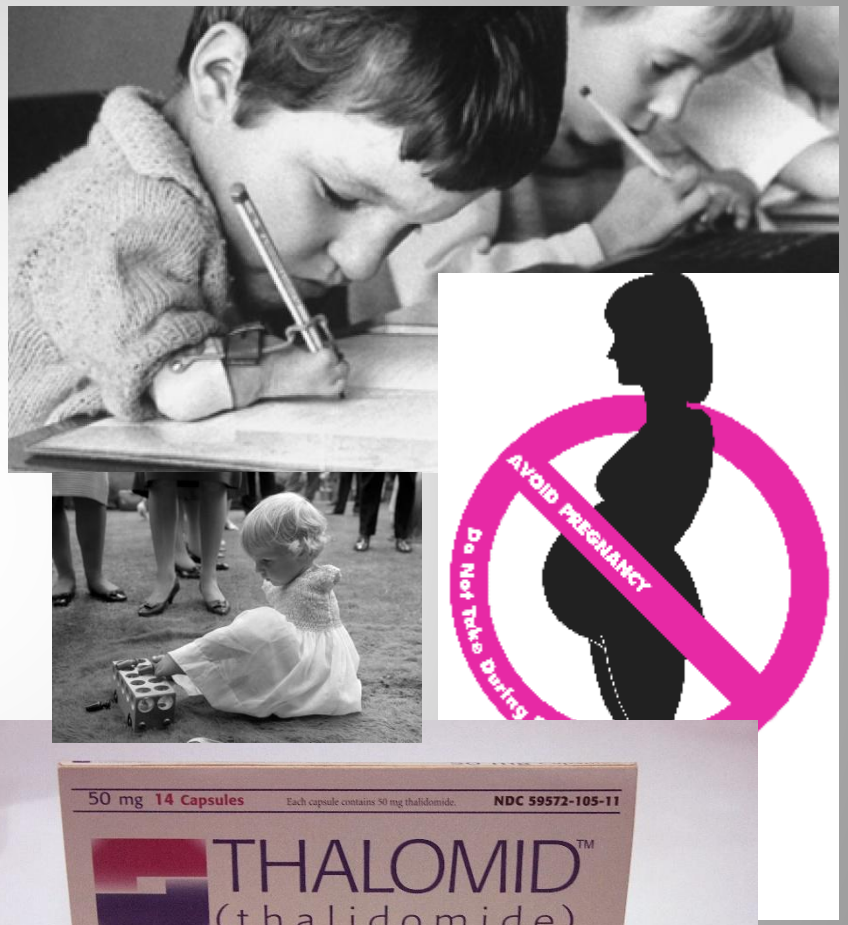
- **Acetaminophen overdose**
  - centriloblar hepatic necrosis
  - Liver failure - transplantation



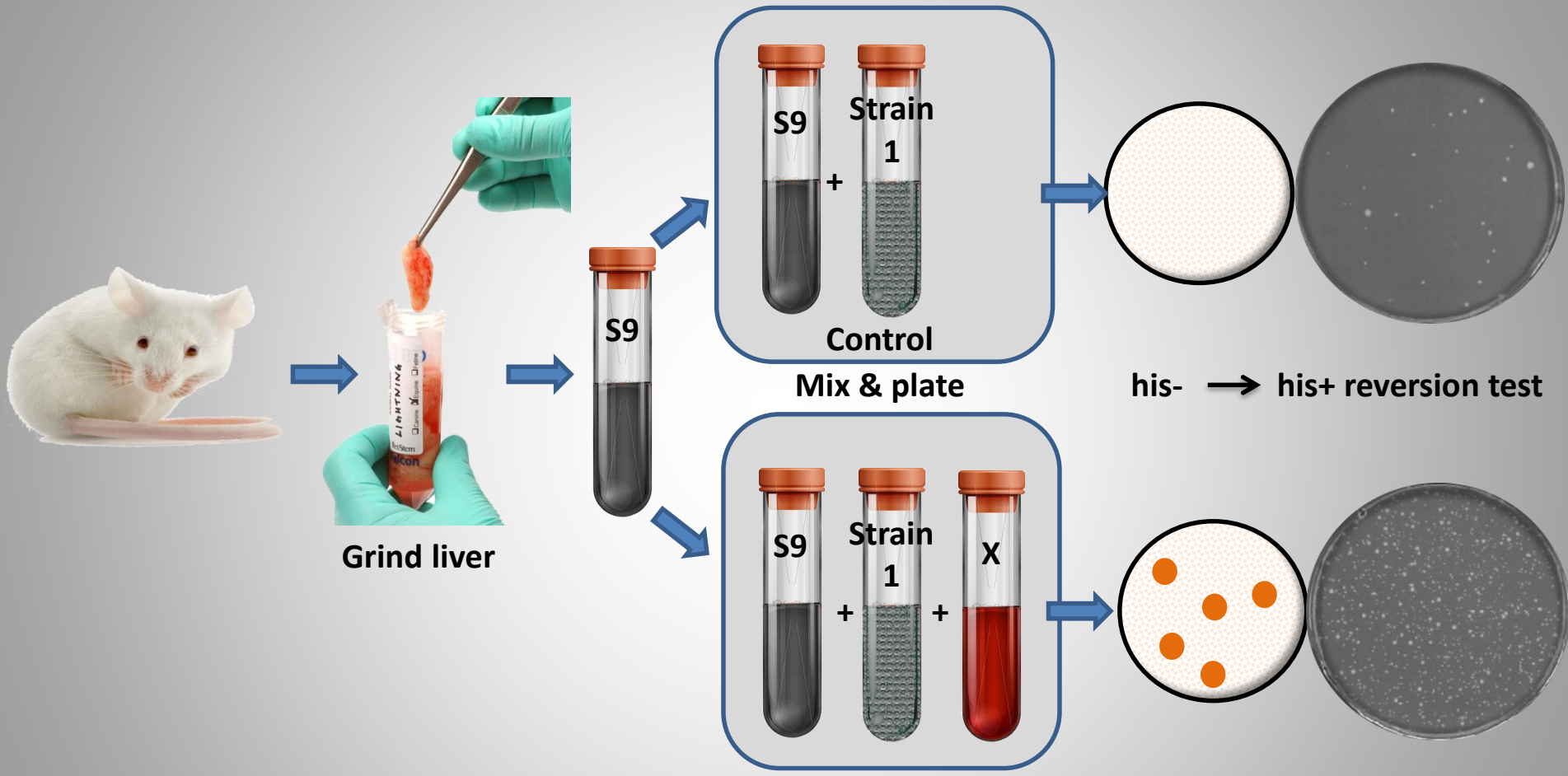


INJURY BY THERAPEUTIC DRUGS

- **Thalidomid (CONTERGAN)**
  - 01.10.1957
  - It was used against nausea and to alleviate morning sickness in pregnant women
  - 10,000 cases were reported of infants with *phocomelia*
  - The negative effects of thalidomide led to the development of more structured drug regulations and control over drug use and development.

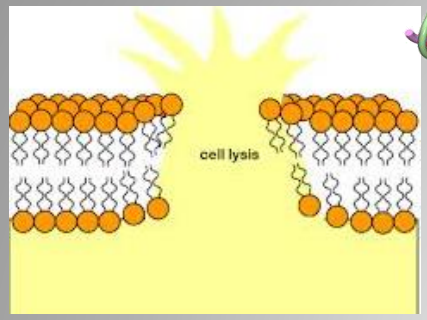


Ames test
(Griffiths et al 1996)

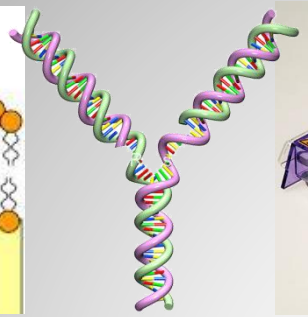


Biological assay to assess the mutagenic potential of chemical compounds

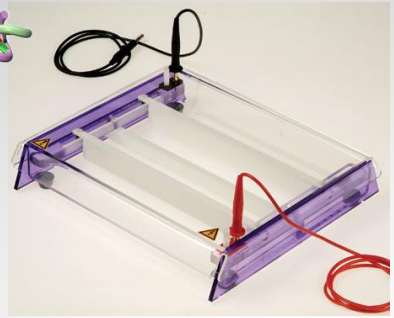
Single Cell Gel Electrophoresis assay - COMET-assay
(Collins et al 1993)



