

Environmental pathology: Exogenous disorders

Under the term of “environmental pathology”, a variety of exogenous disorders, except for infections, are summarized. These include physical injuries (trauma, burn, electric current injuries and irradiation injuries), chemical injuries (injuries by indulgences and exogenous chemicals), and adverse effects of medicines (aspirin, antibiotics and anti-cancer drugs).

Representative cases are presented.

Ref.: Centeno JA, et al. Environmental pathology. Essent Medical Geol 2012: 569-596. doi: 10.1007/978-94-007-4375-5_25

Categorization of disorders

Endogenous disorders (represented by hereditary disorders)

Exogenous disorders (represented by trauma, nutritional disorders and infection)

Environmental pathology

1) Physical injuries

Trauma (Mechanical injuries)

Burn and frost bite (Temperature injuries)

Electric current injuries

Irradiation injuries

2) Chemical injuries

Indulgences (alcohol, smoking, drug use)

Injuries by exogenous chemicals (carbon monoxide, cyanate, mercury)

Adverse effects of medicines (aspirin, antibiotics, anti-cancer drugs)

3) Infection

Chronic organ injuries by environmental factors

- 1) Irradiation-related carcinogenesis (acute myelogenous leukemia, skin cancer and thyroid cancer)
- 2) Alcohol-induced organ injuries (liver, pancreas, brain, peripheral nerve and heart)
- 3) Aspergillus toxin (Aflatoxin)-induced hepatocellular carcinoma
- 4) Smoking-induced chronic obstructive lung disease and lung cancer
- 5) Abestos-induced malignant mesothelioma and lung cancer
- 6) Airborne dust-related pneumoconiosis
- 7) Benzidine (aniline dye) exposure-related urinary bladder carcinoma
- 8) Dichloromethane exposure-related bile duct carcinoma
- 9) Normal-hexane inhalation-related peripheral neuropathy
- 10) Chronic metallic intoxication (organic mercury-related Minamata disease, cadmium-related Itai-itai disease and lead intoxication-related anemia, peripheral neuropathy and renal injury)

Asbestos and asbestos bodies



Original stone of Asbestos



Chrysotile
(white asbestos)
Minimally carcinogenic



Amosite
(brown asbestos)

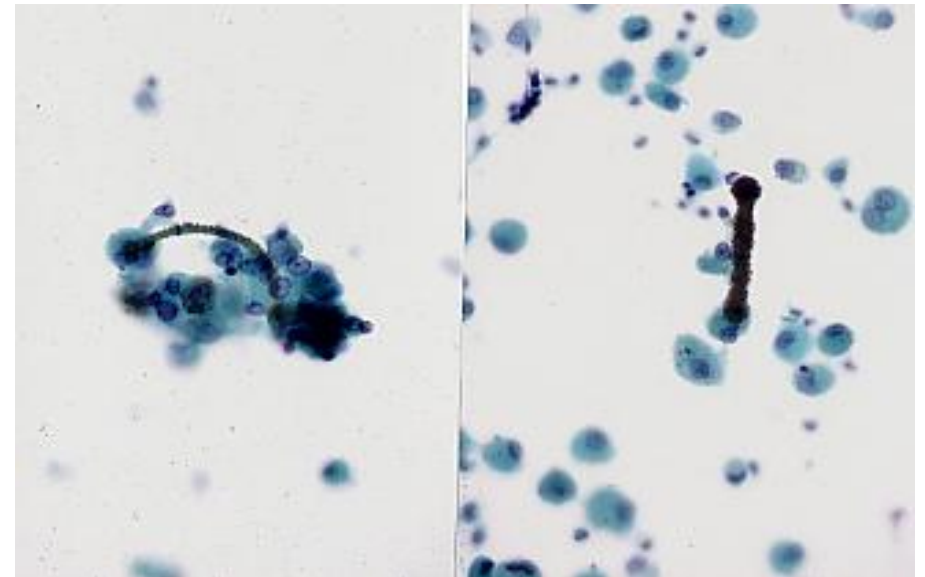


Crocidolite
(blue asbestos)
highly carcinogenic

Asbestos bodies

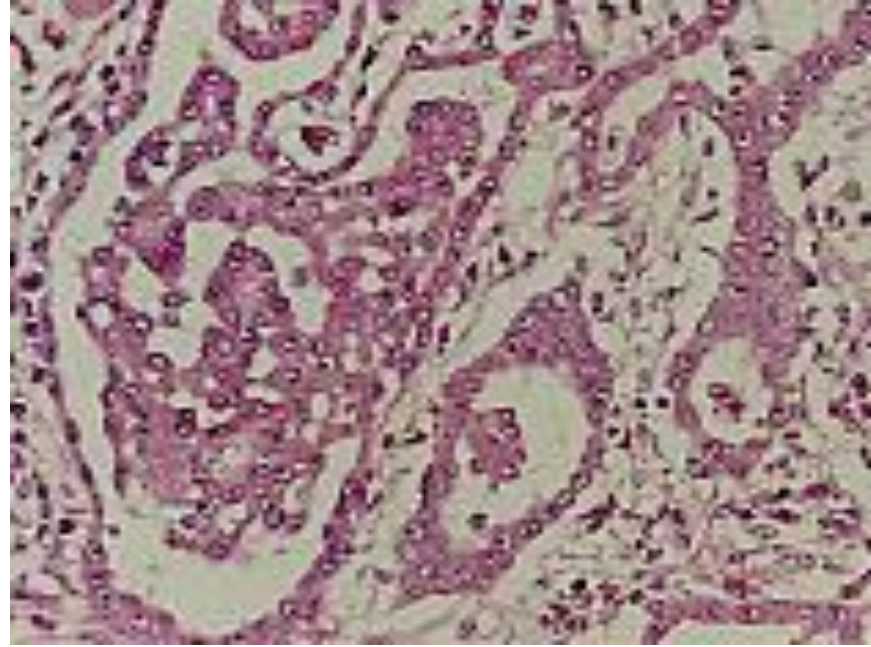


Brown asbestos White asbestos Blue asbestos

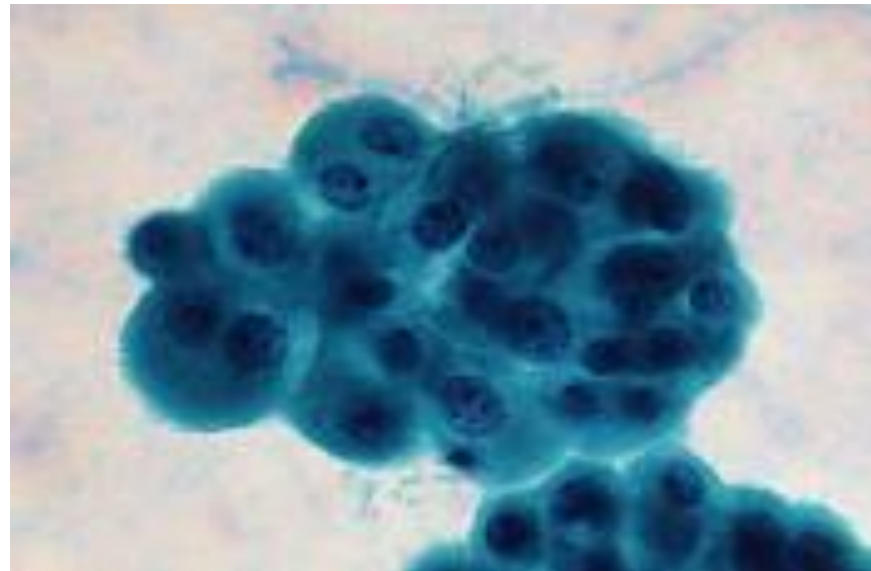


Papanicolaou staining

Malignant mesothelioma of the pleura



H&E



Pap

Smoking and organ injuries

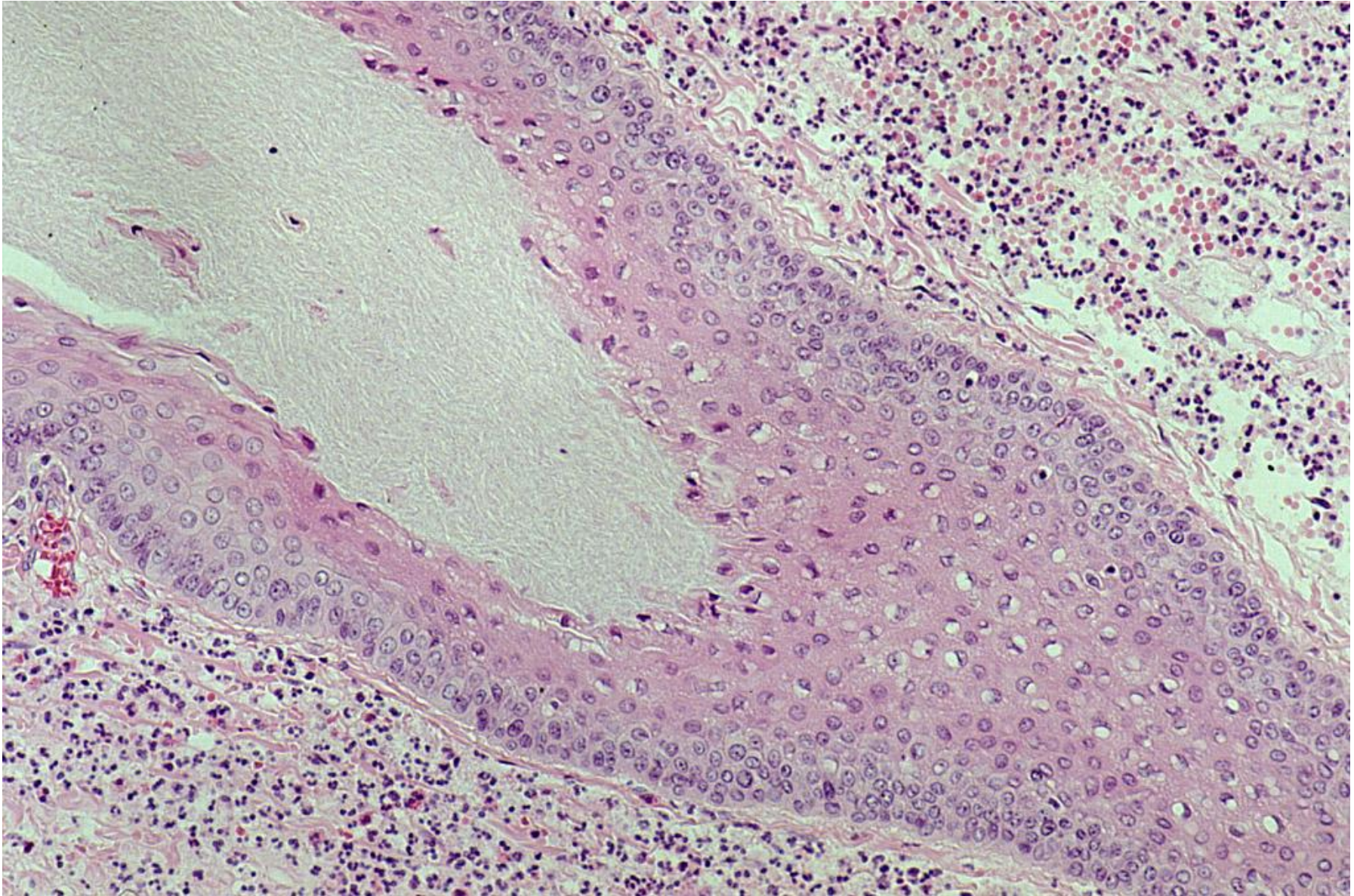
- 1) **Carcinogenesis** (squamous cell carcinoma of the larynx and lung, small cell carcinoma of the lung, urothelial carcinoma of the urinary bladder)
- 2) **Chronic obstructive pulmonary disease (COPD)**
- 3) **Obstructive arteriopathy** (atherosclerosis, Buerger's disease and myocardial infarction)

Infection of exotoxin-producing pathogens

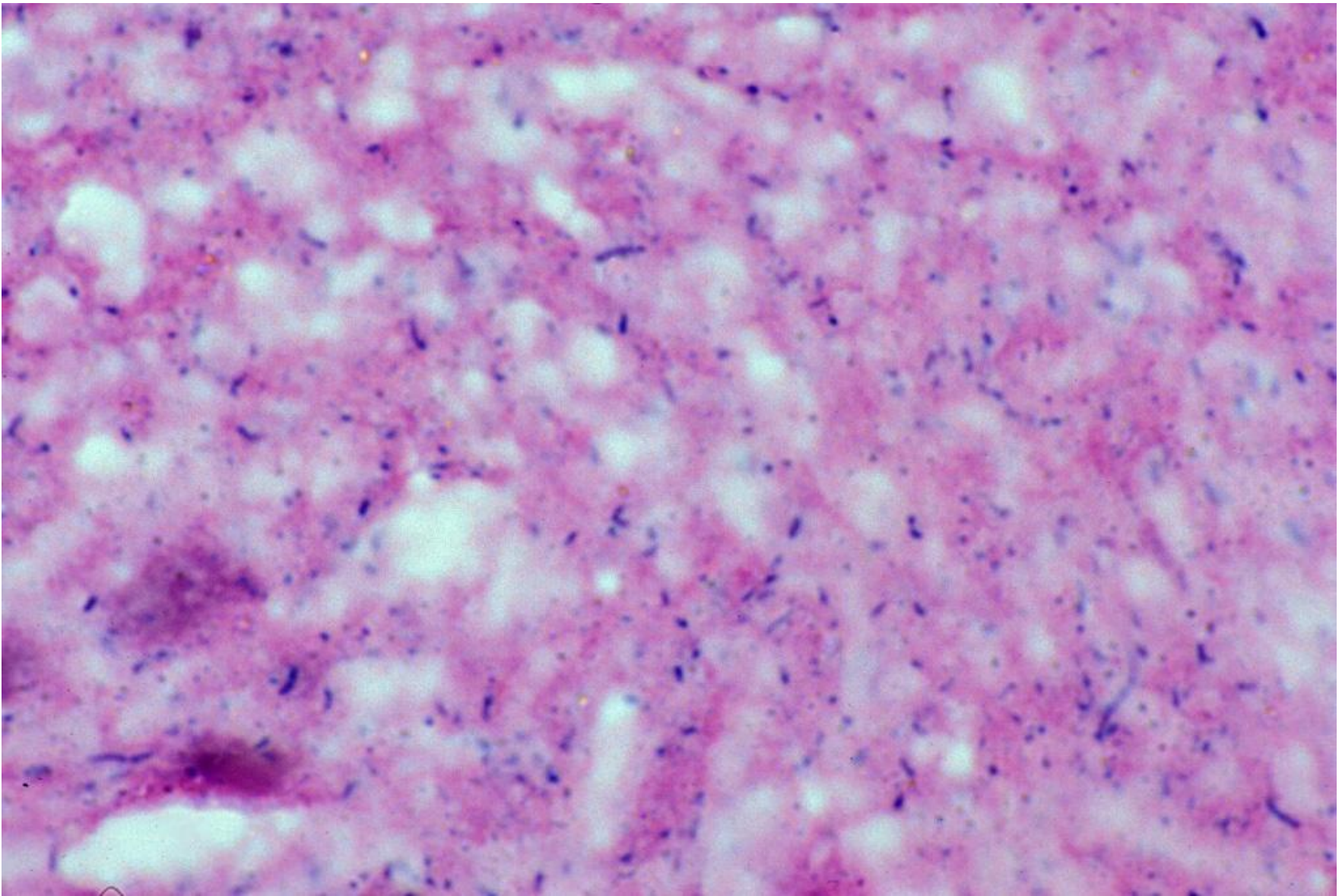
Example case presentation

Diphtheria

(a rare case clinically not diagnosed)



