
CONSULTATIO · ERUDITIO · INVESTIGATIO

Hepatotoxicity of Metals

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Acute Hepatotoxicity

- Acute Hepatocellular

  Panlobular degeneration

  Mononucleosis-like

  Submassive necrosis

  Massive necrosis

  Combined hepatocellular and cholestatic

Acute Hepatotoxicity

- Acute Cholestatic; Pure;
  +hepatocellular injury;
  +bile duct injury, = cholangitis
- Microvesicular steatosis
- Vasculitis, hypersesitivity-type
- Angiitis, necrotizing

Chronic Reactions

- Chronic hepatitis
- Chronic intrahepatic cholestasis
- Macrovesicular steatosis
- Phospholipidosis

Chronic Reactions

- Granulomatous reactions
- Fibrosis
- Cirrhosis
- Sinusoidal dilation

Chronic Reactions

- *Peliosis hepatis*
- *Veno-occlusive disease*
- *Hepatic vein thrombosis*
- *Neoplasia, benign & malignant*

Hepatotoxicity of Metals
Modes of Exposure

- Ingestion: Accidental, suicidal, industrial, domestic, medicinal (prescription of folk remedies)
- Inhalation
- Absorption from skin

Hepatotoxicity of Metals
The Culprits (1)

- Aluminum
- Barium
- Cadmium
- Copper
- Iron
- Arsenic
- Beryllium
- Chromium
- Gold
- Lead

Hepatotoxicity of Metals
The Culprits (2)

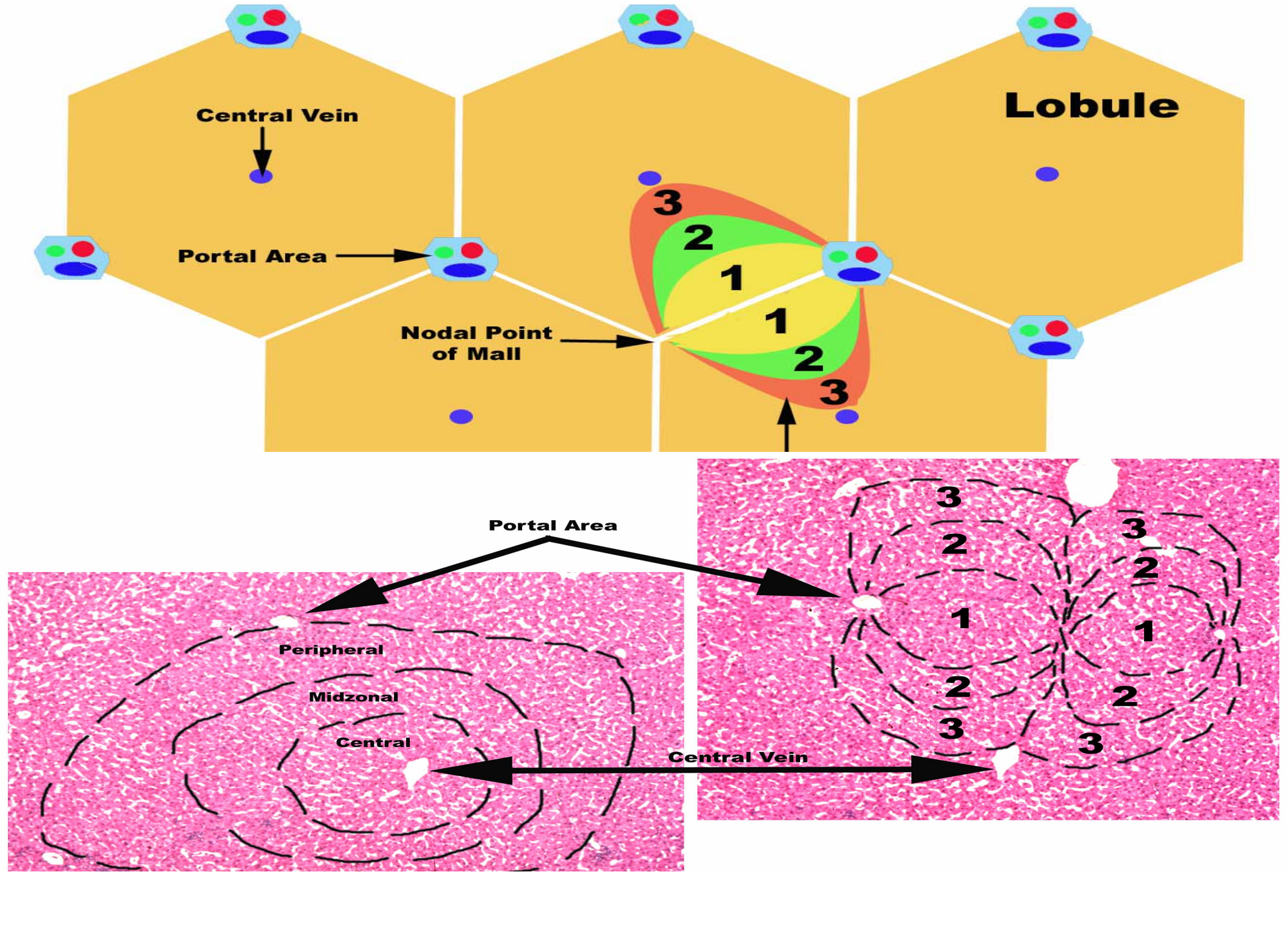
- Manganese
- Phosphorus
- Thallium
- Titanium
- Nickel
- Silver
- Thorium
- Zinc