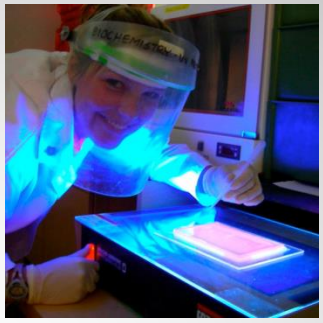
In situ membrain-lysis



DNS „unwinding”

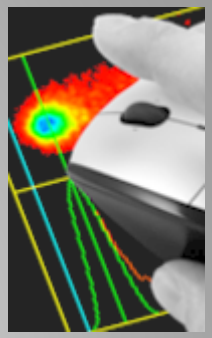


Electroforesis

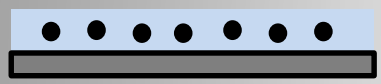


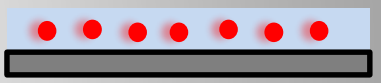
Ethidium-bromid staining

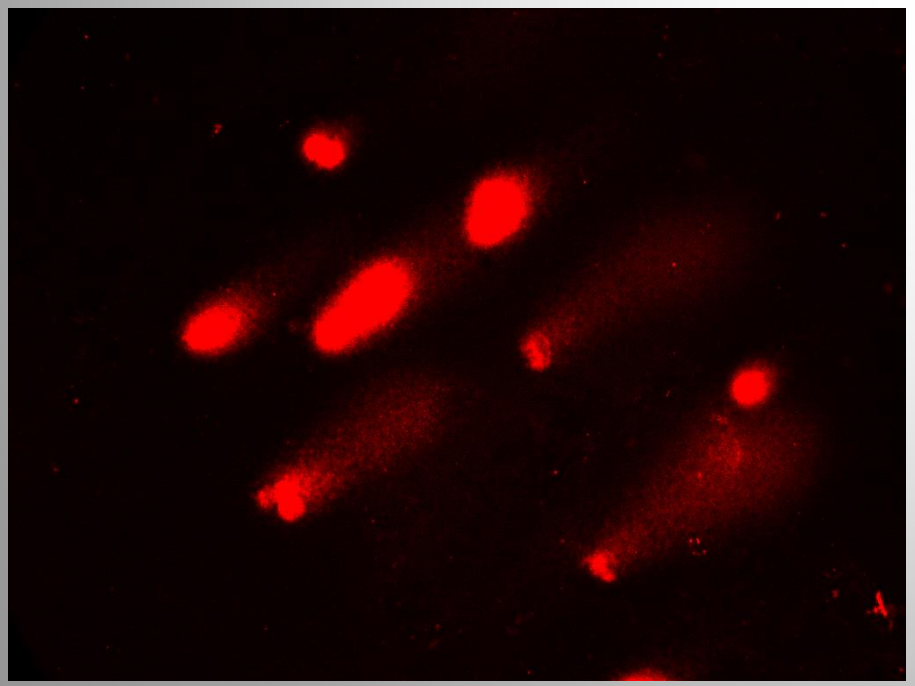
Fluorescens microscop

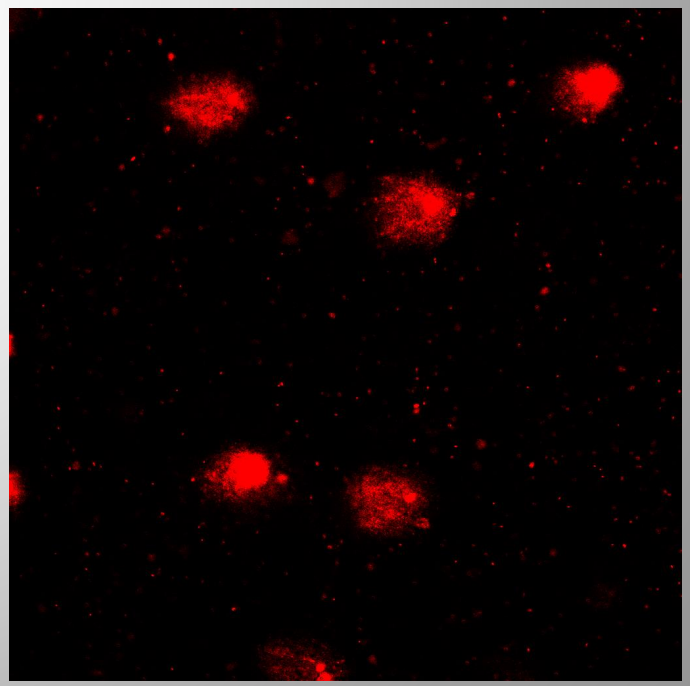


Analisis









INJURY BY THERAPEUTIC DRUGS

How is Safe Use of Drugs Regulated?

Development and Utilization of Medications is stricktly regulated from the Safety and Efficacy aspects through laws, regulations, directives and Good Clinical Practice

>> The Contergan Case<<

INJURY BY THERAPEUTIC DRUGS

Pre-clinical drug development

Subject of research	Safety	Efficacy (comparison to standard treatments)
Tissue models		YY
Small animals (mice, rats)	YY	YY
Bigger animals (monkey, swine)	YYY	YYY

Clinical drug development

Clinical Phase	Subject of research	Number of study subjects (cc.)	Durration of participation	Safety	Efficacy (comparison to standard treatments)
Phase I	Healthy volunteers or voluntary patients	12-24	Days-weeks	YYYYY	Y
Phase II	Patients	24-60	Weeks-months	YYYY	YY
Phase III	Patients	120-1200	Months-years	YYY	YYYYYY

Safety ensured by:

- Significant Serious Advers Events during the patient's participation are reported within 7-15 days to Authorities.
- Periodic reporting to Authorities and Ethic Committees
- Drug interaction monitored by registering the patient's other medications

INJURY BY THERAPEUTIC DRUGS

Clinical drug development

- Required for:
  - New drugs or treatments
  - Marketed drug for new indication
  - Marketed or new drug in new combination with marketed drug
- Conduct of clinical trials must be approved by Regulatory and Ethics Bodies prior start.
- Phase I-II can be open label, but if technically possible, Phase III studies are blinded to physician and patient.
- The new drug is usually compared with one standard treatment (two-arm study), or sometimes with two (three arms).
- Patients are randomly assigned to one or the other treatment arm.
- Marketing approval is based on the Phase III study results.
- Authorities can conduct inspections on the clinical data any time during or after the trial in the hospital where the trial is run or at the sponsor (pharma, biotech, etc.)

INJURY BY THERAPEUTIC DRUGS

Post Marketing Studies –Phase IV

- Aim is to collect efficacy and safety data on a wider population AND to promote the drug
- Simpler study design than Ph I-III, longer durration, several thousands of patients

Other safety control post-marketing

- Doctors are oblidged to report severe advers reactions to Authorities.
- Patients and doctors are oblidged to follow the package inserts.

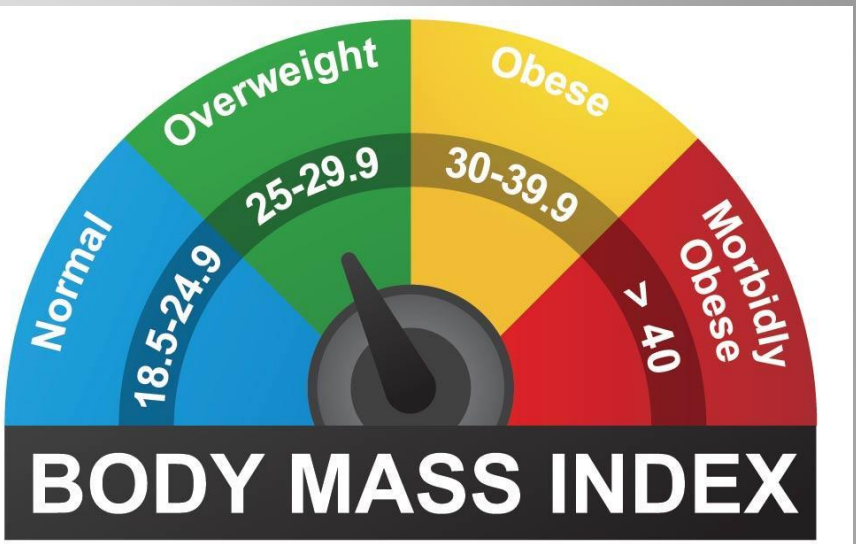
IMPORTANT: Civilian control of drug marketing through laws and regulatory bodies – so that drugs truely heal, not only are commercially useful.