Pseudomembrane formation by *Corynebacterium diphtheriae* infection
(pharyngeal mucosa, H&E)



Diphtherial pseudomembrane (pharyngeal mucosa, Gram staining).
Gram-positive rods seen



Scanning electron micrograph of *Corynebacterium diphtheriae*

Traumatic organ injuries

1) Head injury (cerebral contusion)

- a) coup injury

- b) contrecoup injury

2) Abdominal injury

- Splenic and hepatic rupture (hemorrhage)

- Intestinal rupture (peritonitis)

3) Thoracic injury

- hemothorax and pneumothorax

Case presentation-1

Traumatic fracture (femoral neck fracture
and tibia/fibula fracture)

Aspiration of mochi (rice cake)

Tracheal burn

Cold death

Electrocution

Cyanide intoxication



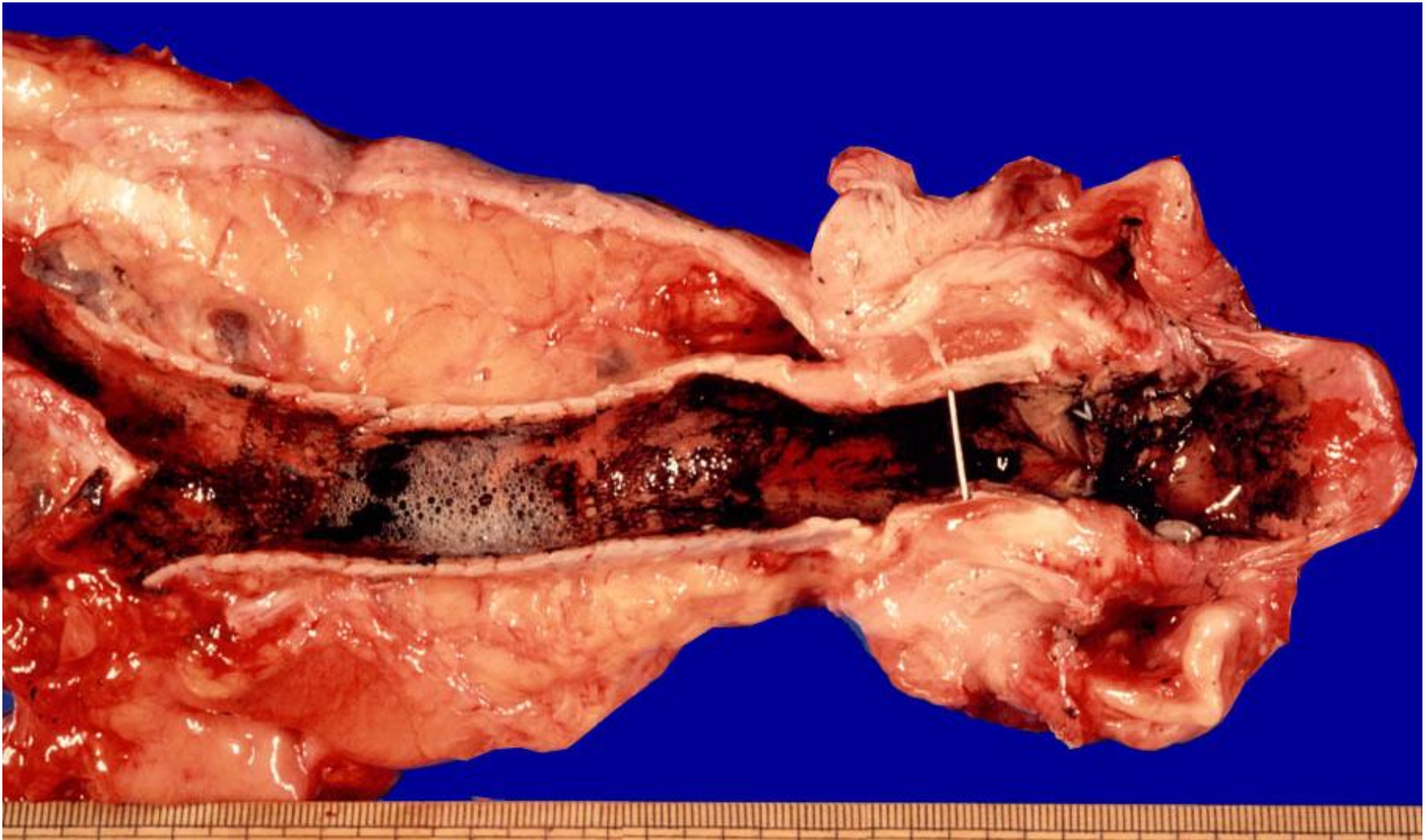
Femoral neck fracture of the aged



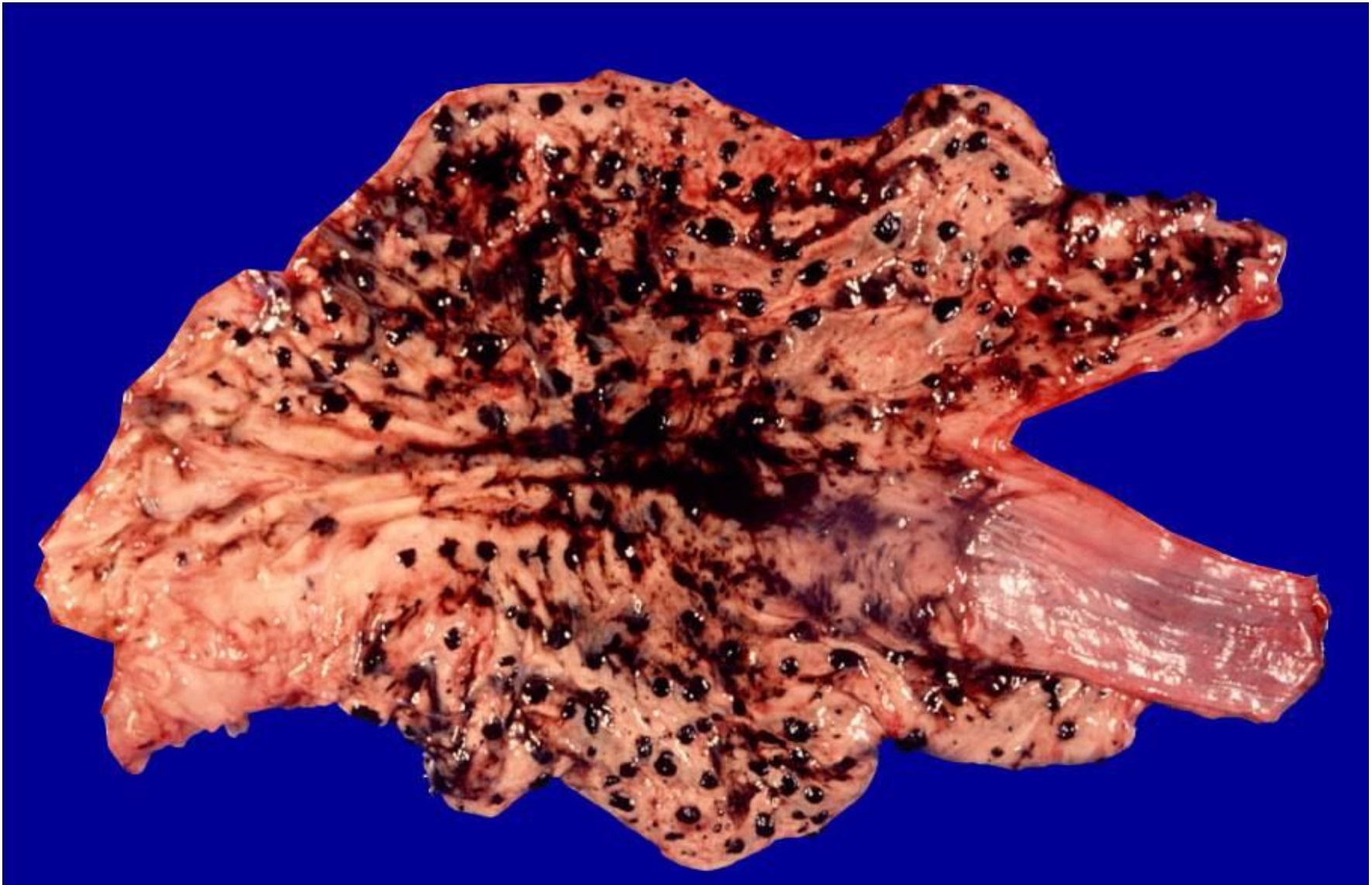
Fracture of the tibia and fibula of the youth, due to an accident by skiing



Aspiration of mochi (rice cake) in a forensic autopsy case. The mochi (arrow) completely obliterated the inlet of the larynx. The accident increases in a new year season, because mochi is served as a new year-celebration diet in Japan.



A case burnt to death. The burn of the airway is shown.
The inhalation burn is lethal.



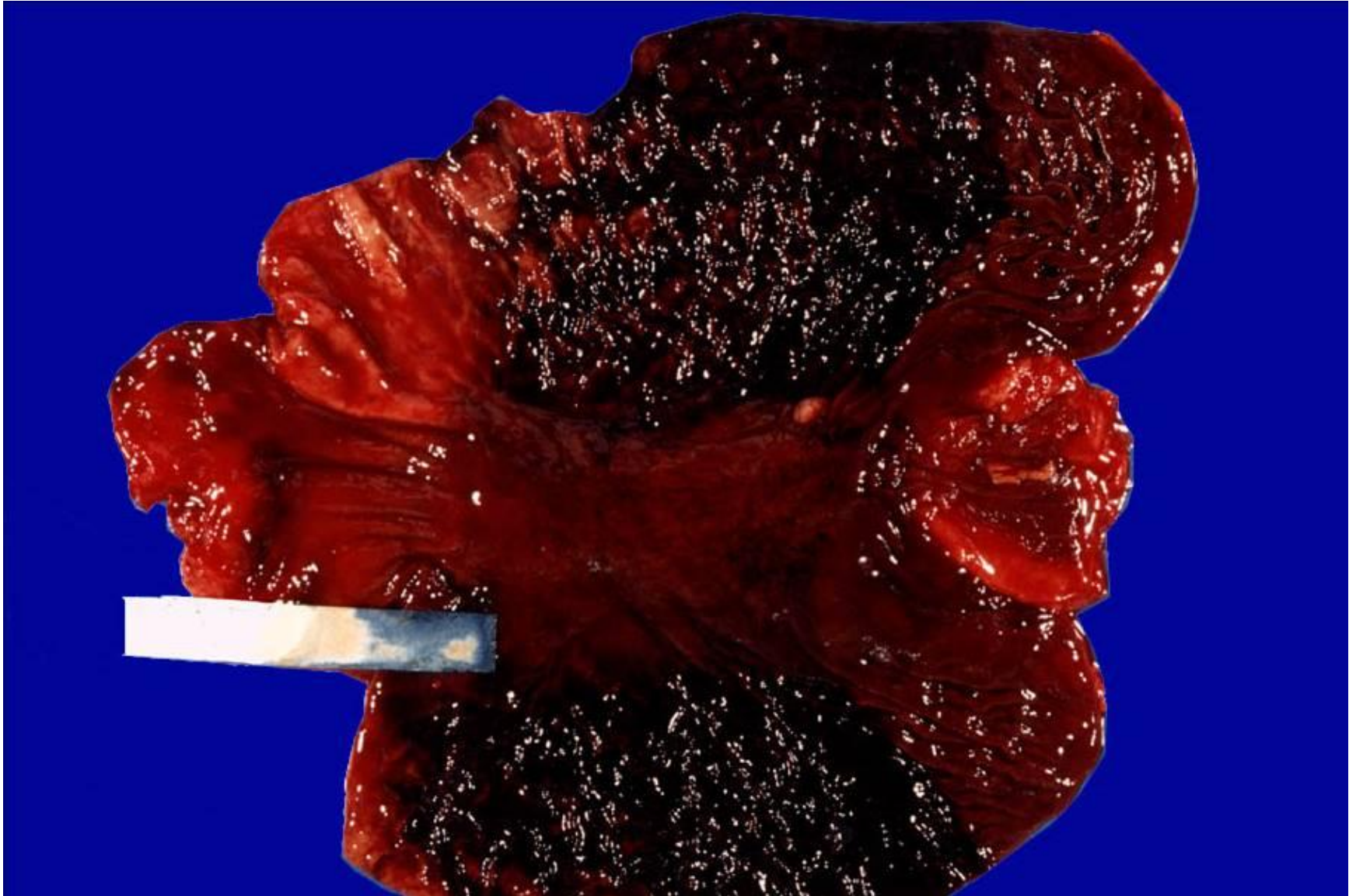
The gastric mucosa in a case frozen to death. The petechial hemorrhage in the gastric mucosa is evident.



The heart blood in a case frozen to death. The blood in the left ventricle (left) remains red in color because of the persistence of oxyhemoglobin in the red blood cells at low temperature. The blood in the right ventricle is shown in the right side.



A case of electrocution. The inlet of the electricity on the hand was ulcerated.



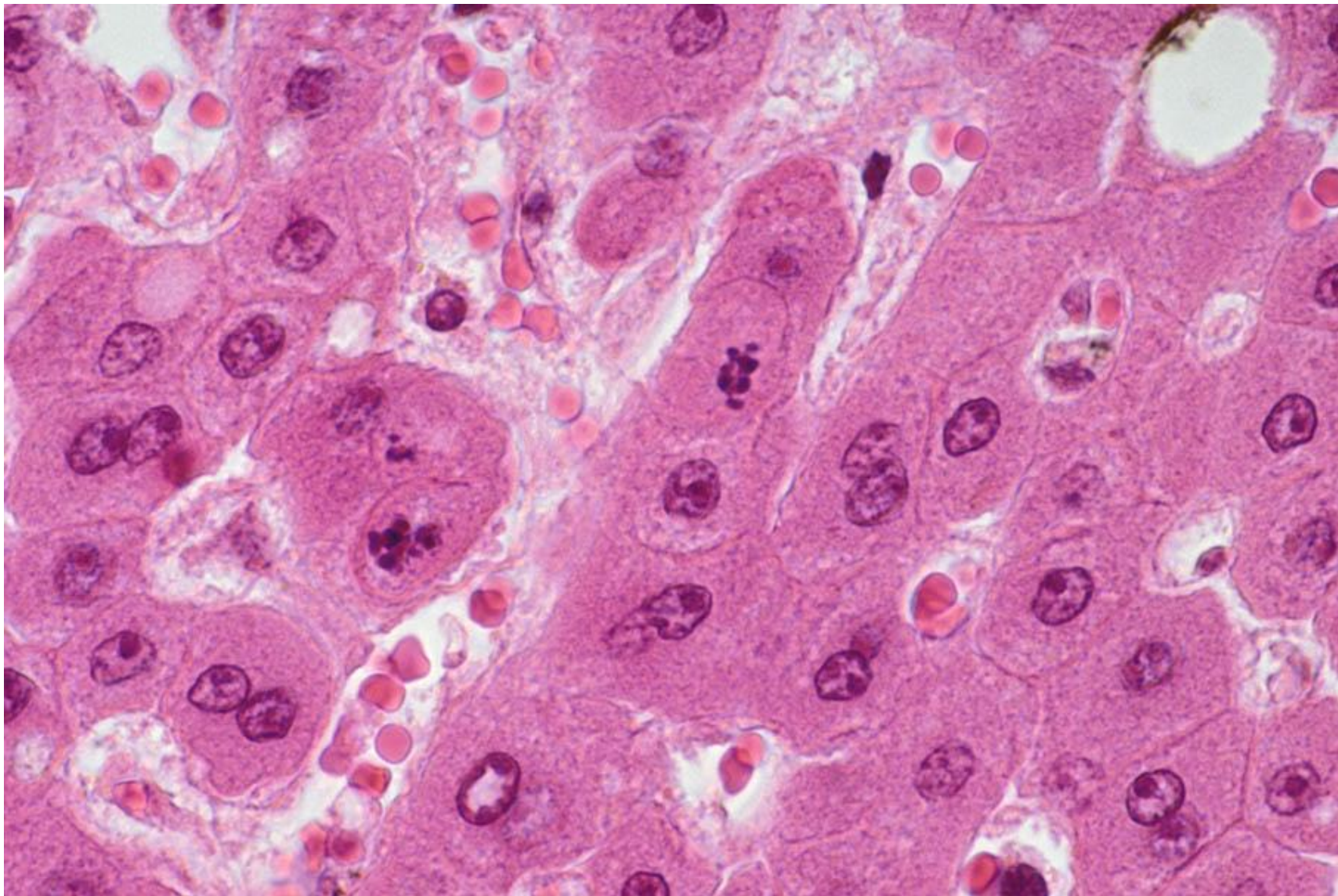
Gastric mucosa in a case of cyanate intoxication. Diffuse mucosal hemorrhage is seen in the gastric body.