Hepatotoxicity of Metals
Identification/Quantitation of Metals (1)

- Histopathology: Brown (e.g. Fe) or black pigment (e.g. Au or Ti)
- Polarizing microscopy (e.g. Au, Ti, Ba)
- Special stains: Prussian blue (Fe); rhodanine (Cu); Victoria blue (Cu-binding protein)

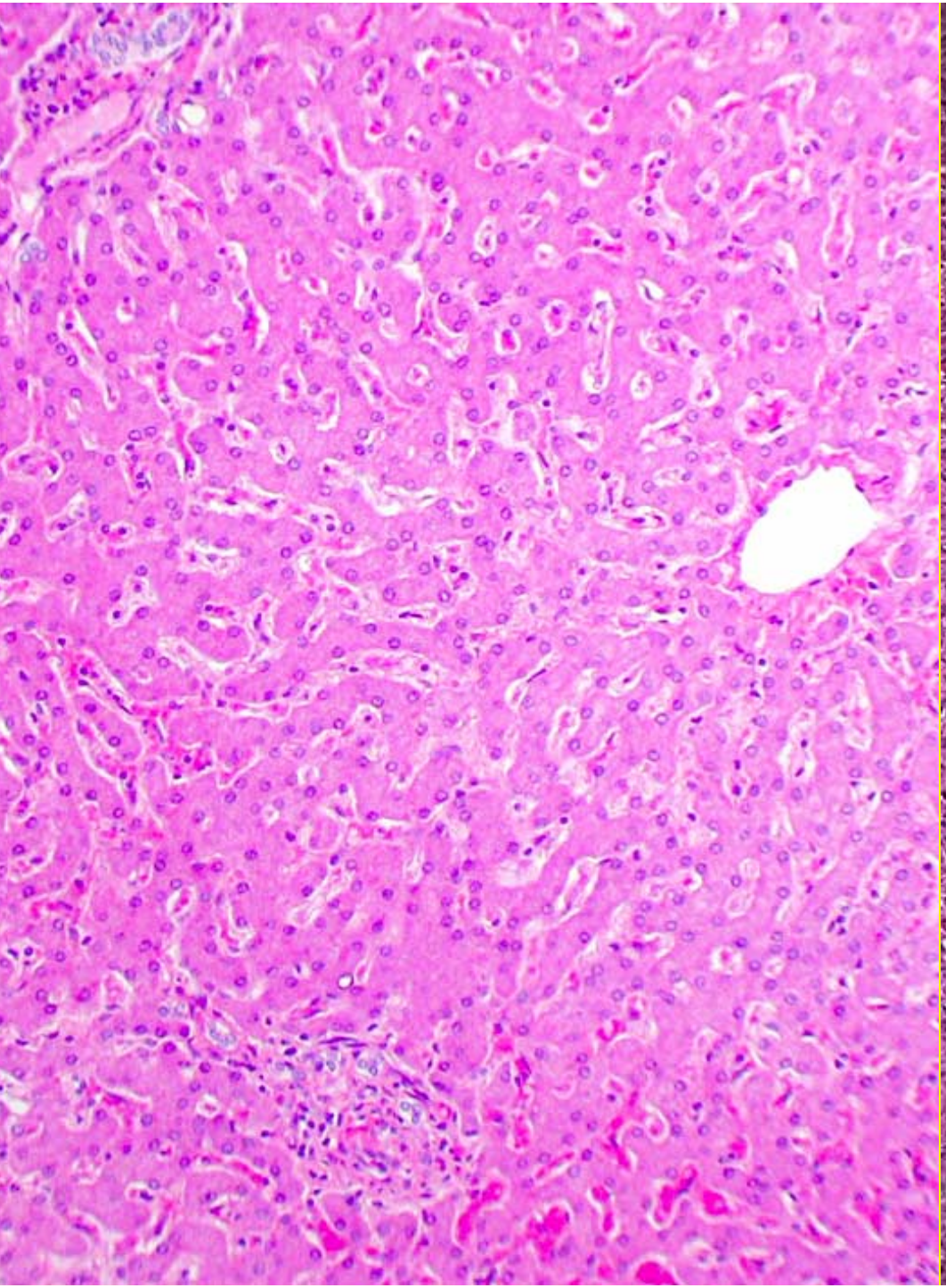
Hepatotoxicity of Metals
Identification/Quantitation of Metals (2)