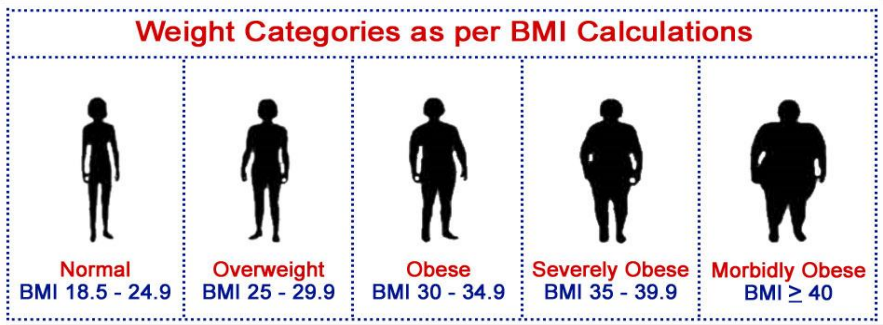
References:
- ICH-GCP: http://www.ich.org/about/mission.html
- European Medicines Agency: http://www.ema.europa.eu/ema/
- US Food and Drug Administration: https://www.fda.gov/

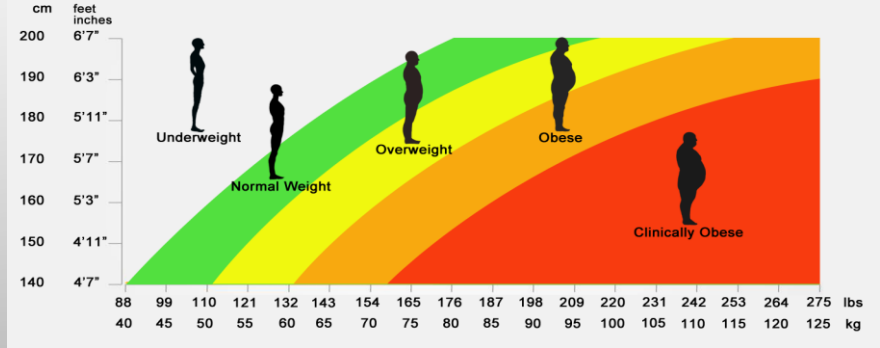
OBESITY

Definition

- A state of increased body weight, caused by adipose tissue accumulation, that is of sufficient magnitude to produce adverse health effects.
- To measure body mass index (BMI) is used
- BMI is calculated as (weight in kilograms)/(height in meters)2, or kg/m2.
- BMI greater than 30 kg/m2 imparts a health risk.





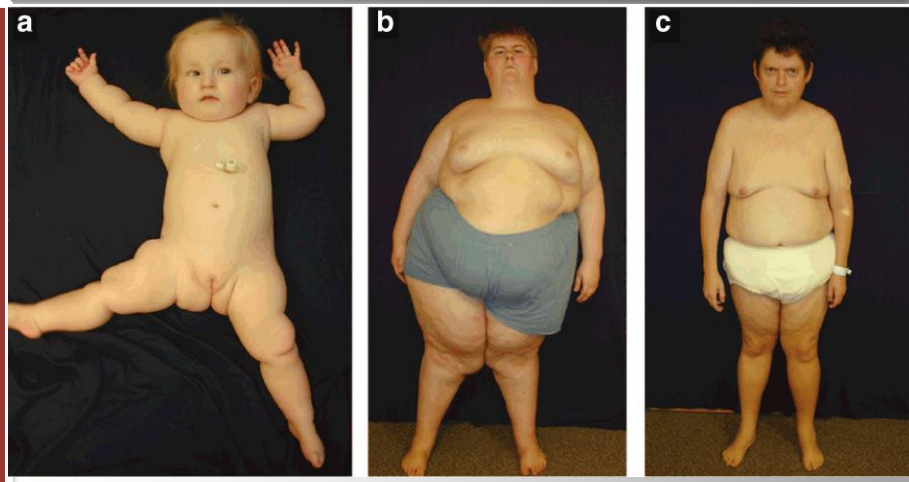


OBESITY

Etiology

- Genetic factors
  - Sex
  - Genetic syndromes
    - Prader-Willi syndrome (a, b, c)
    - Laurence-Moon-Biedl syndrome
    - Hypogonadism, Klinefelter-syndrome
  - Leptin gene or Leptin receptor gene

- Environmental factors
  - Excessive food intake
  - Physical inactivity
  - Socio-cultural and economic factors
  - Metabolic imbalances
    - Hypothyreodism
    - Cushing's disease



Laurence-Moon-Bardet-Biedl syndrome

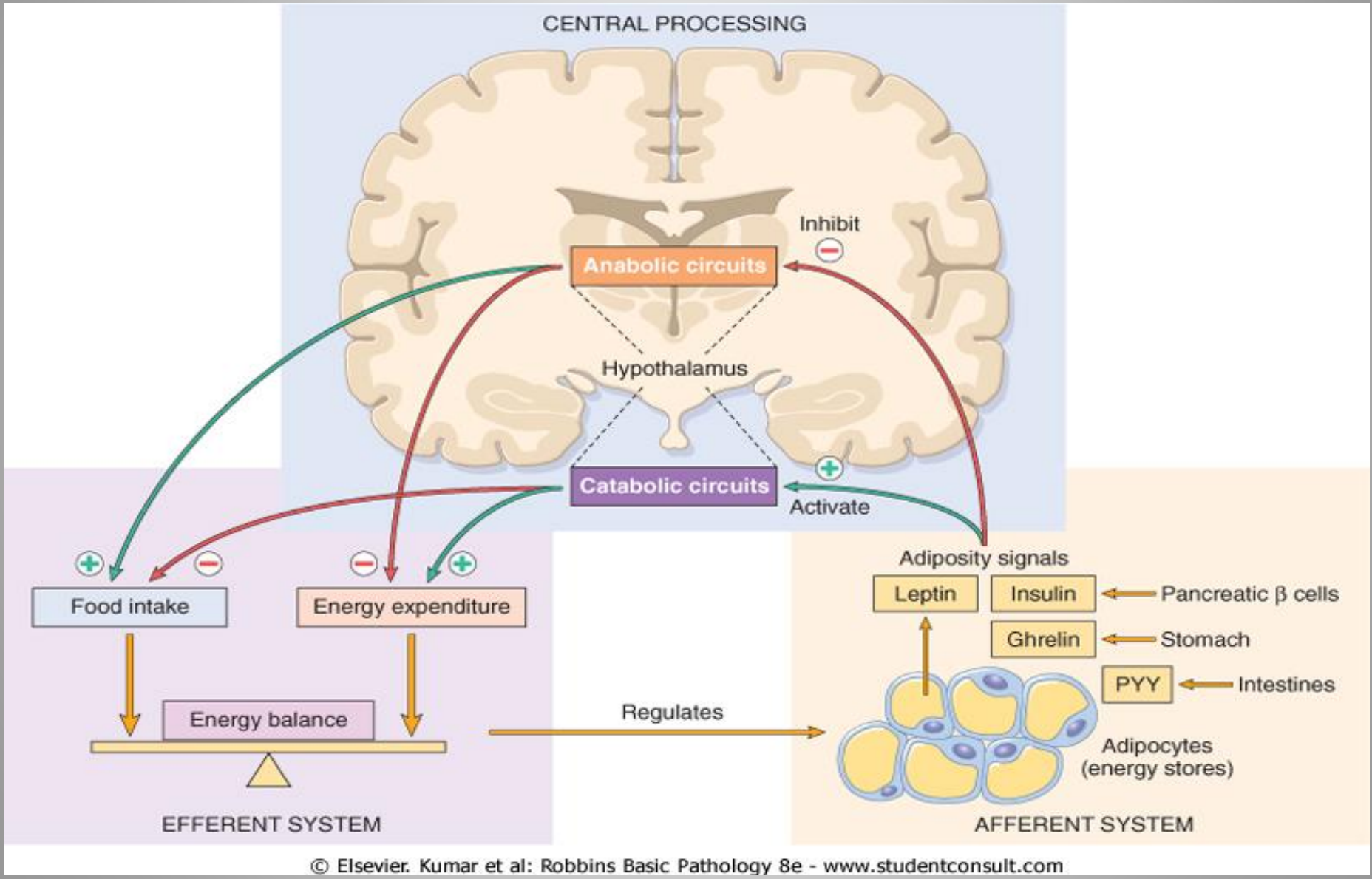
- Autosomal recessive genetic disorder
  - Obesity
  - Retinal degeneration
  - Extra digits on the hands and feet
  - Intellectual impairment
- Gene responsible on chromosome 16