Exogenous chemicals and toxins and their effects

Chemicals/toxins	injury
methanol	blindness
carbon monoxide (CO)	hypoxic brain injury
carbon tetrachloride (CCl ₄)	centrilobular necrosis and fatty change of the liver
normal hexane	peripheral neuropathy (chronic intoxication)
benzidine (aniline dye)	urinary bladder carcinoma (chronic exposure)
asbestos	pneumoconiosis, lung cancer, malignant mesothelioma (chronic exposure)
cyanate	intracellular asphyxia by inhibition of cytochrome oxidases
lead	anemia, encephalopathy, neuropathy, Fanconi syndrome, lead hue of the skin
mercuric chloride	ulcers of the gastrointestinal tract, calcification and necrosis of the renal tubules

Case presentation-2

- 1) Colchicine intoxication
- 2) Fat embolism by traumatic fracture
- 3) Crush syndrome
- 4) Systemic burn
- 5) Burn due to diabetic peripheral neuropathy
- 6) Venomous snake bite
- 7) Alcoholic hepatitis



Colchicine intoxication due to ingestion of the leaves of *Cochicum autumnale* (meadow saffron). Metaphasic mitotic figures are scattered in the hepatocytes (H&E). Colchicine hampers the action of the mitotic spindle. Accidentally, the patient took the leaves of *C. autumnale* in a spring season.

The leaves of *Colchicum autumnale* and *Allium victorialis* in the spring season are indistinguishable



Colchicum autumnale



Allium victorialis

Colchicine is a toxic alkaloid included in *colchicum autumnale* (meadow saffron or autumn crocus). *Allium victorialis* (ascetic garlic) is a popular mountain vegetable containing spicy garlic-like smell.

The flowers of *Colchicum autumnale* and *Allium victorialis* seen in the autumn season are completely different.



The flower of *Colchicum autumnale*

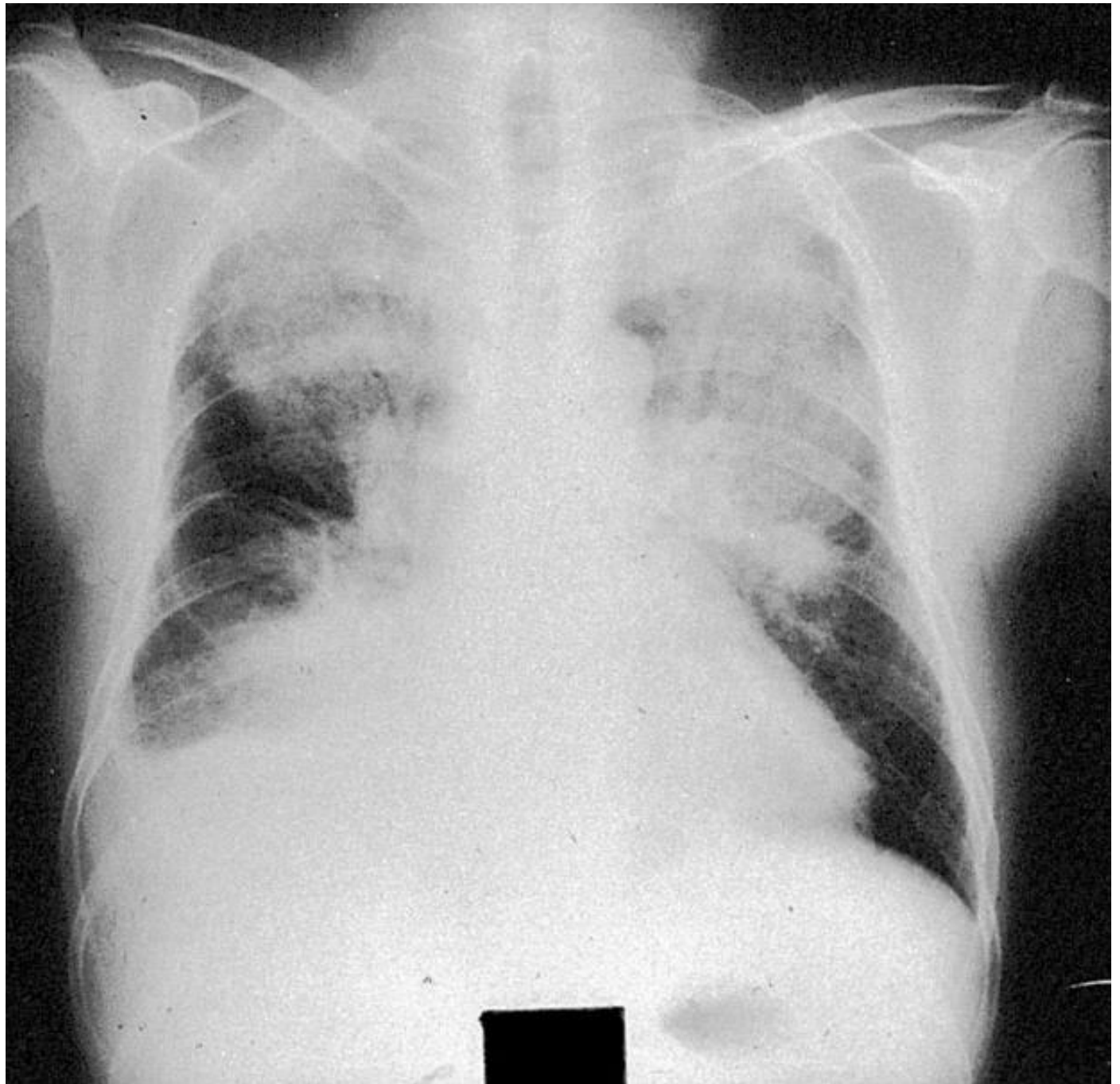


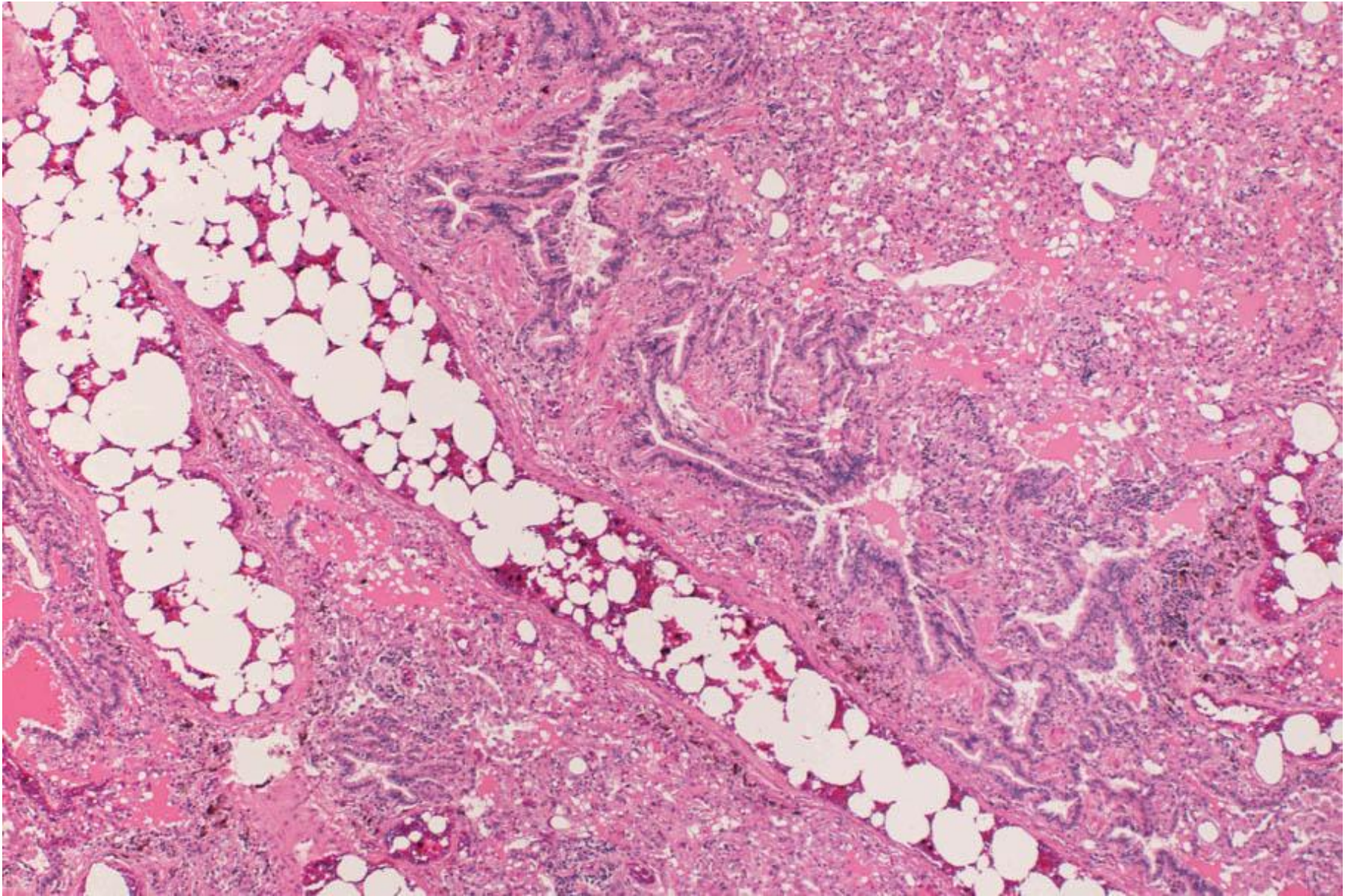
The flower of *Allium victorialis*

The bulbs of *Colchicum autumnale* are ovate and bear the lanceolate leaves in spring. The leaves blight and diapause in June. The saffron-like flowers bloom from September to October.

Fat embolism caused by multiple fractures of the femur and pelvis

A 67 y-o female patient fell down from the roof of the house during snow shoveling. Fat embolism syndrome occurs when fat enters the blood stream. Symptoms include petechial rash, a decreased level of consciousness and shortness of breath. X-ray features of pulmonary edema are shown.





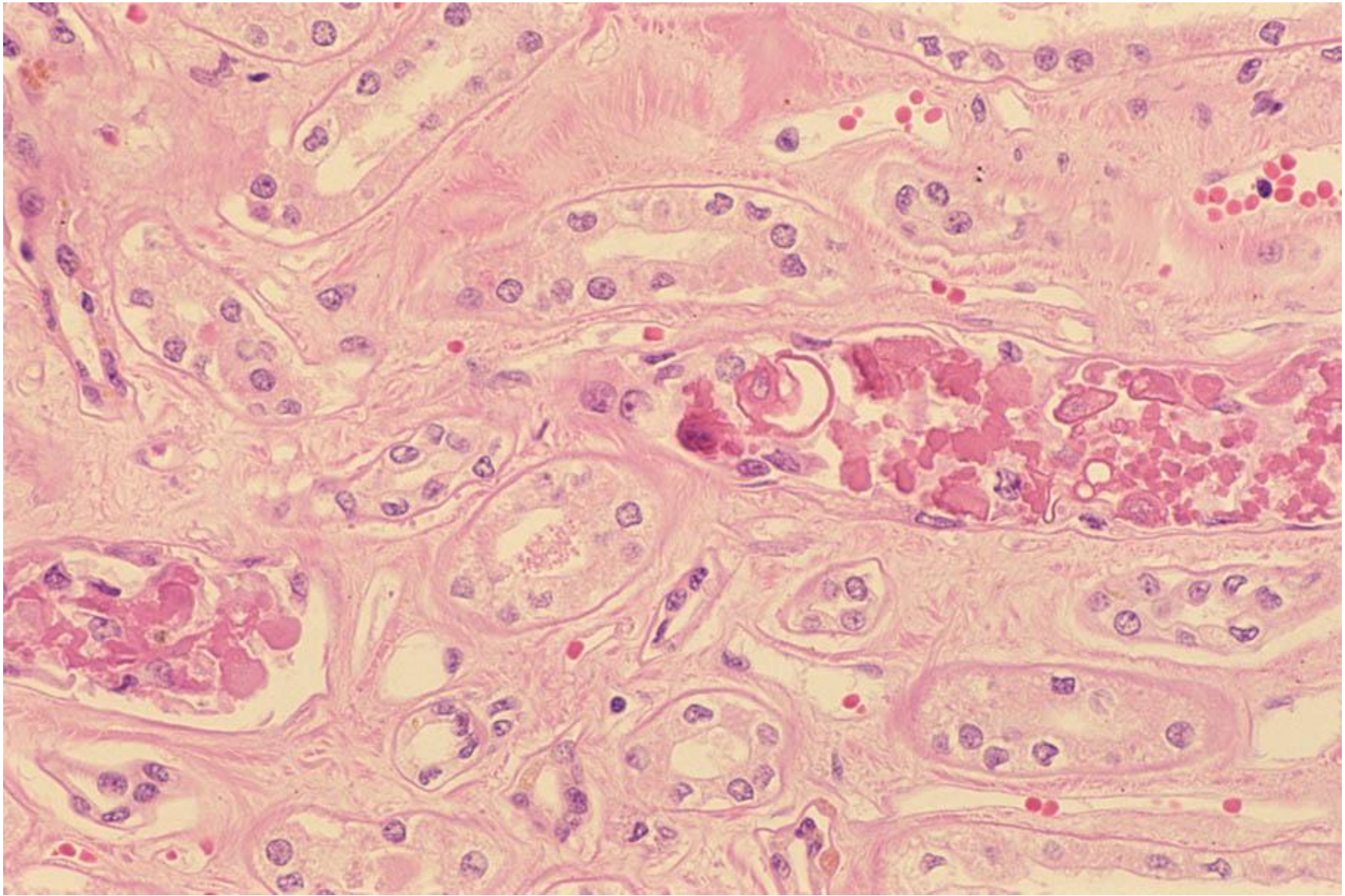
A 67 y-o female patient fell down from the roof of the house during snow shoveling. At autopsy, fat embolism is evident in the pulmonary artery branches (H&E).