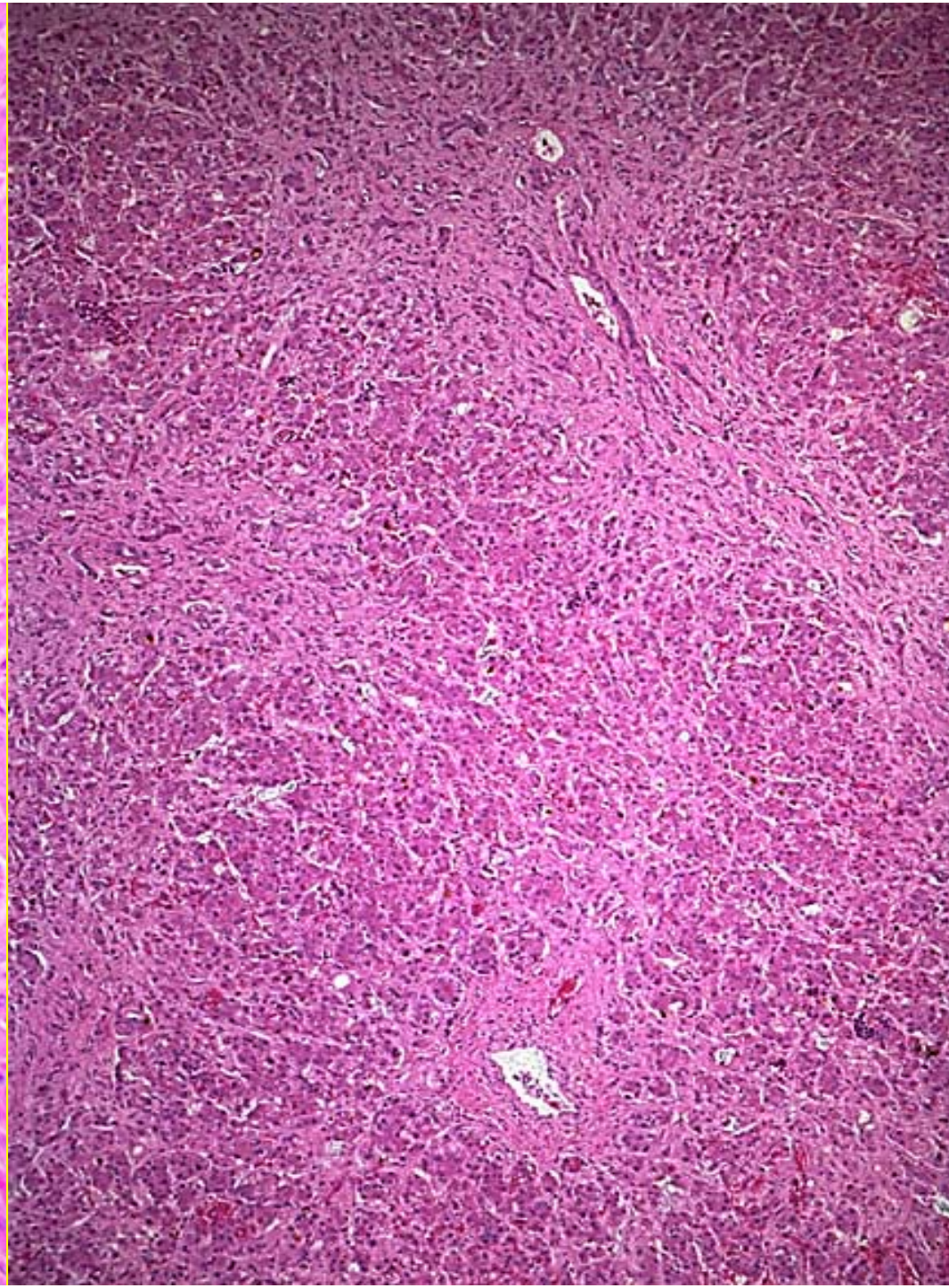
- Scanning EM and X-ray microanalysis
- Confocal Raman microscopy
- Atomic absorption spectrophotometry
  - Flame AAS
  - Graphite-furnace AAS
  - Inductively Coupled Plasma (ICP) and ICP-Mass spectrometry