OBESITY

Localisation

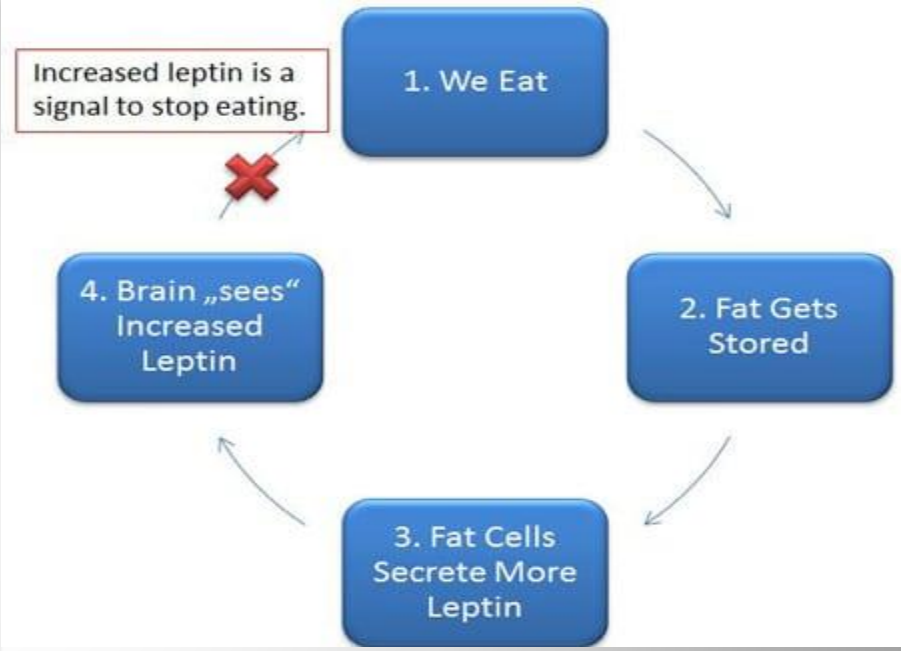
- Obesity are related not only to the total body weight but also to the distribution of the stored fat.:
  - **Central, or visceral**, obesity, in which fat accumulates in the trunk and in the abdominal cavity (above the waist), called **„Apple”**
  - Accumulation of fat in a diffuse distribution in subcutaneous tissue (bellowe the waist), **„Pear”**

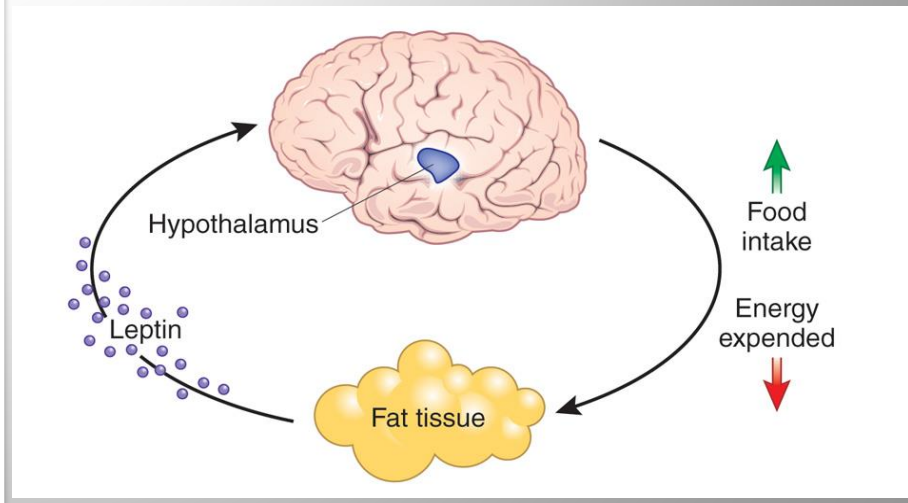
OBESITY



AFFERENT SYSTEM - Leptin

- LEP gene's product
- Widely accepted as the most important known regulator of body fatness in mammals
- Secreted by fat cells, and its output is regulated by the adequacy of fat stores
- BMI and body fat stores are directly related to leptin secretion
- With abundant adipose tissue, leptin secretion is stimulated
- The hormone crosses the blood–brain barrier and travels to the hypothalamus, where it reduces food intake by *stimulating* POMC/CART neurons and *inhibiting* NPY/AgRP neurons.