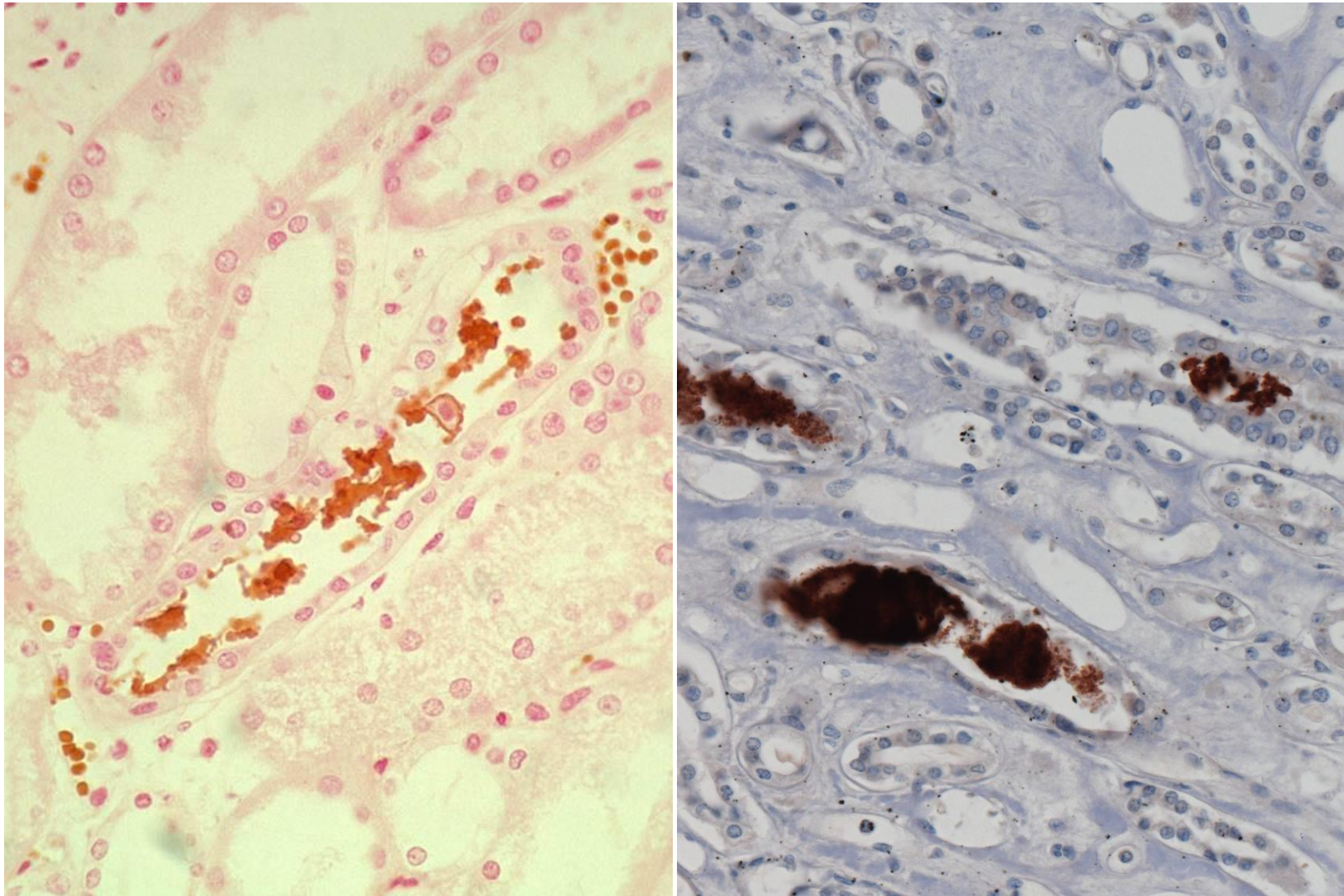
A 67 y-o female patient fell down from the roof of the house during snow shoveling. In the conjunctival mucosa, multiple petechiae are formed as a result of fat embolism (macro).

Cause of death from traumatic injuries

- 1) Hemorrhage into the body cavities
- 2) Fat embolism due to severe bone fracture
- 3) Traumatic rupture of internal organs
- 4) Secondary infection
- 5) Acute renal failure due to crush syndrome



Heme (myoglobin) casts in renal tubules in **crush syndrome** (H&E)



Heme (myoglobin) casts in renal tubules in **crush syndrome** (left: benzidine reaction, right: immunostaining for myoglobin)

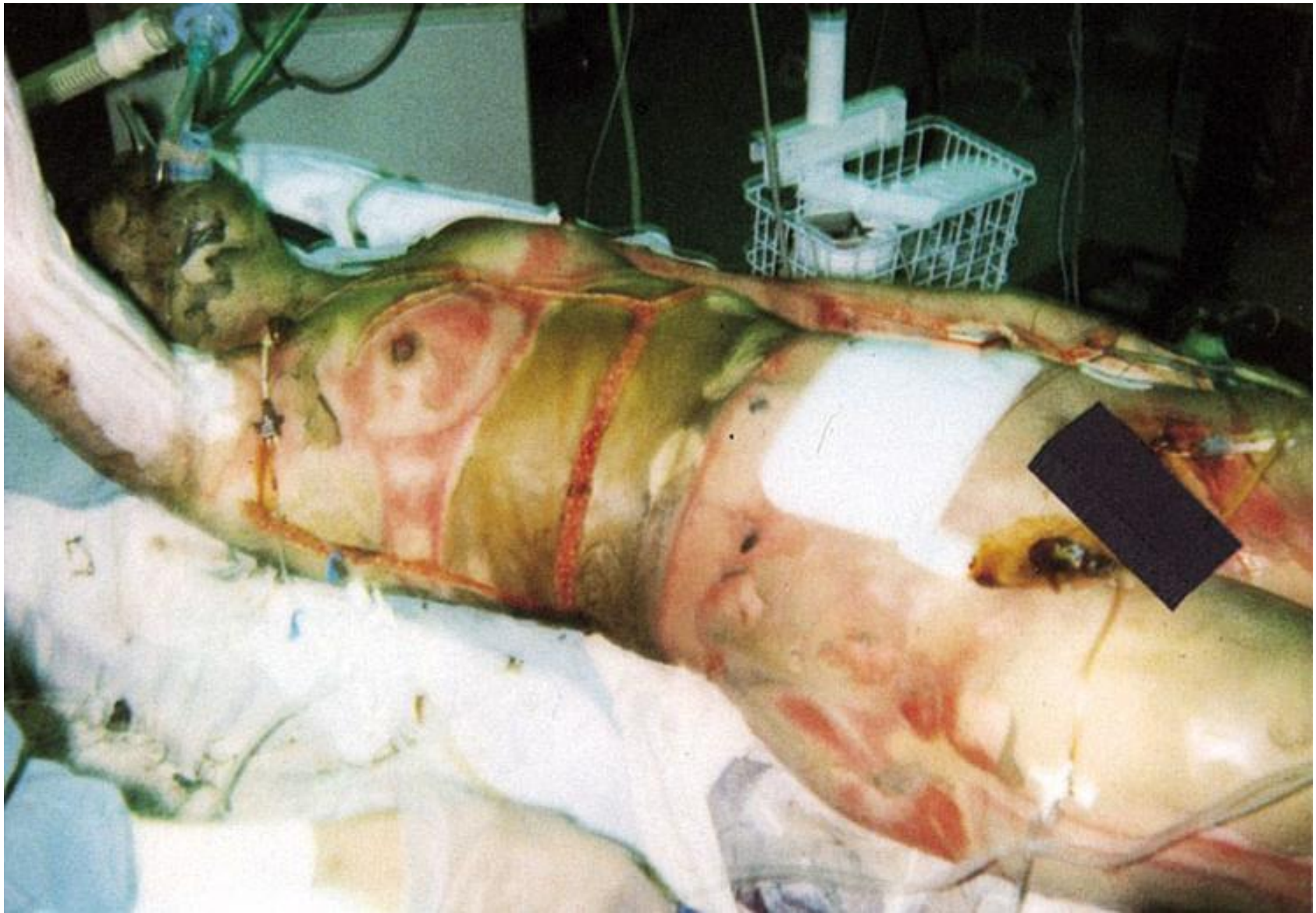
Burn

1) Classification of burn

- (1) the first degree burn (superficial)
- (2) the second degree burn (bulla formation)
- (3) the third degree burn (entire skin layer involved)

2) Complications of burn

- (1) Airway burn
- (2) Decrease of circulatory blood volume (shock)
- (3) Curling ulcer (acute gastric ulcer)
- (4) Infection (particularly, Pseudomonas infection)

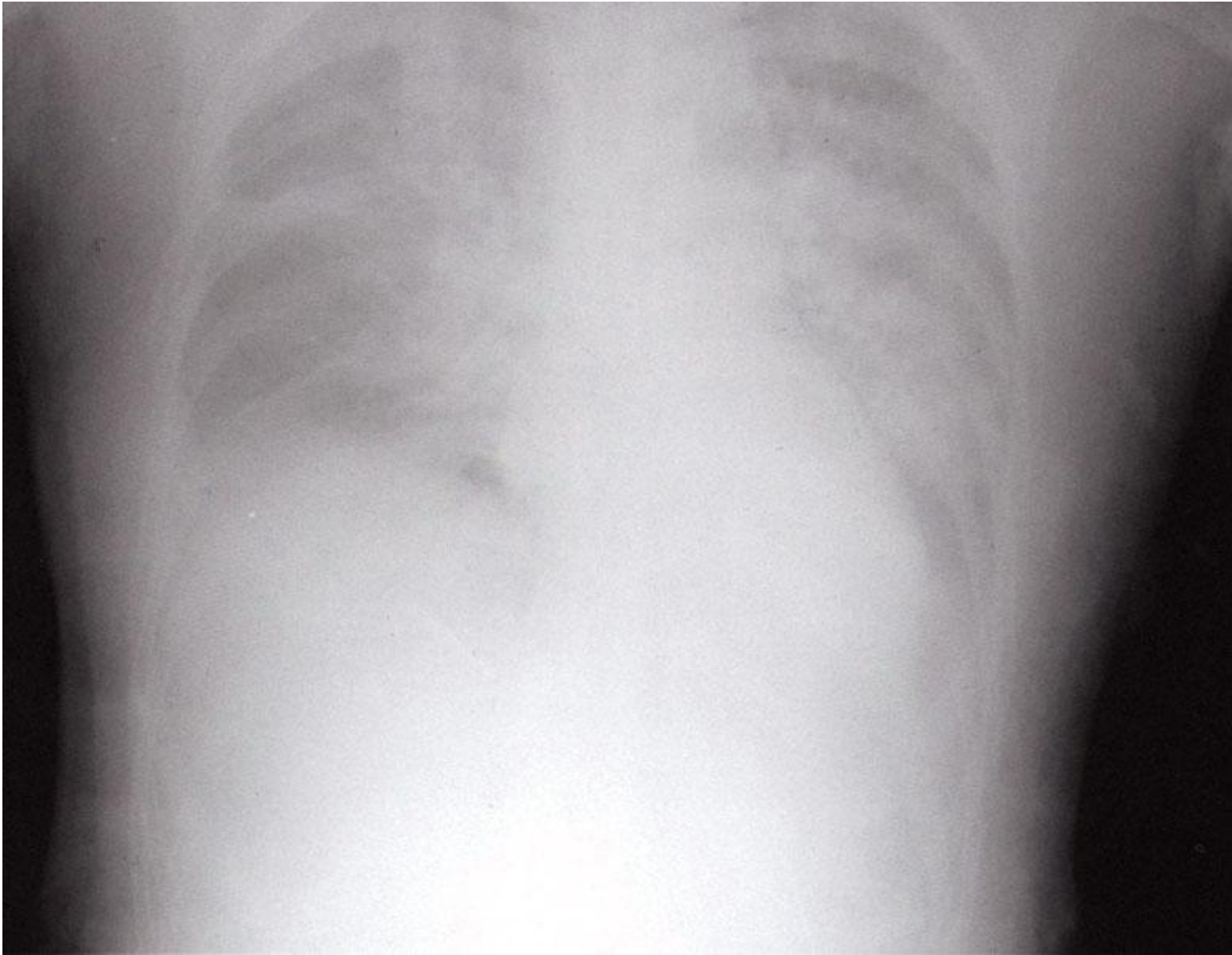


Systemic burn after relief incisions on the trunk (macro)

全身熱傷(下半身)



Systemic burn. The lower extremities are mostly spared (macro)



Chest X-ray 35 hours after the **systemic burn**. Marked pulmonary edema occurred.

Foot care is important for diabetes mellitus!



Atherosclerotic dry gangrene is seen on the 1st and 2nd toes.



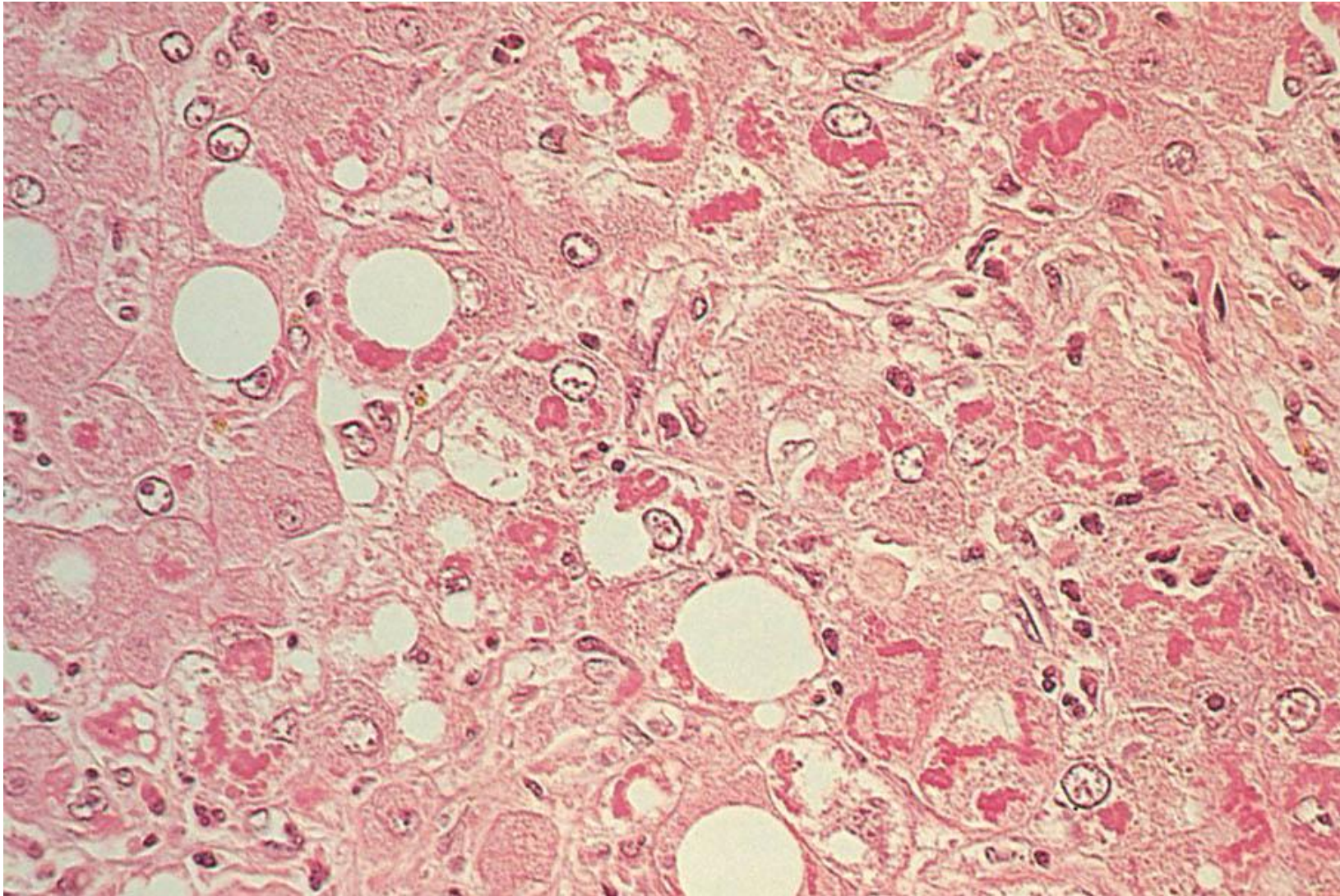
Severe burn with diabetic peripheral neuropathy. Loss of sensation accelerated burn caused by the use of a fan-heater. Amputation was performed due to progression of necrotizing fasciitis.