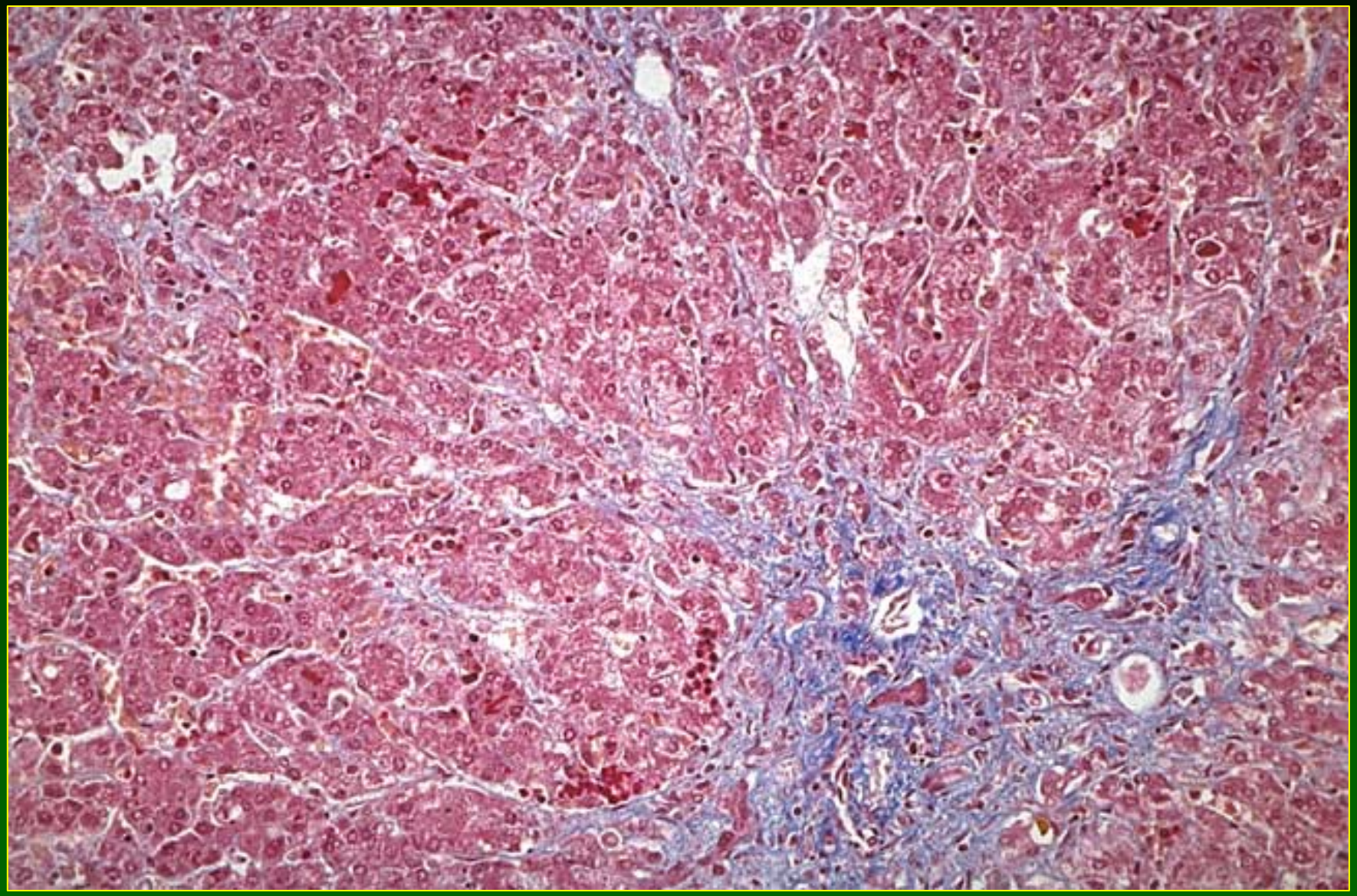

Central Vein
Portal Area
Nodal Point
of Mall
Lobule
3
2
1
1
2
3
Portal Area
Peripheral
Midzonal
Central
Central Vein
3
2
1
2
3
3
2
1
2
3