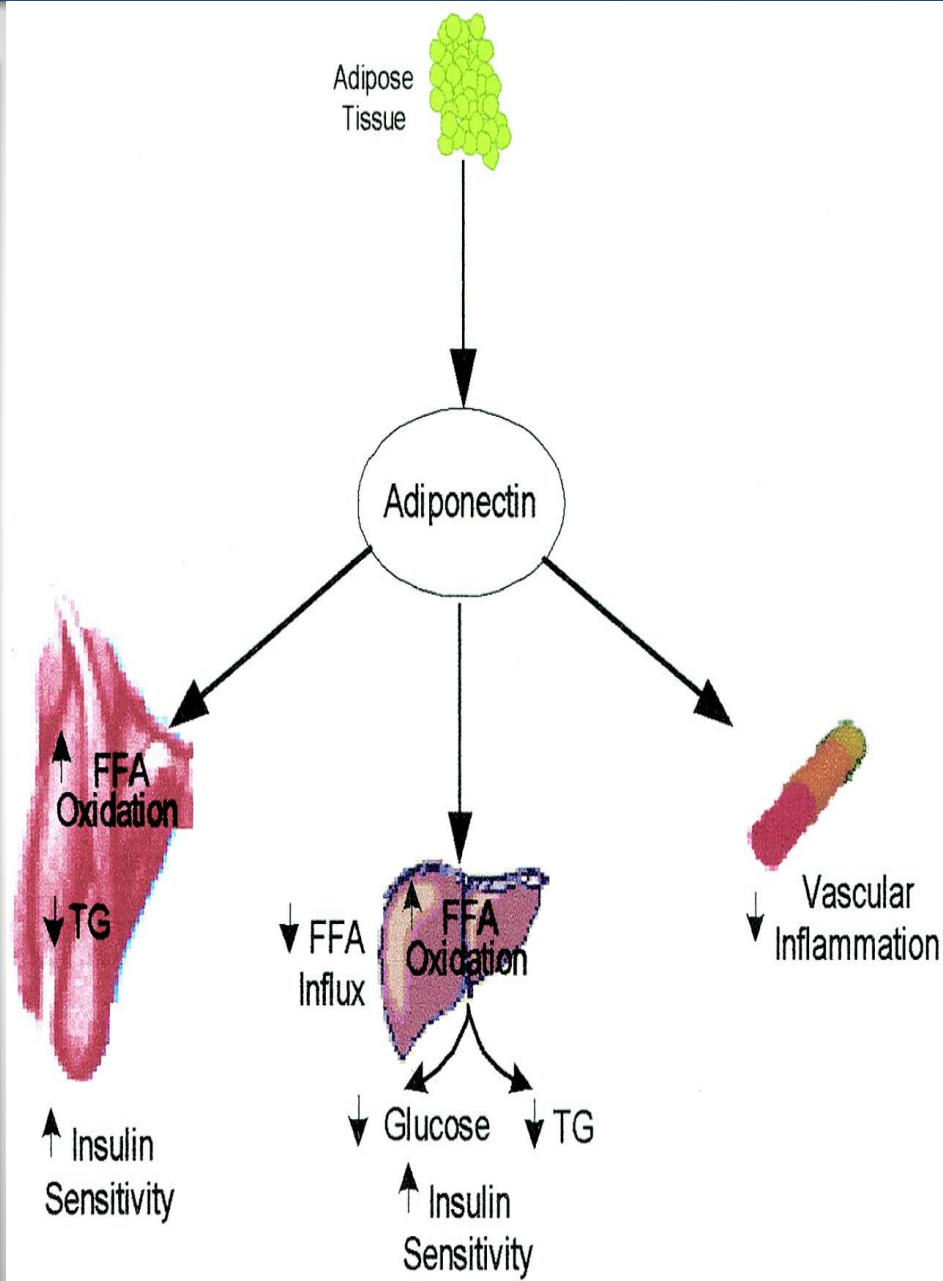




AFFERENT SYSTEM

Adiponectin

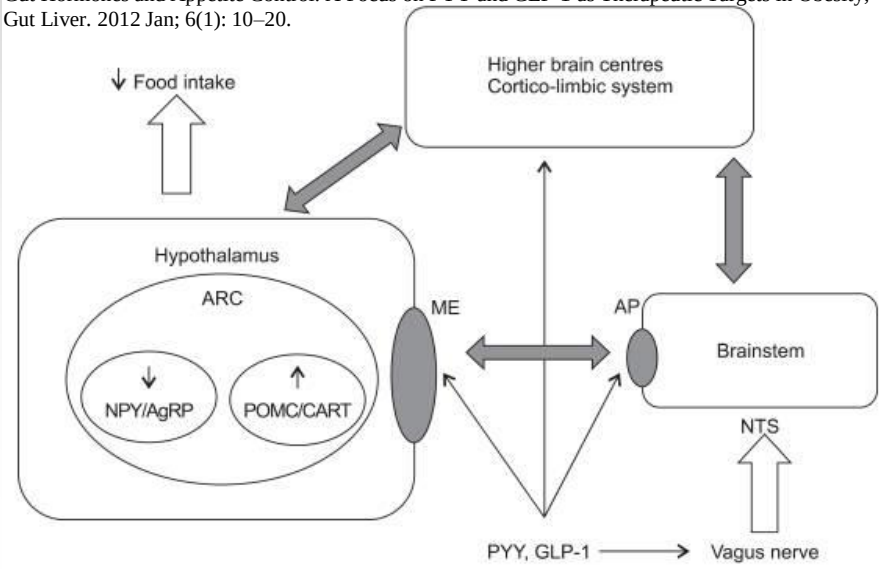
- Produced in the adipose tissue
- Serum levels are lower in obese than in lean individuals
- “fat-burning molecule” and the “guardian angel against obesity.”
- It directs fatty acids to muscle for their oxidation
- It decreases the influx of fatty acids (FFA) to the liver and the total hepatic triglyceride (TG) content
- Decreases glucose production in the liver, causing an increase in insulin sensitivity
- Anti-diabetic, anti-inflammatory, anti-atherogenic, anti- proliferative, and cardioprotective effects



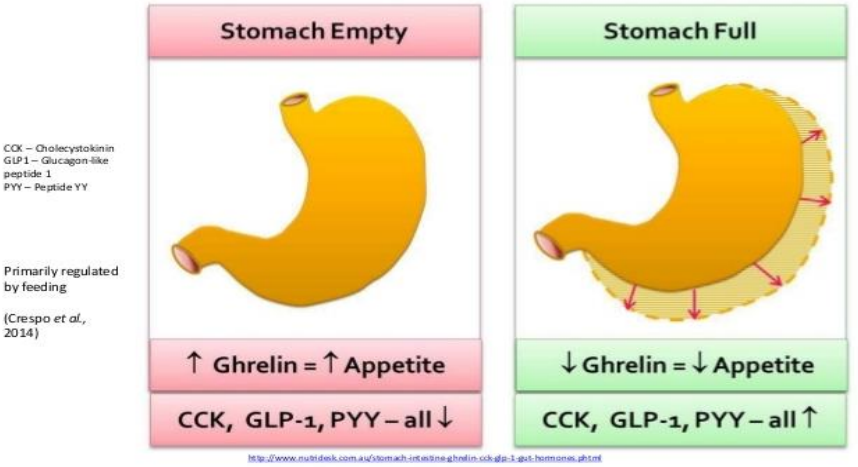
AFFERENT SYSTEM – Gut Hormones

- **Ghrelin**
  - Produced in the stomach and the arcuate nucleus of the hypothalamus.
  - It increases food intake
  - Stimulates the NPY/AgRP neurons in the hypothalamus
- **Peptide YY (PYY)**
  - secreted from endocrine cells in the ileum and the colon
  - It decreases appetite and augments a sense of fullness, thereby decreasing food intake
  - stimulates POMC/CART neurons in the hypothalamus

Gut Hormones and Appetite Control: A Focus on PYY and GLP-1 as Therapeutic Targets in Obesity, Gut Liver. 2012 Jan; 6(1): 10–20.



PYY, peptide tyrosine tyrosine; GLP-1, glucagon-like peptide 1; ARC, arcuate nucleus; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; ME, median eminence; AP, area postrema; NTS, nucleus of the tractus solitaries.



Clinical Consequences of Obesity

- Central obesity is a known **risk factor** for
  - T2DM
  - Cardiovascular disease
  - Cancer

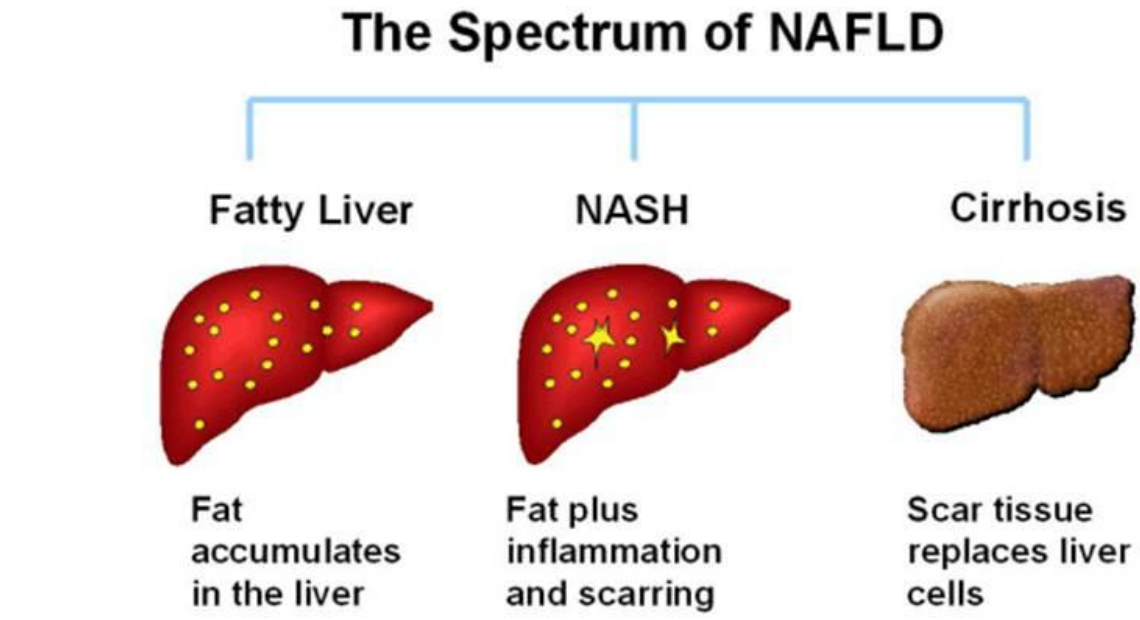
- Central obesity stands at the center of *metabolic syndrome*
  - abnormalities of glucose
  - lipid metabolism
  - hypertension
  - systemic proinflammatory state