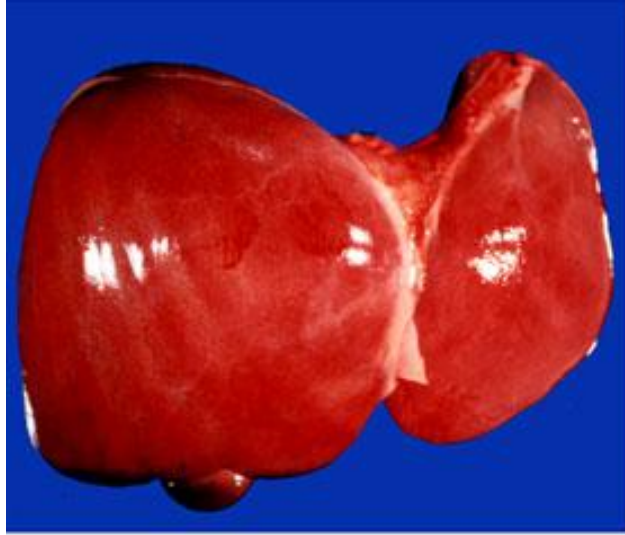
A pit viper *Gloydius blomhoffii*, called Mamushi, is the most common venomous snake in Japan. Both hemolytic toxin and neurotoxin are contained. Injection of the antivenom serum is needed. Severe bites require intensive care.



A pit viper *Gloydius blomhoffii*, called Mamushi, is the most common venomous snake in Japan. The snake bit the left 2nd finger of an 81 y-o farmer during his mowing the grass. The site of bite is encircled. The left-sided panels shows 40 minutes after the bite. In the right-sided panels, marked swelling of the hand and forearm on the next day is shown.



Alcoholic hepatitis. A 52 y-o male patient drank alcohol for 30 years (taking 180 g ethanol/day). In the biopsy specimen, fatty change and Mallory body formation are evident. Neutrophilic infiltration is mildly associated. H&E



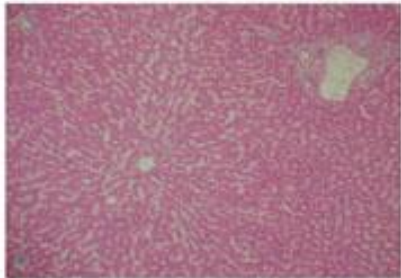
Normal liver



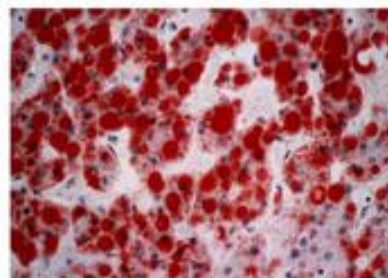
Fatty liver



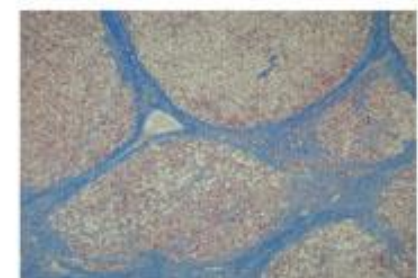
Liver cirrhosis



H&E



Oil red O



Masson trichrome

Alcoholic liver diseases (from fatty liver to liver cirrhosis)

Alcohol abuse (chronic alcoholism)

- 1) Alcoholic hepatitis and alcoholic cirrhosis
- 2) Acute and chronic pancreatitis
- 3) Alcoholic (dilated) cardiomyopathy
- 4) Alcoholic myopathy and alcoholic peripheral neuropathy
- 5) Encephalopathy (Wernicke–Korsakoff syndrome)

=thiamine (vitamin B1) deficiency

Wernicke syndrome: ophthalmoplegia, ataxia and confusion

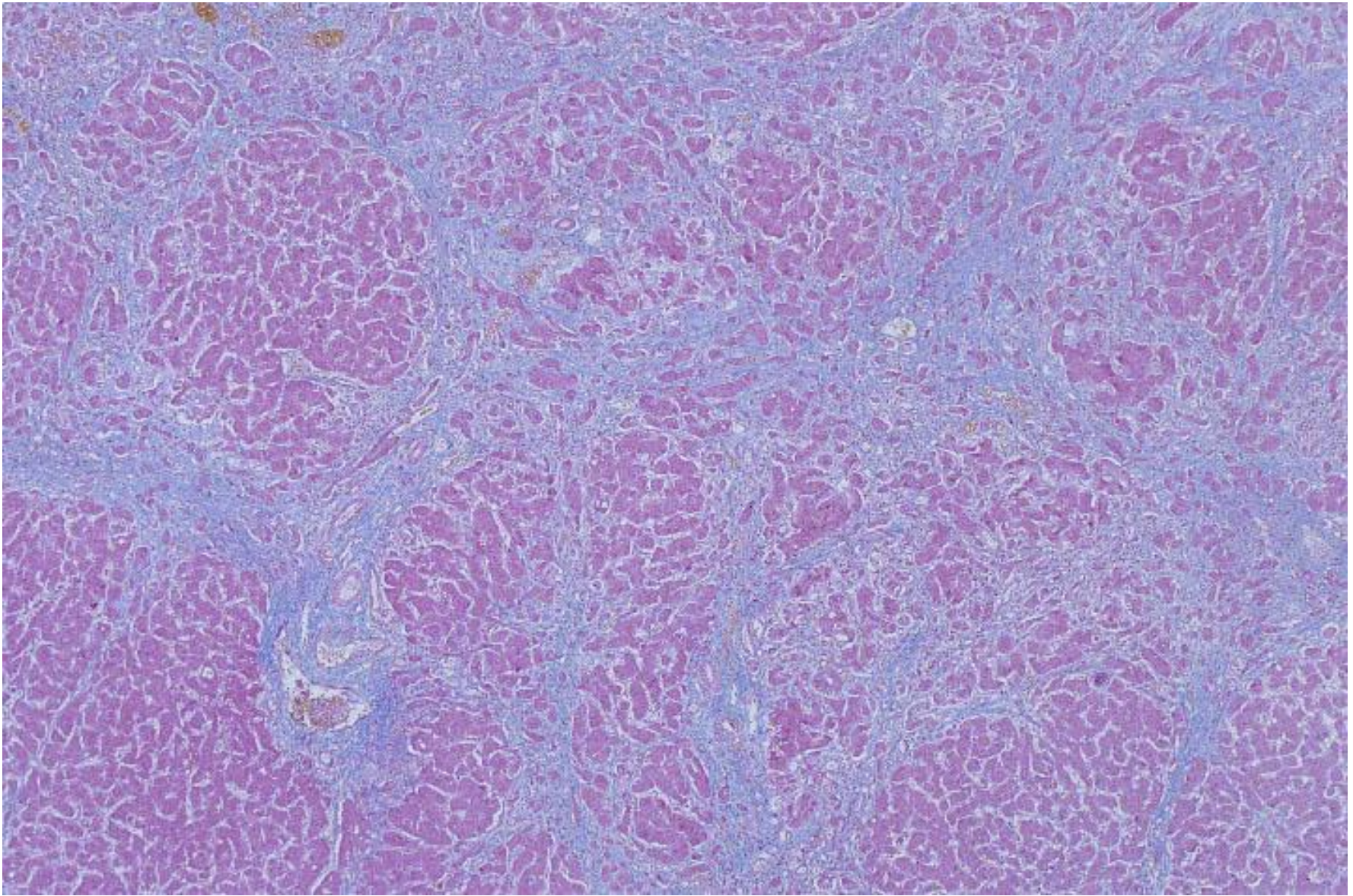
Korsakoff syndrome: amnesia and confabulation

Case presentation-3

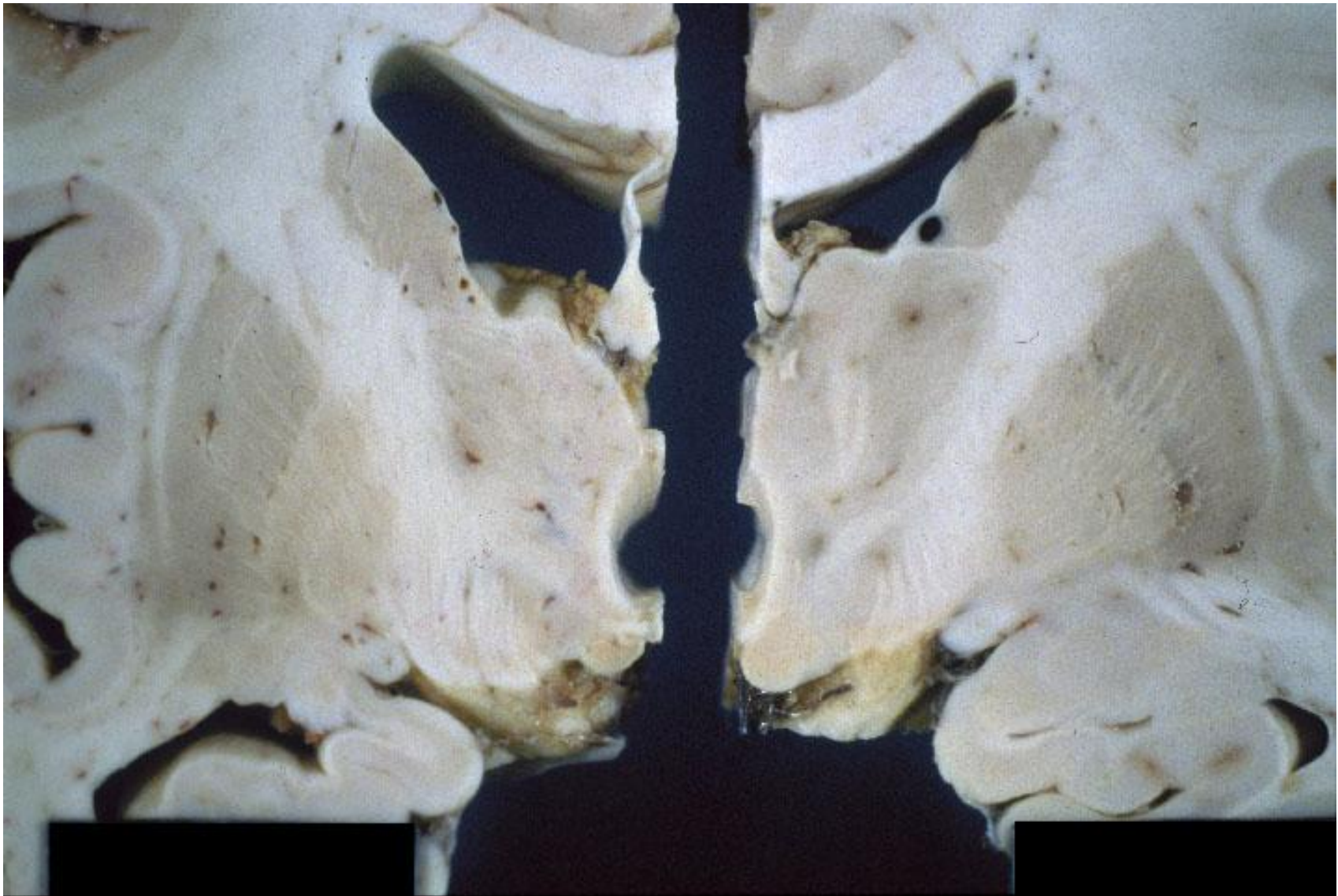
- 1) Wernicke encephalopathy (vitamin B1 deficiency)
- 2) Reye syndrome
- 3) Influenza encephalopathy
- 4) Black nail
- 5) Adriamycin cardiomyopathy
- 6) 5-fluorouracil (5-FU)-induced gastroenteropathy



Alcoholic liver disease = alcoholic liver fibrosis (macro)

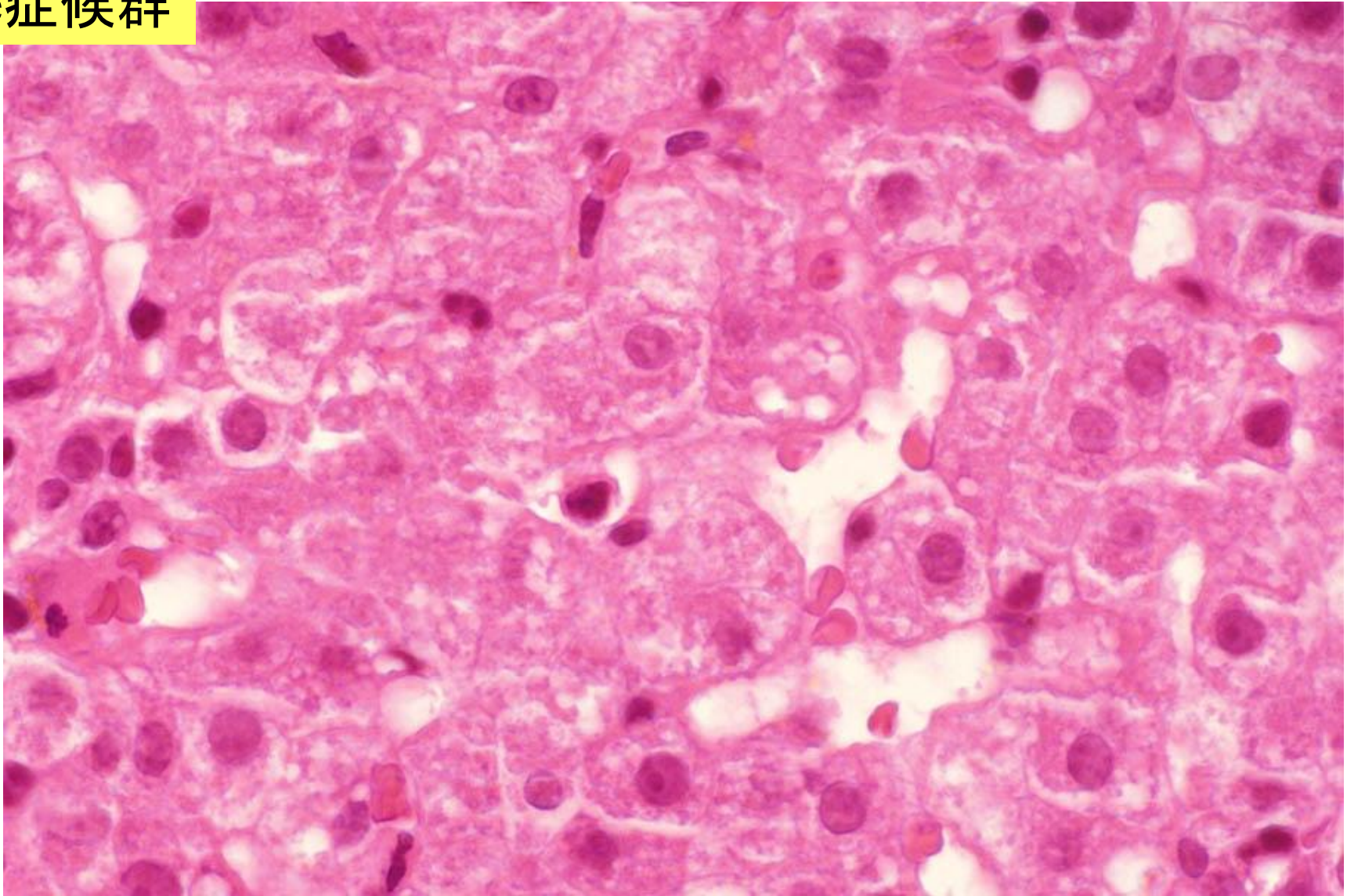


Alcoholic liver disease = alcoholic liver fibrosis (Azan)