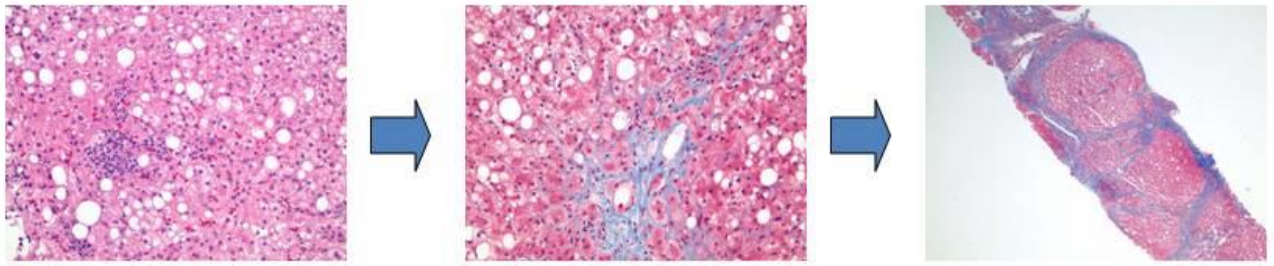
Clinical Consequences of Obesity

- Obesity is associated with insulin resistance and hyperinsulinemia T2DM
- Obese persons generally have hypertriglyceridemia and low HDL cholesterol levels
- Nonalcoholic fatty liver disease
- Cholelithiasis (gallstones)
- Hypoventilation syndrome (OHS)
- Degenerative joint disease (osteoarthritis)
- C-reactive protein (CRP) and proinflammatory cytokines like TNF levels elevated

Clinical Consequences of Obesity

- **Nonalcoholic fatty liver disease (NAFLD)**



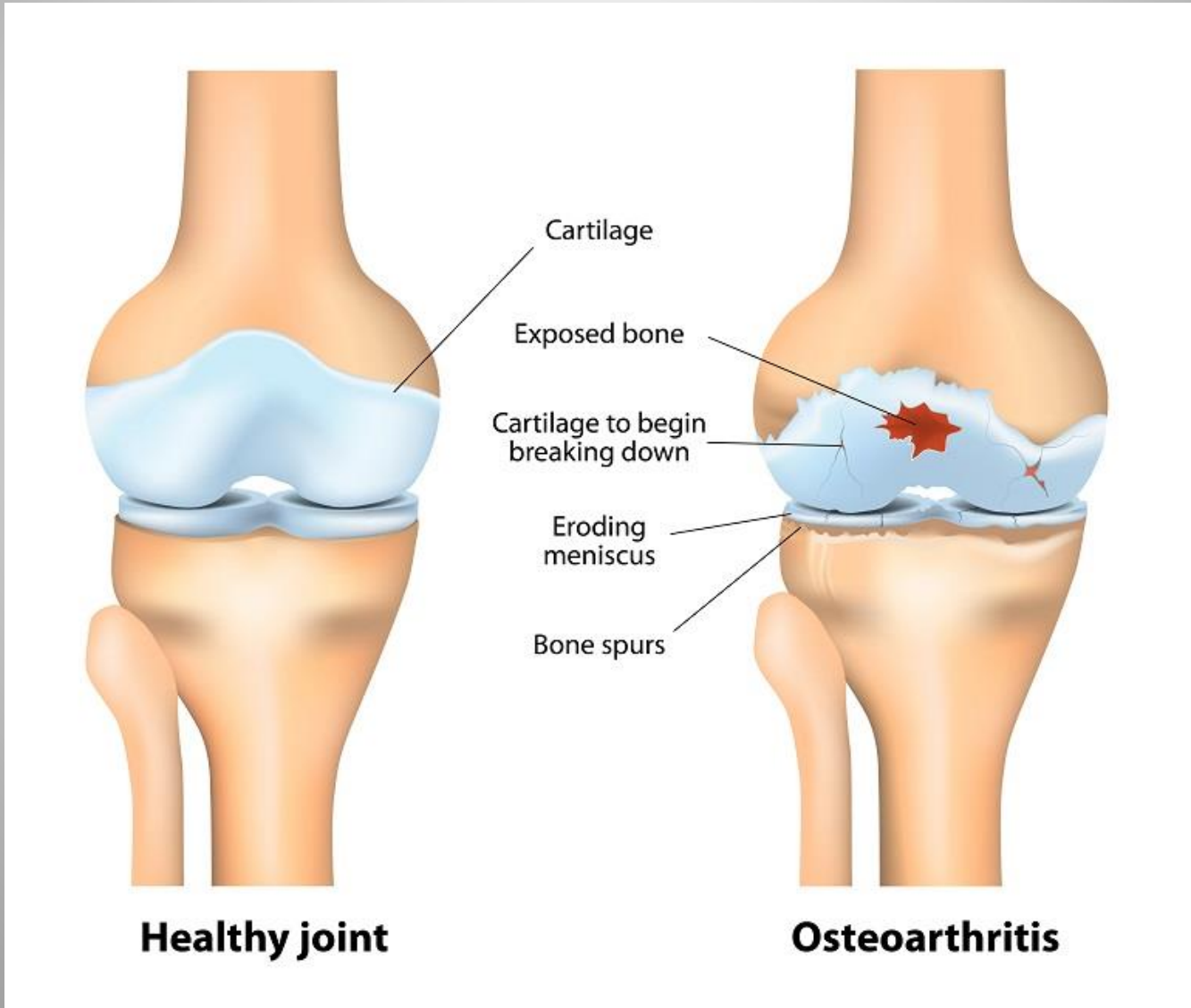


Clinical Consequences of Obesity

Cholelithiasis (gallstones)

Clinical Consequences of Obesity

- **Degenerative joint disease (osteoarthritis)**



Clinical Consequences of Obesity

- **Hypoventilation syndrome (OHS)**

Obesity Hypoventilation Syndrome

Criteria A-C must be met

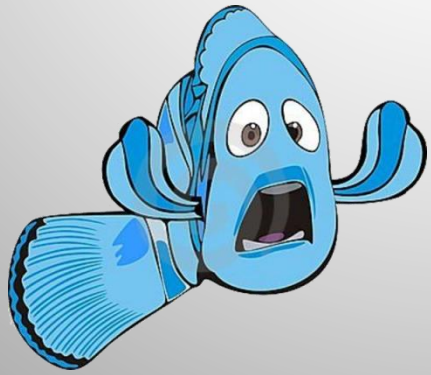
A. $PaCO_2$ > 45 mm Hg during wakefulness

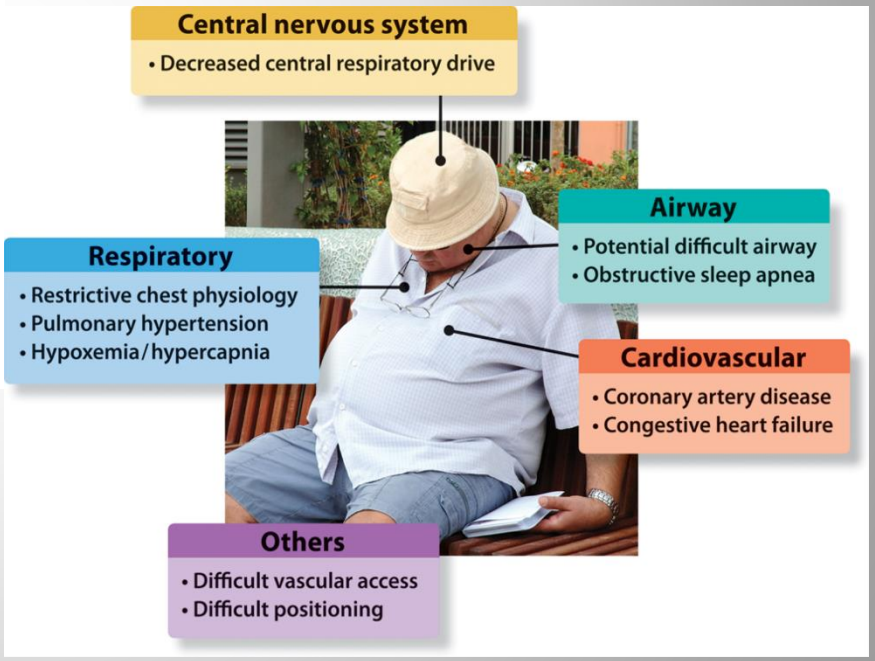
B. Obesity (BMI > 30 kg/m^2; > 95th percentile for age and sex for children).

C. Hypoventilation is not primarily due to other causes

Pickwickian Syndrome

Auchinchloss et al. J Clin Invest 1955; 34:1537
ICSD-3





From: Obesity Hypoventilation Syndrome:A Review of Epidemiology, Pathophysiology, and Perioperative Considerations, Anesthes. 2012;117(1):188-205.

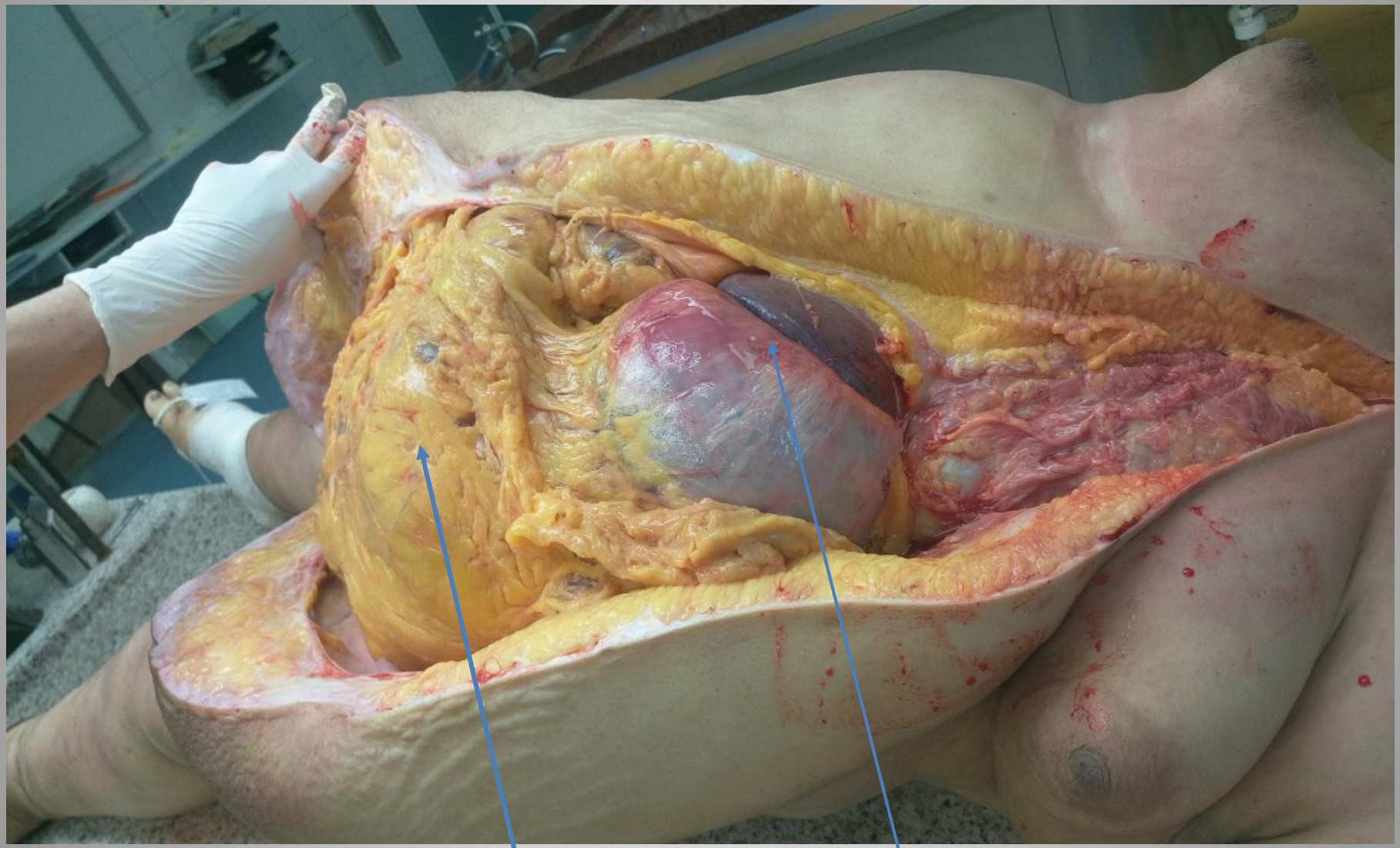
Obesity and Cancer

- Mechanism
  - Elevated insulin levels-rise in levels of free insulinlike growth factor-1 (IGF-1)
  - Effects on steroid hormones
  - Reduced adiponectin secretion
  - Proinflammatory state
- Males: esophagus, thyroid, colon, kidney
  - Obesity causes 14% of cancer death in men
- Women: esophagus, endometrium, gallbladder, kidney
  - Obesity causes 20% of cancer death in women