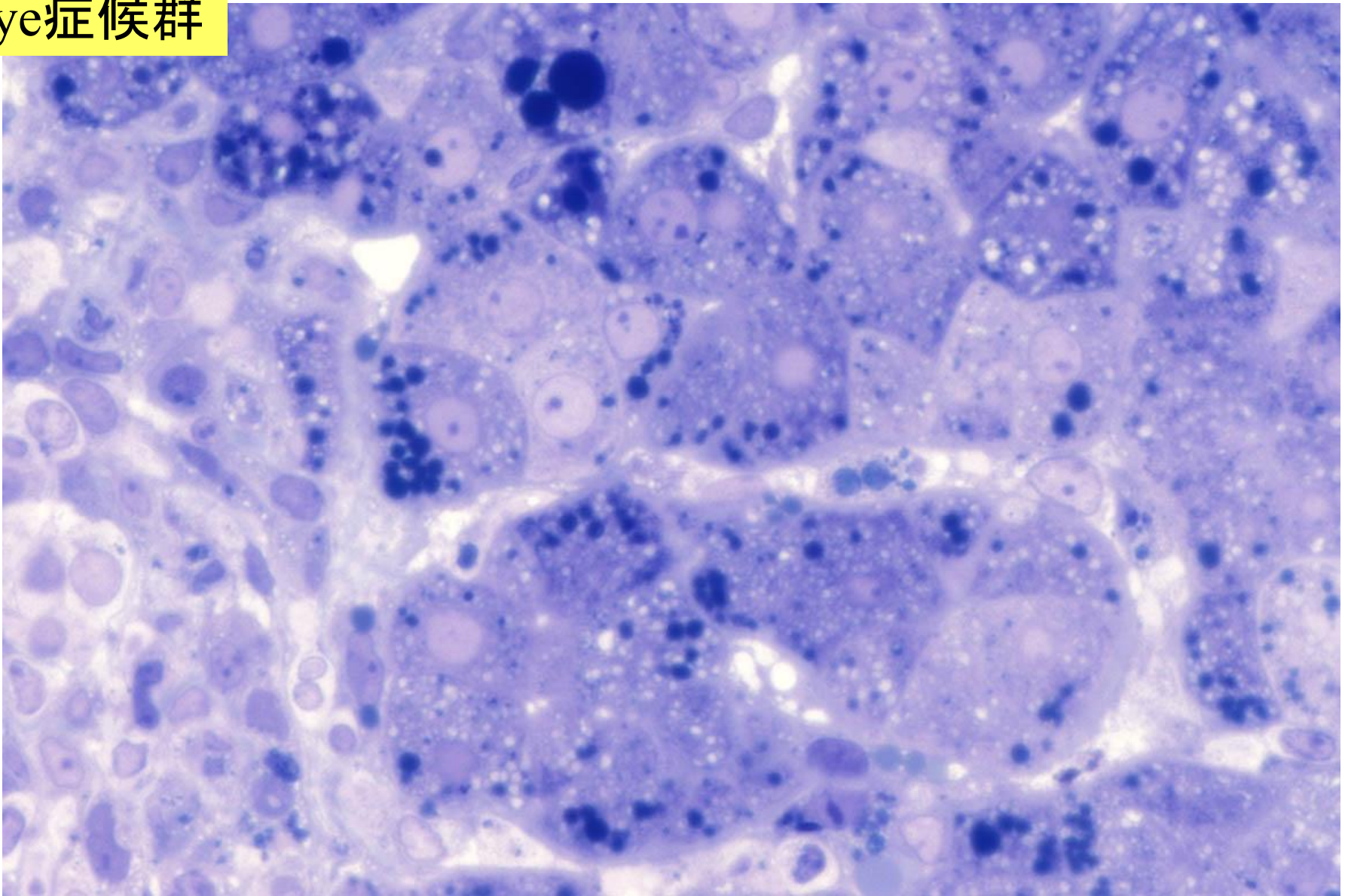
Gross appearance of alcoholism-related Wernicke encephalopathy: atrophy of the mamillary body (left). Compare with the normal control (right). Wernicke encephalopathy is clinically featured by ophthalmoplegia, ataxia and confusion.

Reye症候群



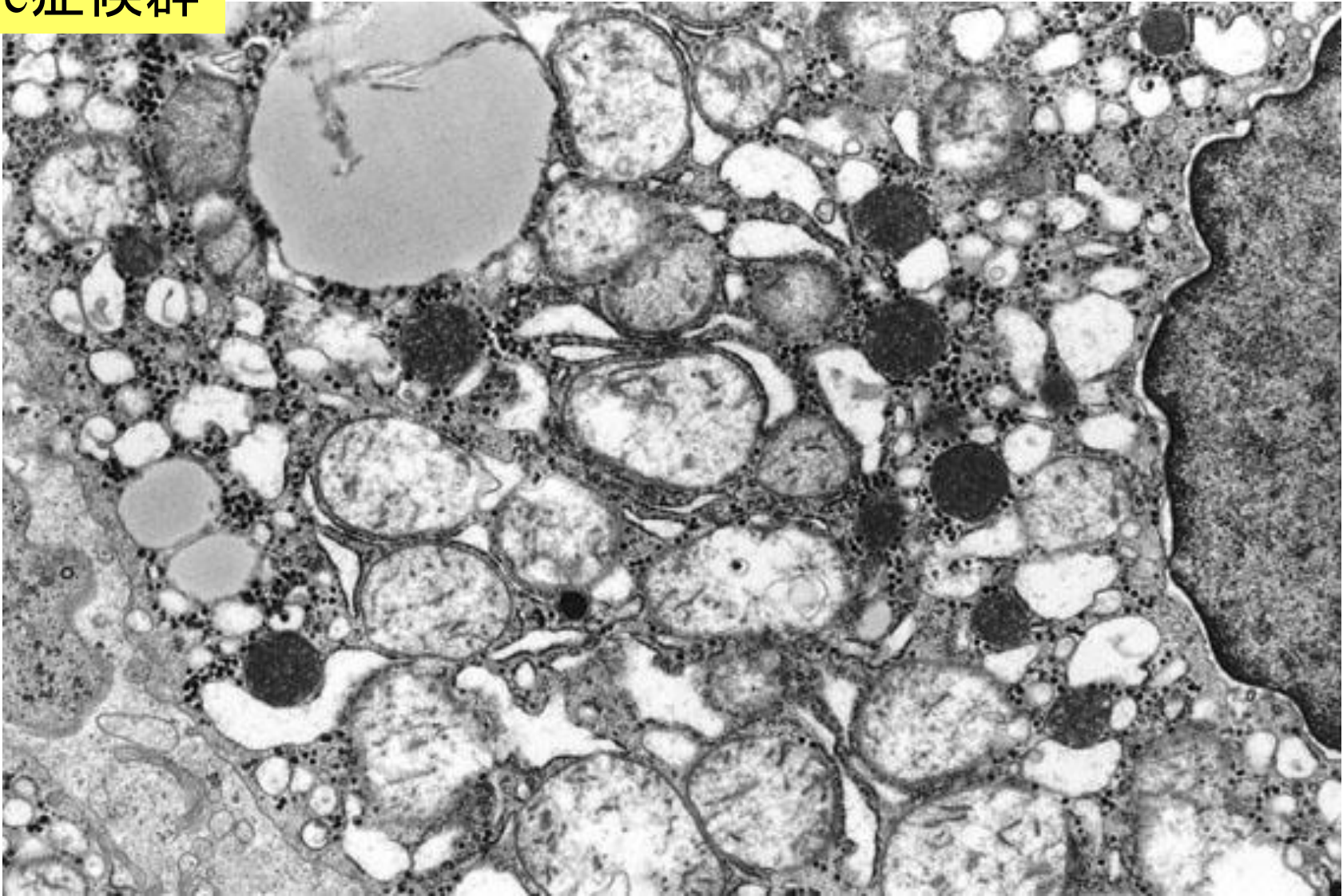
Reye syndrome seen in a 6 y-o girl who took aspirin for high fever.
The autopsy liver reveals fine-droplet fatty change. H&E

Reye症候群



Reye syndrome seen in a 6 y-o girl who took aspirin for high fever.
The autopsy liver reveals fine-droplet fatty change. Toluidine blue staining
in thick section for EM study

Reye症候群



Reye syndrome seen in a 6 y-o girl who took aspirin for high fever. EM study for the autopsy liver reveals fine fat droplets and derangement or loss of cristae of the mitochondria. EM

Reye症候群



Reye syndrome in a 6 y-o girl. Grossly, the brain is markedly swollen, weighing 1,500 g. Mitochondrial dysfunction is the mechanism of the brain damage.

Adverse effects of analgesics

1. Aspirin (acetylsalicylic acid)

a) Gastroduodenal ulcer

b) Reye syndrome (fine fatty change of the liver and encephalopathy)

~ use of aspirin against acute febrile viral infection in children may provoke acute encephalopathy=Reye syndrome~