Obesity-Autopsy case

Middle age female, with the weight close to 200 kg

Obesity Autopsy case

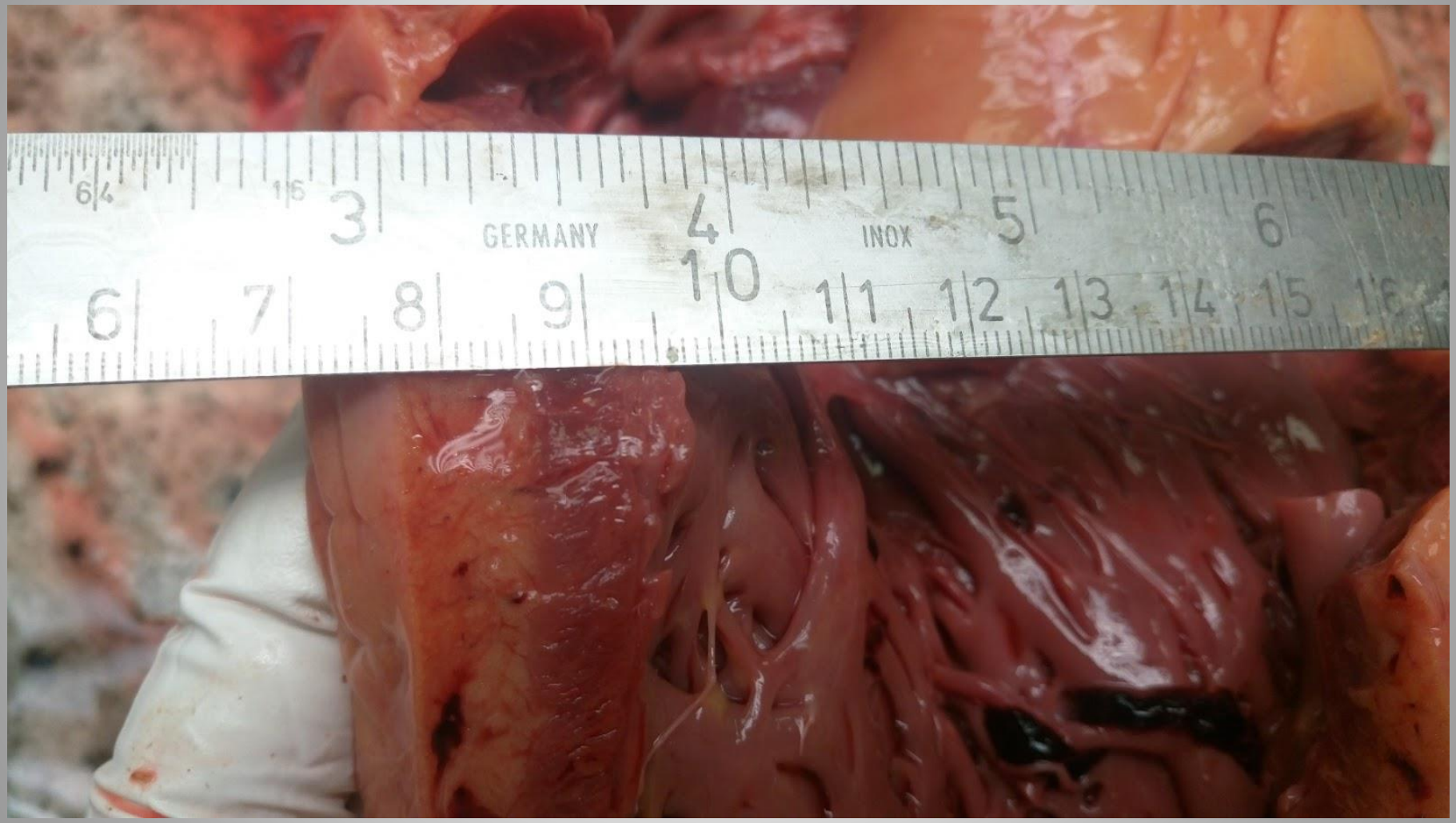


Sever mesentherial adiposity and organomegaly

Obesity Autopsy case

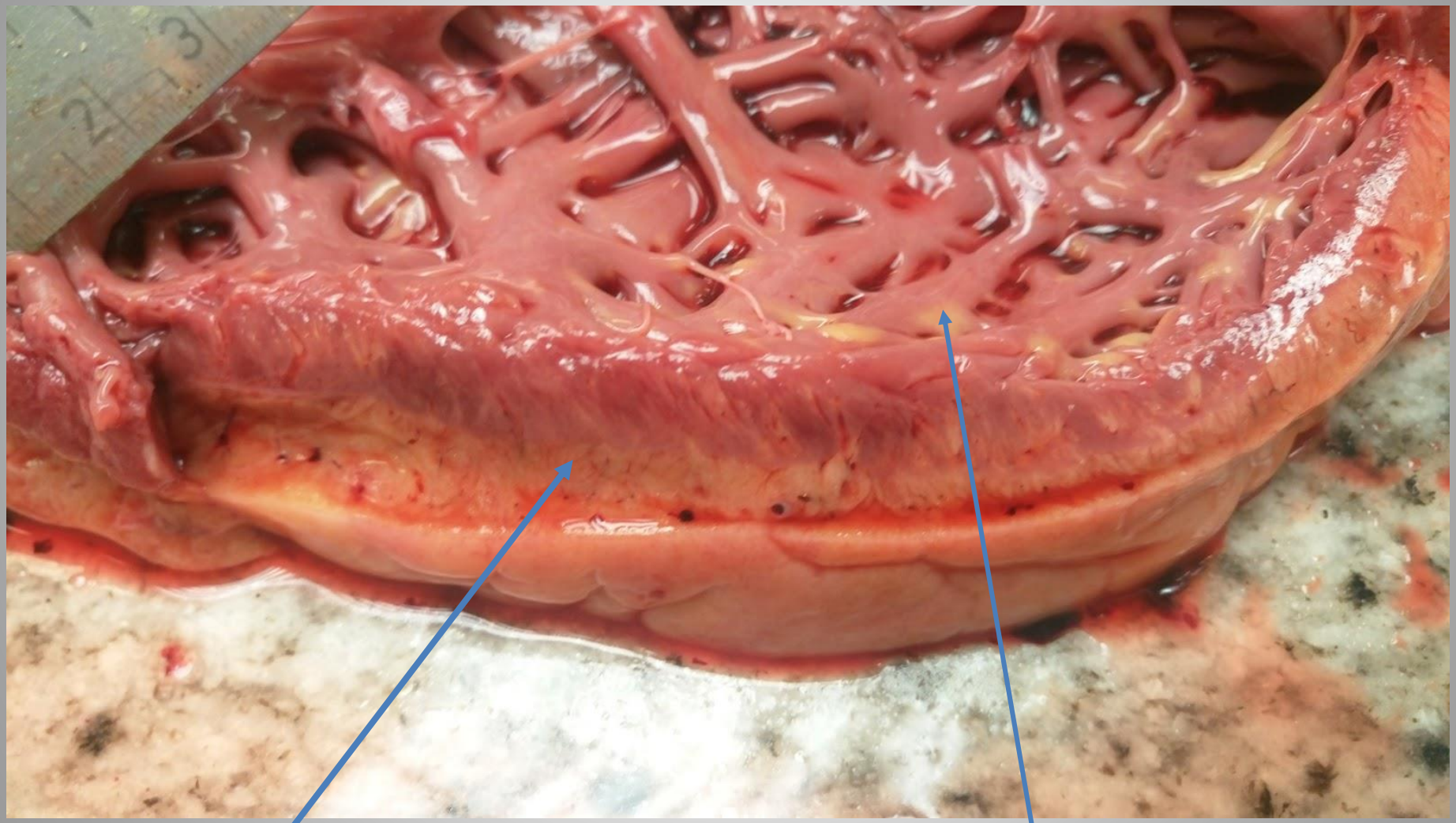
Cross section of abdominal wall – severe adiposity with chronic degeneration

Obesity Autopsy case



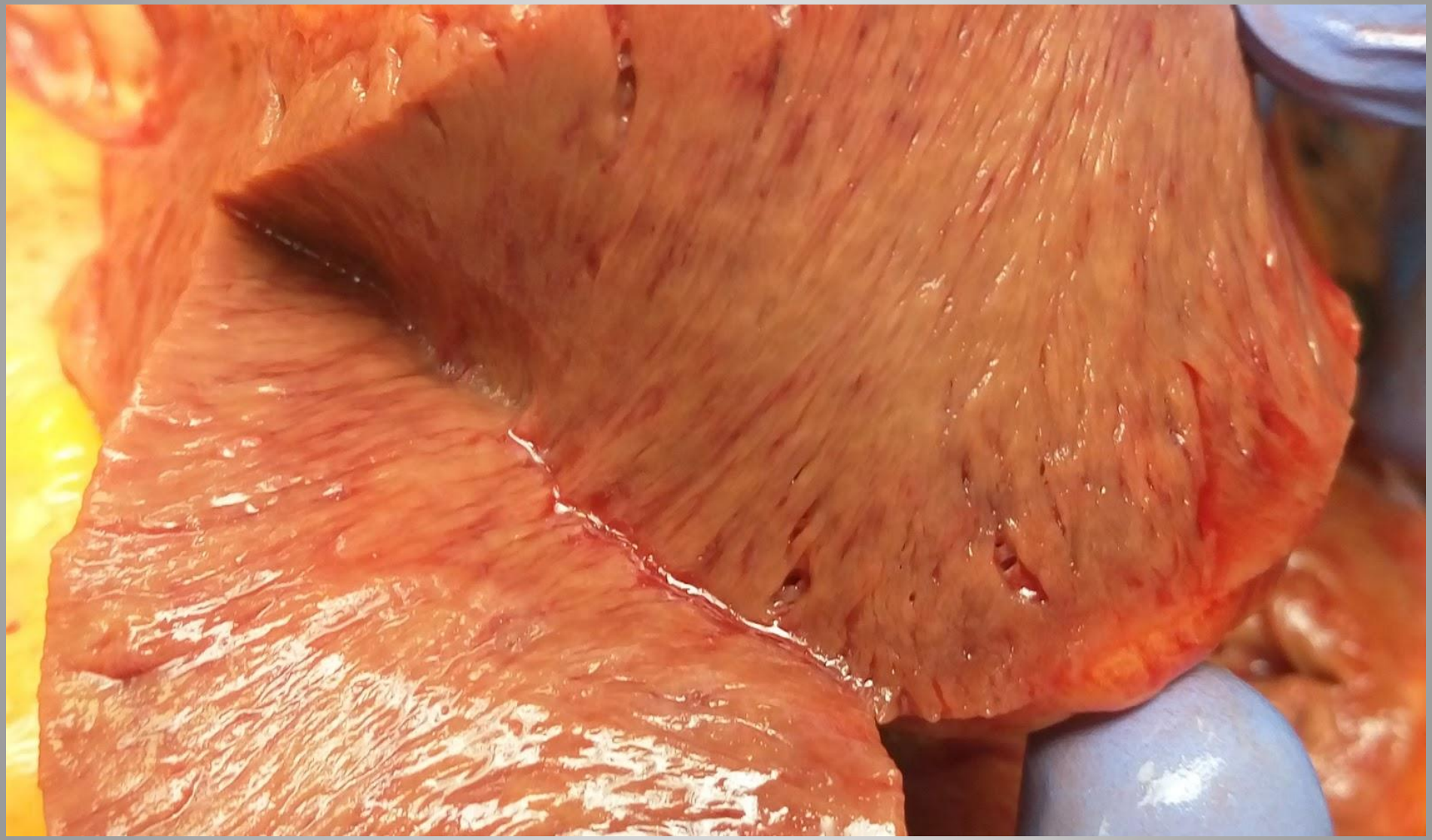
Diameter of right ventricule: around 20 mm (normal is 3-5 mm)

Obesity Autopsy case



Severe fatty infiltration in myocardium of the right ventricule and insular-trabecular fatty change

Obesity Autopsy case



Diffuse fatty degeneration in the myocardium

Obesity Autopsy case

In contrast: Heart in ageing cachexia – total loss of subepicardial fat tissue