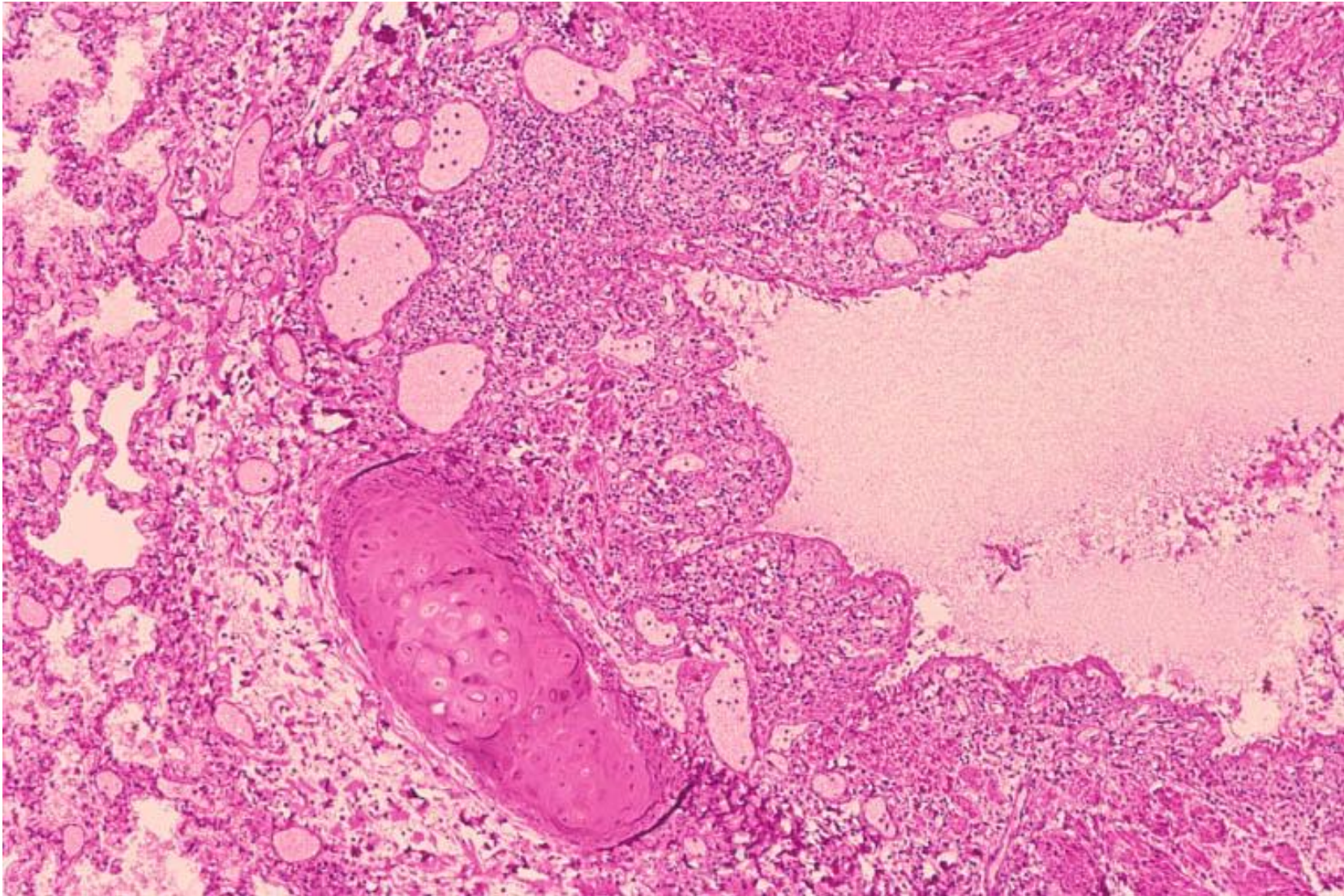
c) Aspirin asthma

2. Non-steroidal anti-inflammatory drugs (NSAIDs)

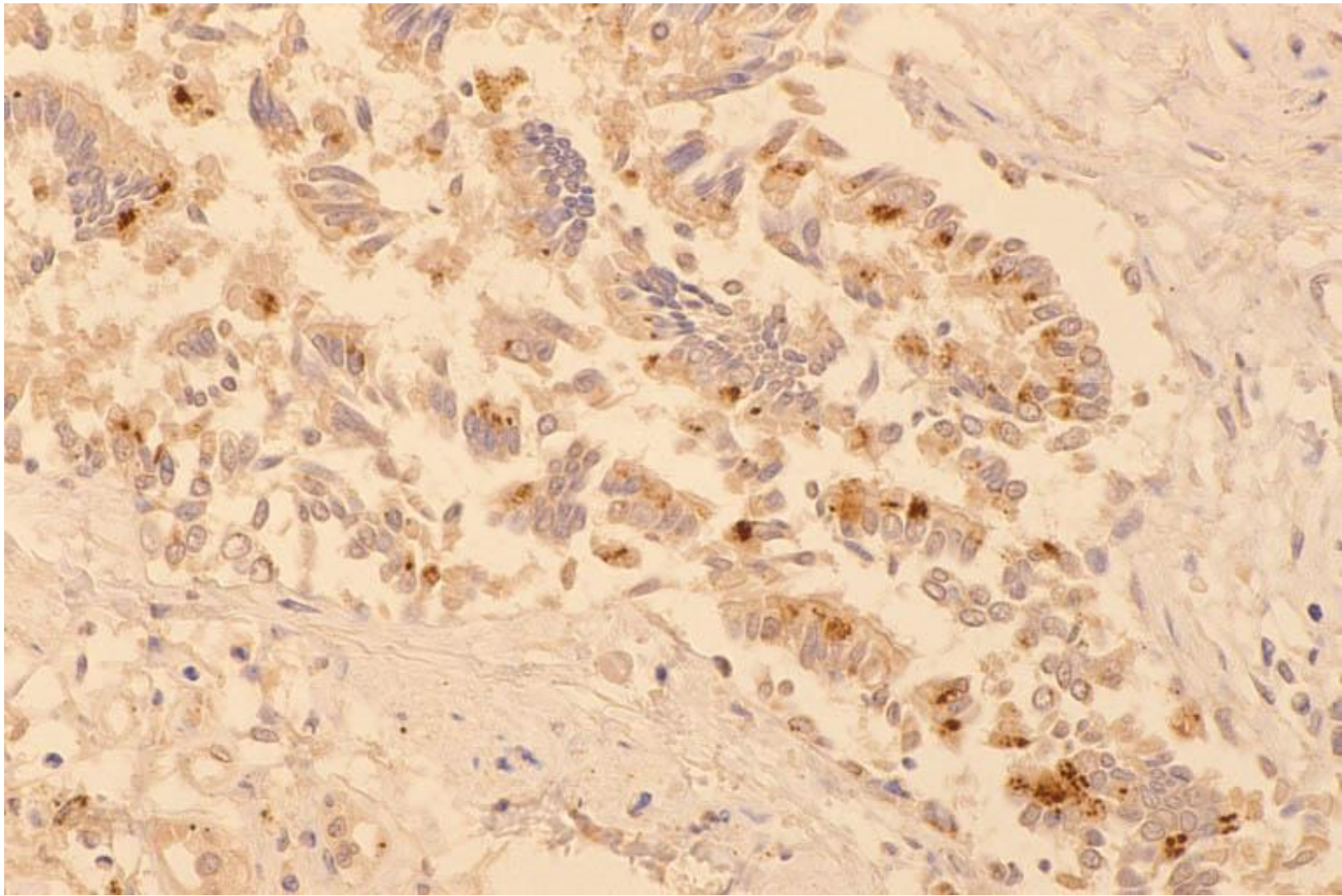
NSAIDs are closely related to influenza encephalopathy in children

~ Do not use NSAIDs for febrile children, except for acetoaminophen~

Diclofenac sodium (Voltaren/Loxonin), Indomethacin, Mefenamic acid (Pontal/ponstel), Sulpyrine (Metamizole/Dipyrone/Methylone)



An 11 y-o obese boy used Indomethacine suppository to relieve high fever caused by influenza. He soon died of acute encephalopathy. Forensic autopsy identified bronchitis. H&E



An 11 y-o obese boy used Indomethacine suppository to relieve high fever caused by influenza. He soon died of acute encephalopathy. The cytoplasm of the bronchial mucosal epithelial cells, type A influenza virus antigens were demonstrated, confirming the diagnosis of influenza A. Don't use NSAIDs for children. Immunostaining for influenza virus A antigens

Anthracyclines for infusion (colored anti-cancer drugs)



Doxorubicin
(Adriamycin)



Daunorubicin



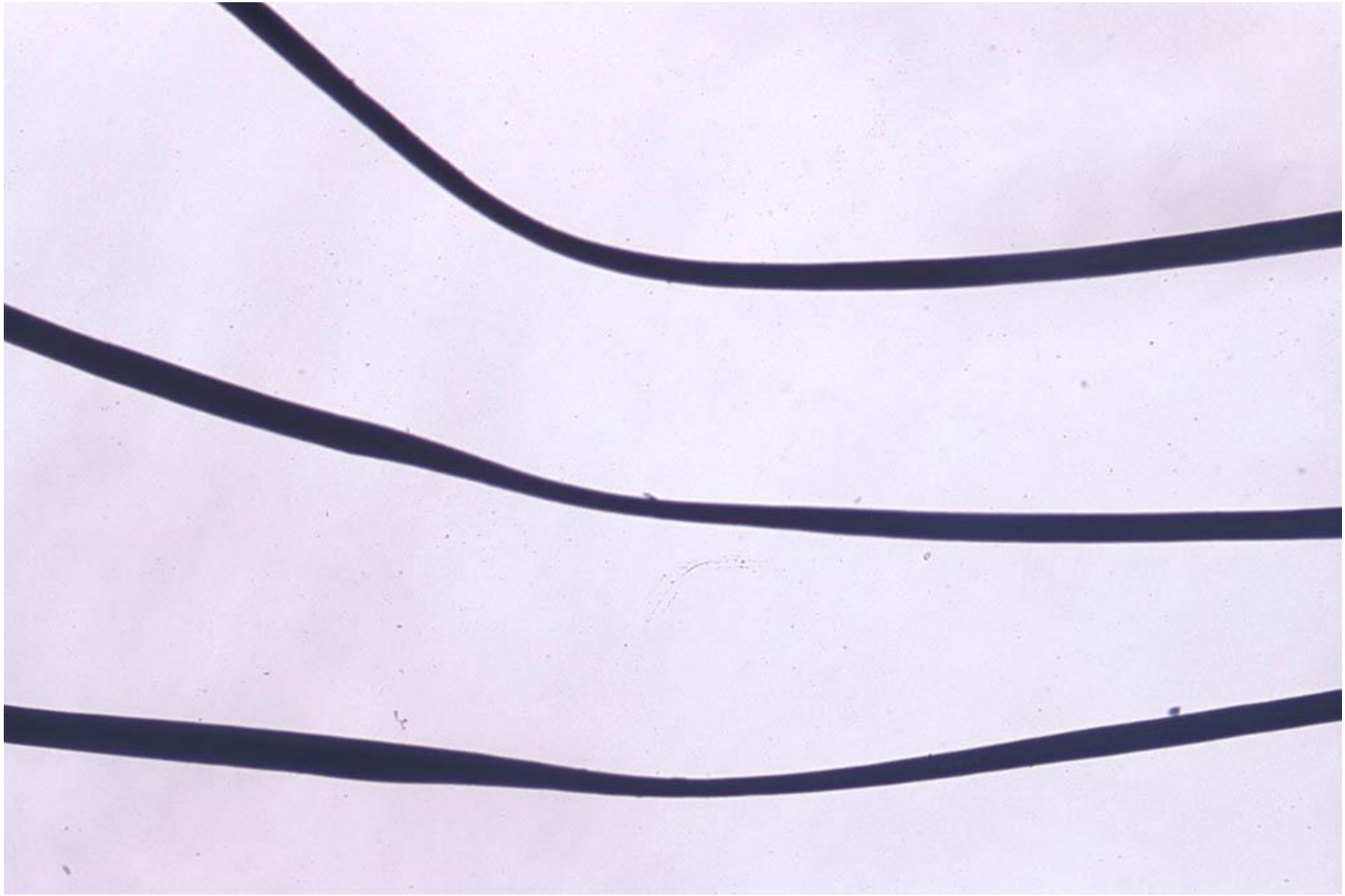
Mitoxantrone



Pirarubicin



Aclarubicin



Deformed hair (after chemotherapy for breast cancer): periodic thinning of hair, corresponding to the chemotherapeutic period

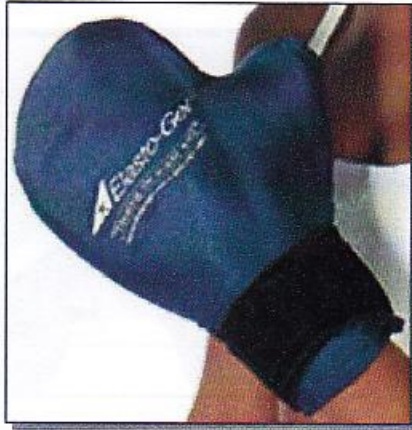


Black nails: deposition of black color in the nail caused by chemotherapy against breast cancer



Nail detachment caused by chemotherapy with Docetaxel (Taxotere) for breast cancer: a frequent adverse effect of this anti-cancer drug

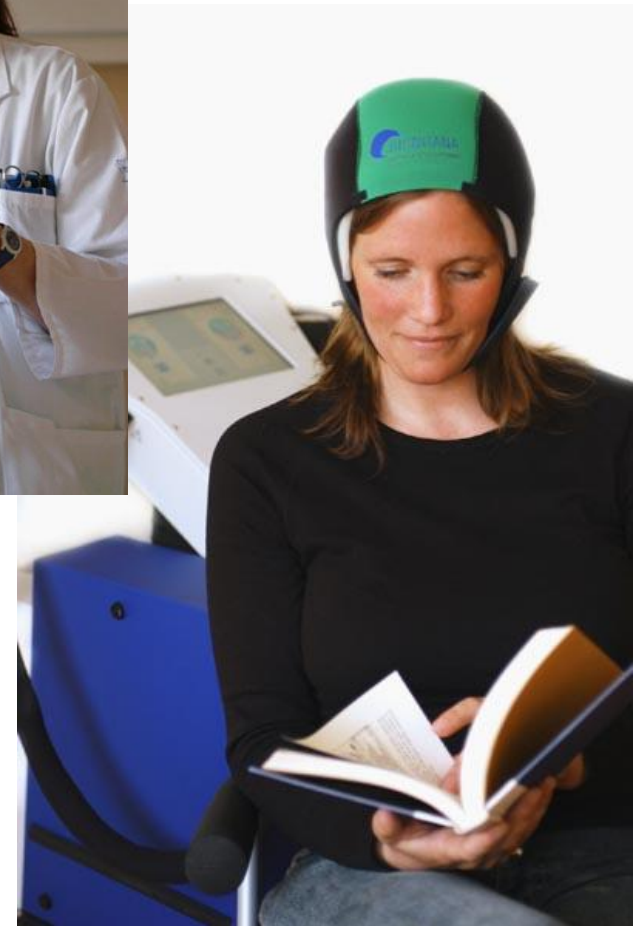
Goods for preventing hair loss and nail deformity

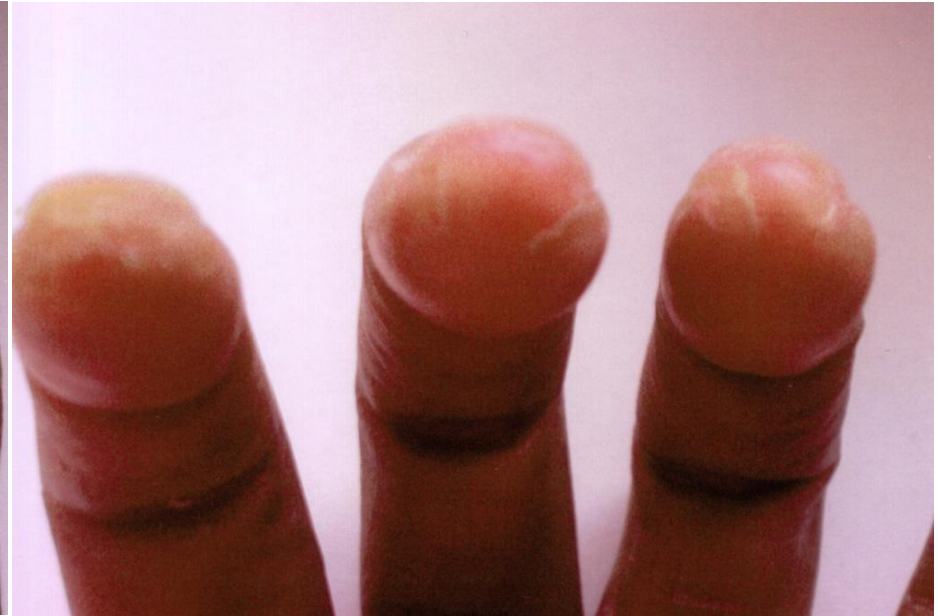


Elasto-Gel (MASI)
(low temperature cap, gloves and socks)



DigniCap





Hand foot syndrome-1 (adverse effects of Capecitabine: 5-FU derivative)



Hand foot syndrome-2 (adverse effects of Capecitabine: 5-FU derivative)

Adverse effects of medicines

Medicines are a kind of double-edged swords
(pros and cons)

Antibiotics

- 1) Production of drug-resistant bacteria
 - a) transmission of plasmids containing drug-resistance genes
 - b) mutations of the somatic bacterial genes
- 2) Direct cell injuries or allergic reactions

Example: aplastic anemia caused by chloramphenicol

Adverse effects of anti-cancer drugs

1) Cytotoxicities:

hair loss, nail abnormalities, nausea/vomiting, diarrhea, bone marrow suppression

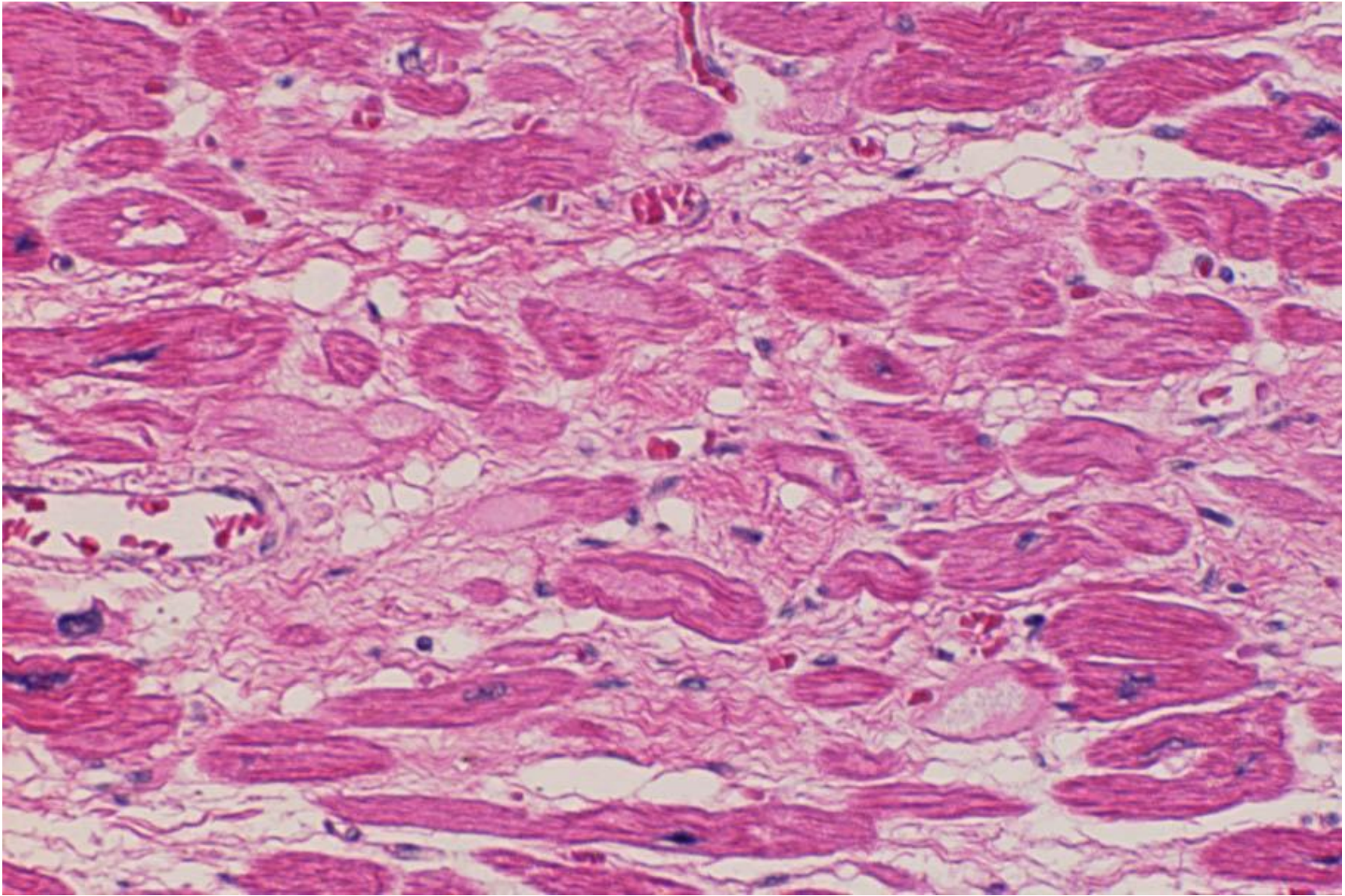
2) Adverse effects specific to the respective drugs

a) Adriamycin cardiomyopathy

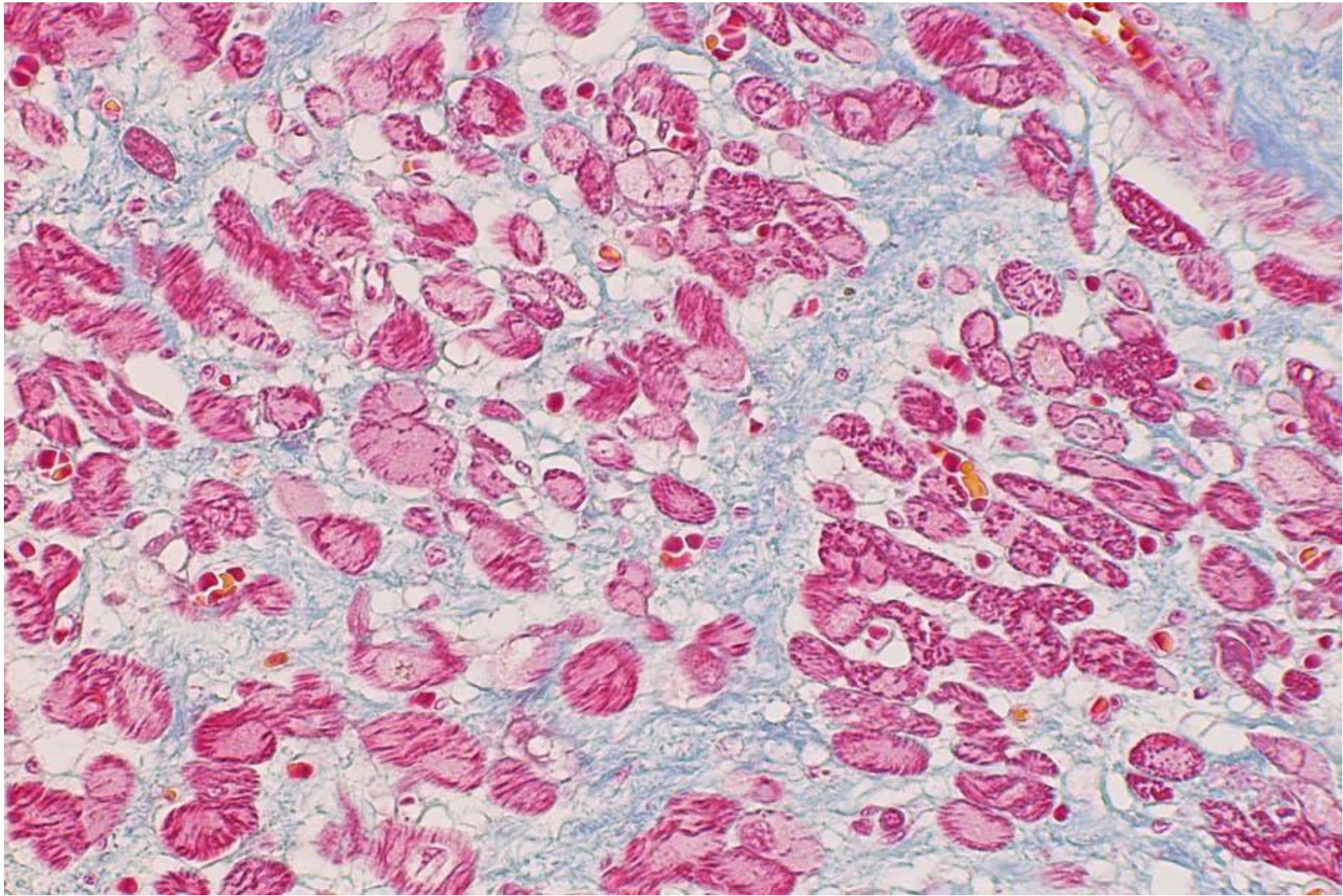
b) Cisplatin nephropathy

3) Carcinogenicities:

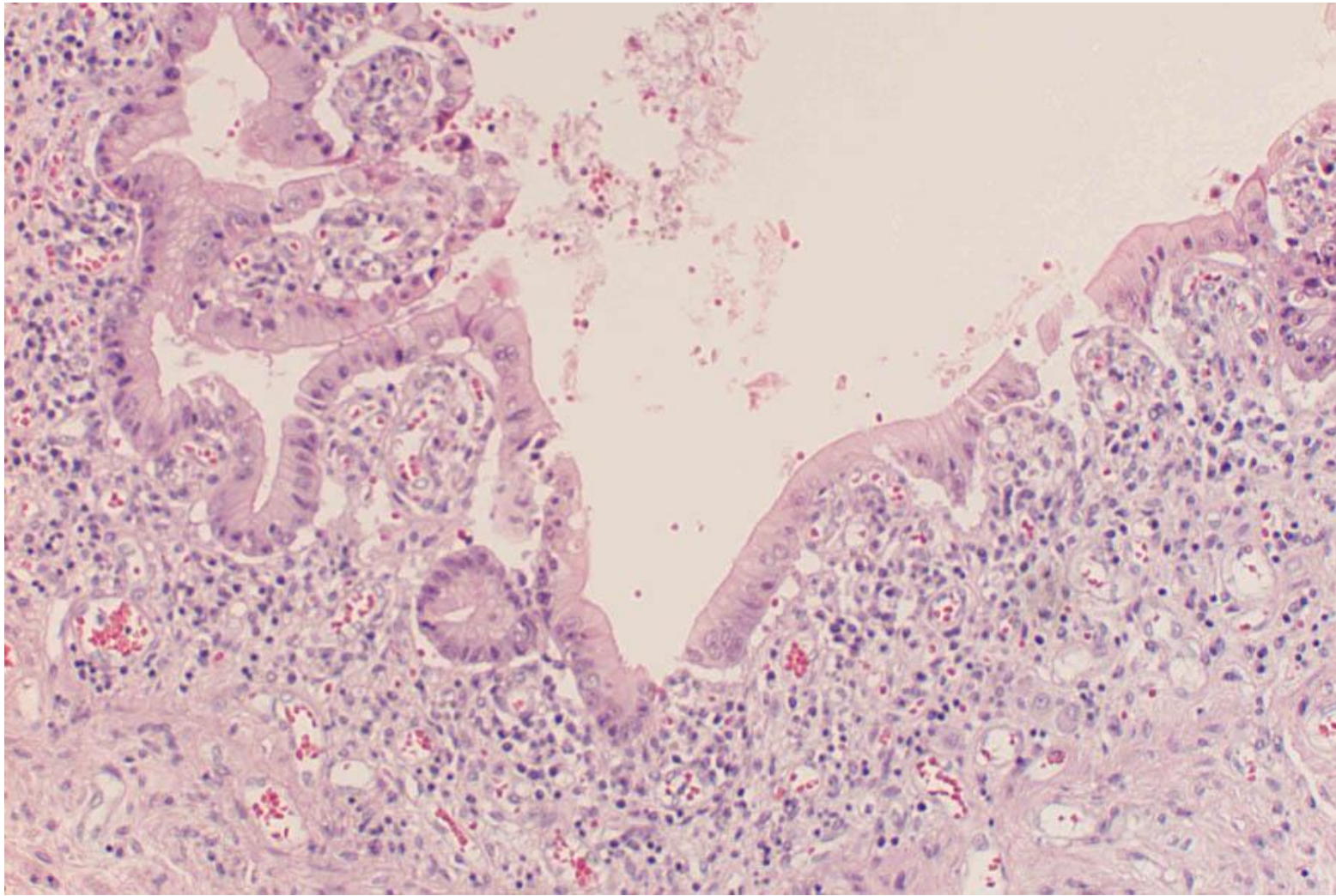
acute leukemia and other malignancies



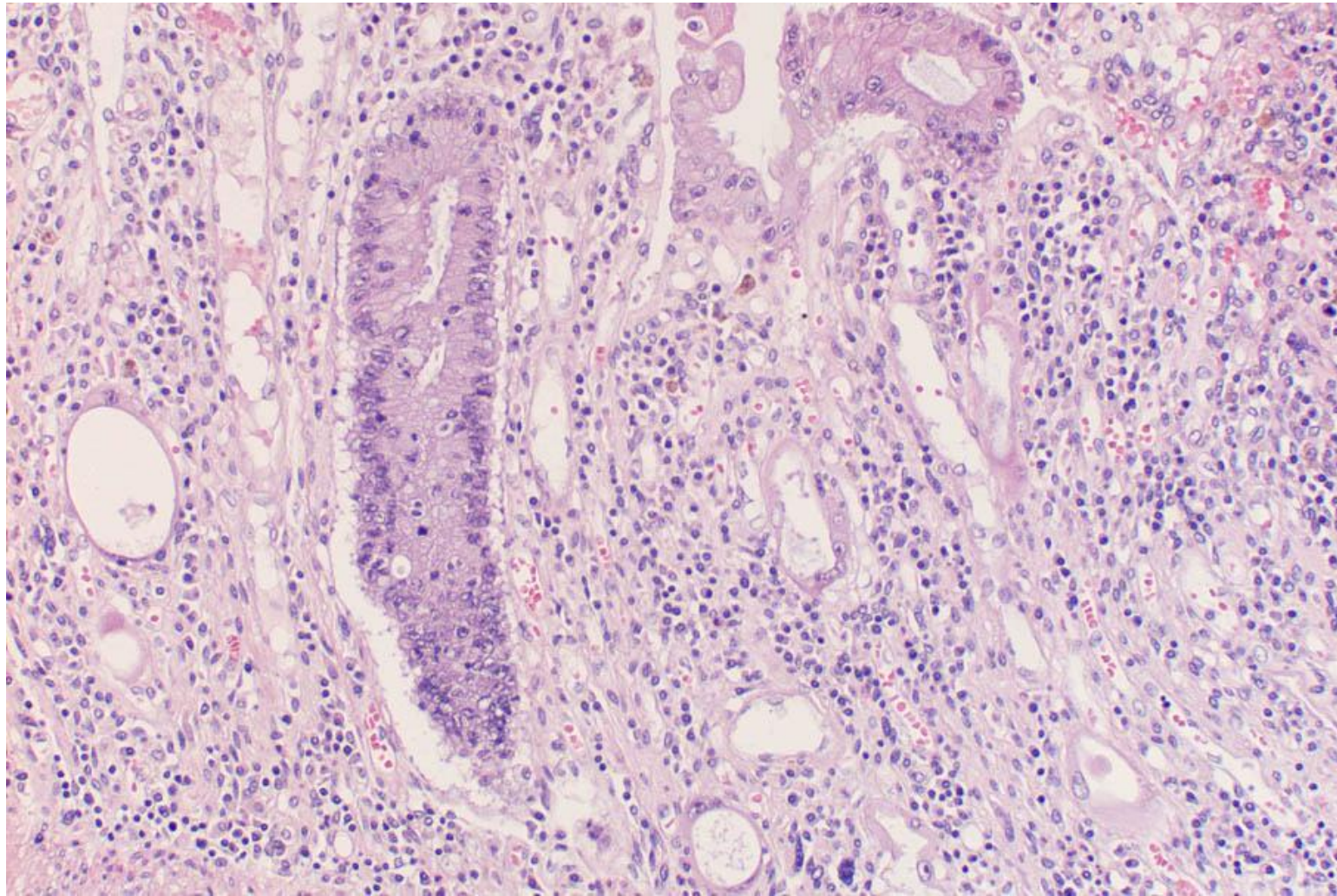
Adriamycin cardiomyopathy lethal to the young female patient with acute myelogenous leukemia: Adriamycin-induced interstitial fibrosis and loss of myofibrils in cardiomyocytes (H&E)



Adriamycin cardiomyopathy lethal to the young female patient with acute myelogenous leukemia: Adriamycin-induced interstitial fibrosis and loss of myofibrils in cardiomyocytes (Azan)



Severe adverse effects of oral 5-FU derivatives on the small bowel mucosa. A 67 y-o female patient with bile duct carcinoma continued to take the medicine until death, in spite of the persistence of intractable diarrhea and aphagia. The patient might have a deficient dihydropyrimidine dehydrogenase (DPD), a 5-FU metabolizing enzyme. At autopsy, loss of intestinal crypt epithelial cells is evident (H&E).



Severe adverse effects of oral 5-FU derivatives on the colonic mucosa. A 67 y-o female patient with bile duct carcinoma continued to take the medicine until death, in spite of the persistence of intractable diarrhea and aphagia. The patient might have a deficient dihydropyrimidine dehydrogenase (DPD), a 5-FU metabolizing enzyme. At autopsy, loss of colonic crypt epithelial cells is evident (H&E).

Three kinds of cells in the body

Renewing cell	Thymic cortical lymphocytes, germinal center lymphocytes in the lymphoid tissue, hematopoietic stem cells, epidermal keratinocytes, hair follicle epithelial cells, gastrointestinal mucosal epithelial cells, spermatogonia of the testis and cancer cells
Stabilized cell	Hepatocytes, renal tubular epithelial cells, lung alveolar epithelial cells, mammary ductal cells, glia cells, endothelial cells, mesothelial cells, fibroblasts, adipocytes, smooth muscle cells, Schwann cells, osteoblasts, etc.
Stable cell	Neurons, striated muscle cells, cardiomyocytes, ova

Radiation injuries

Radiation injuries are caused via formation of free radicals.

- 1) Skin injury (dermatitis and ulcer formation)
- 2) Lung injury (acute/chronic interstitial lung lesions)
- 3) Gastrointestinal mucosal injury
- 4) Bone marrow suppression
- 5) Carcinogenesis (late-stage adverse effects)
 - a) Acute myelogenous leukemia: AML (NOT ALL)
 - b) Solid malignancies of the bone, skin, thyroid, lung or breast

Radiosensitivity of the cell

Sensitivity	Cells	Features
Highly sensitive	Lymphoid cells, hematopoietic cells, stem cells, gastrointestinal epithelial cells, cancer cells	Renewing cells with active mitoses, particularly the cells in mitosis
Moderately sensitive	Fibroblasts, endothelial cells, cells in elastic tissue, salivary gland cells, cells in the eye ball	
Lowly sensitive	Bone, cartilage, muscle cells, central nervous system, kidney, liver, most endocrine cells	Non-mitotic or poorly mitotic cells