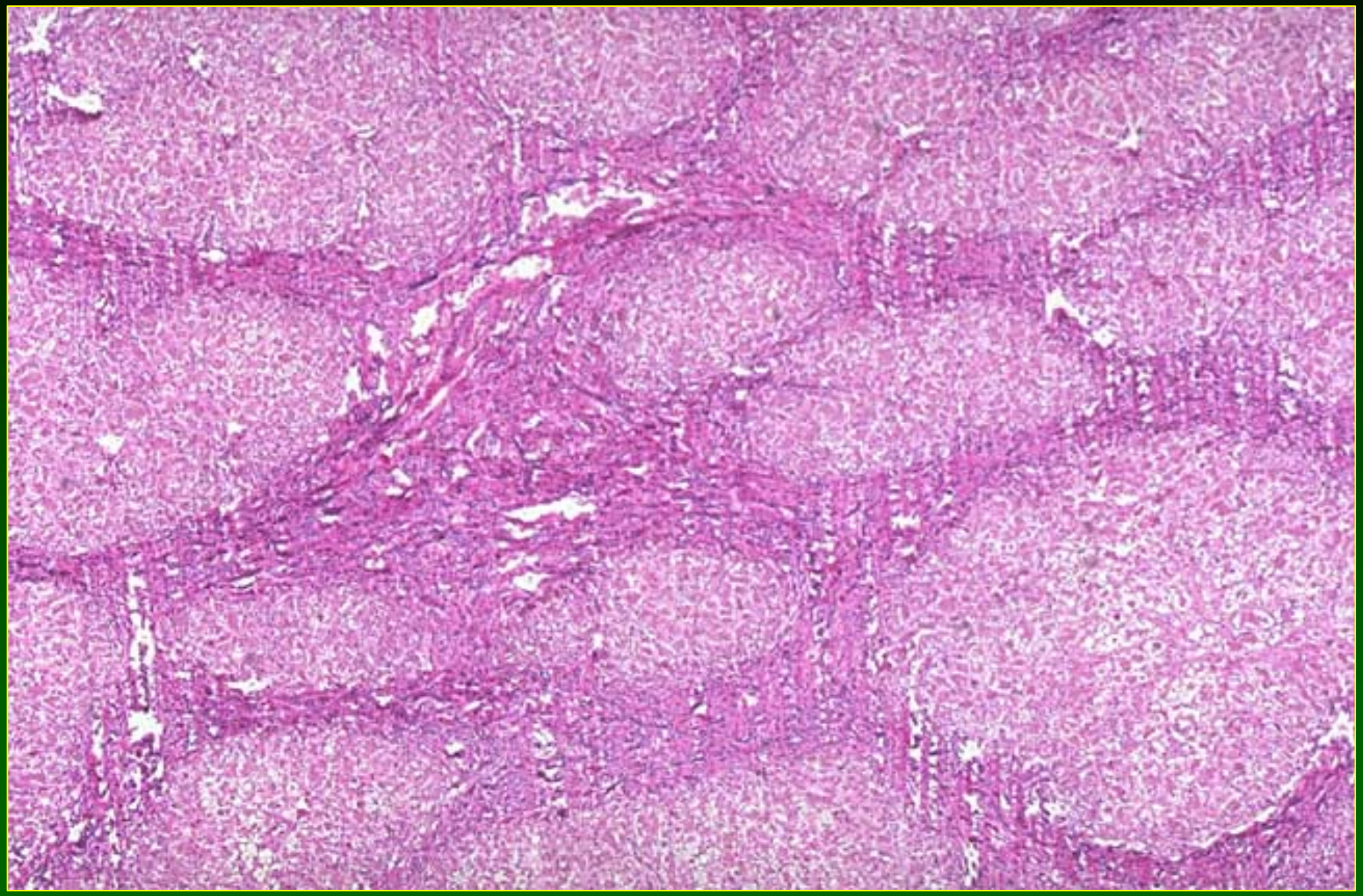
Hepatotoxicity of Metals
Aluminum

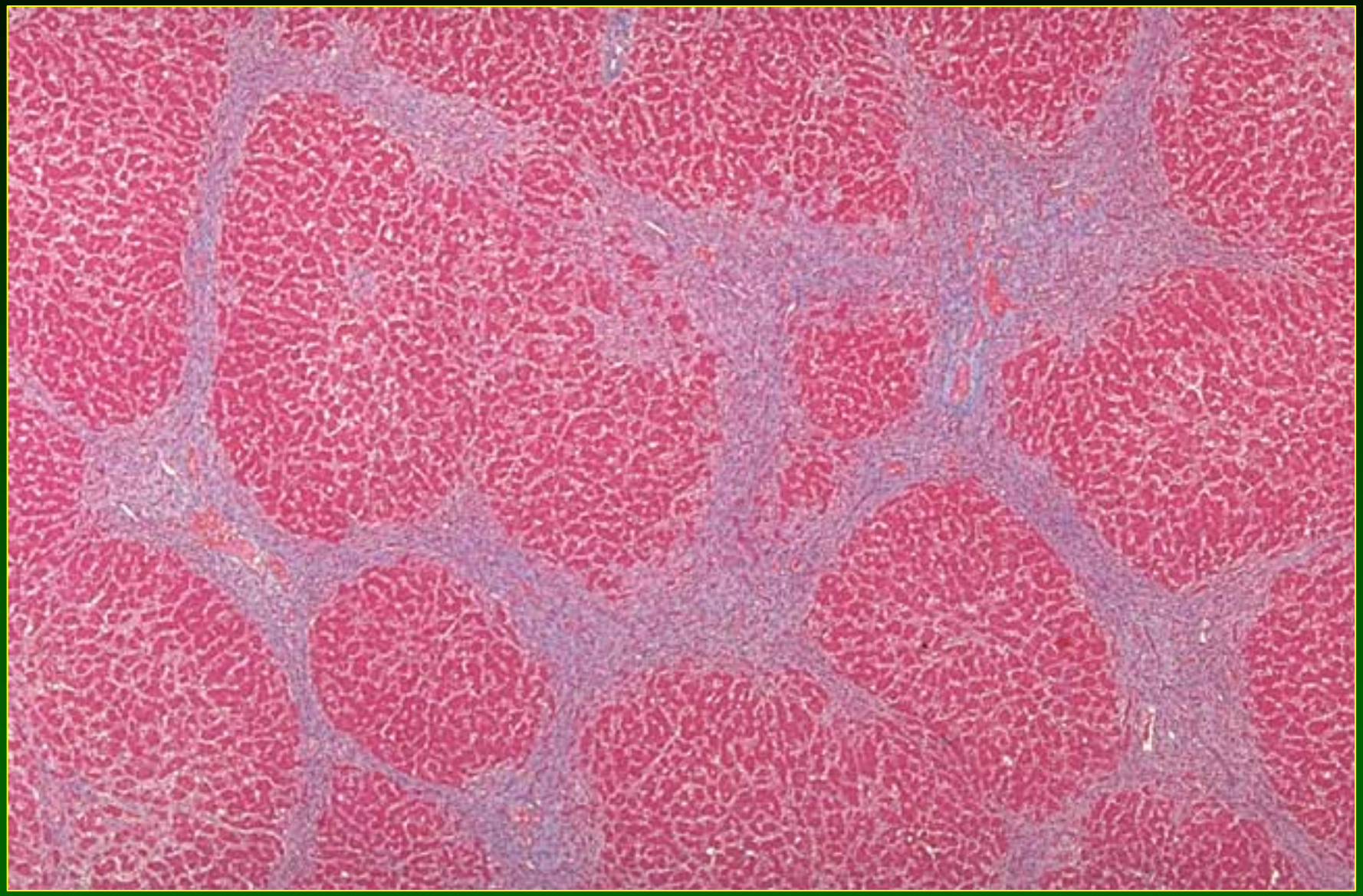
- Non-caseating granulomas in patients on long term hemodialysis (Kurumay et al, 1989)
- Contributes to hepatic injury in children on total parenteral nutrition (Klein et al, 1984)





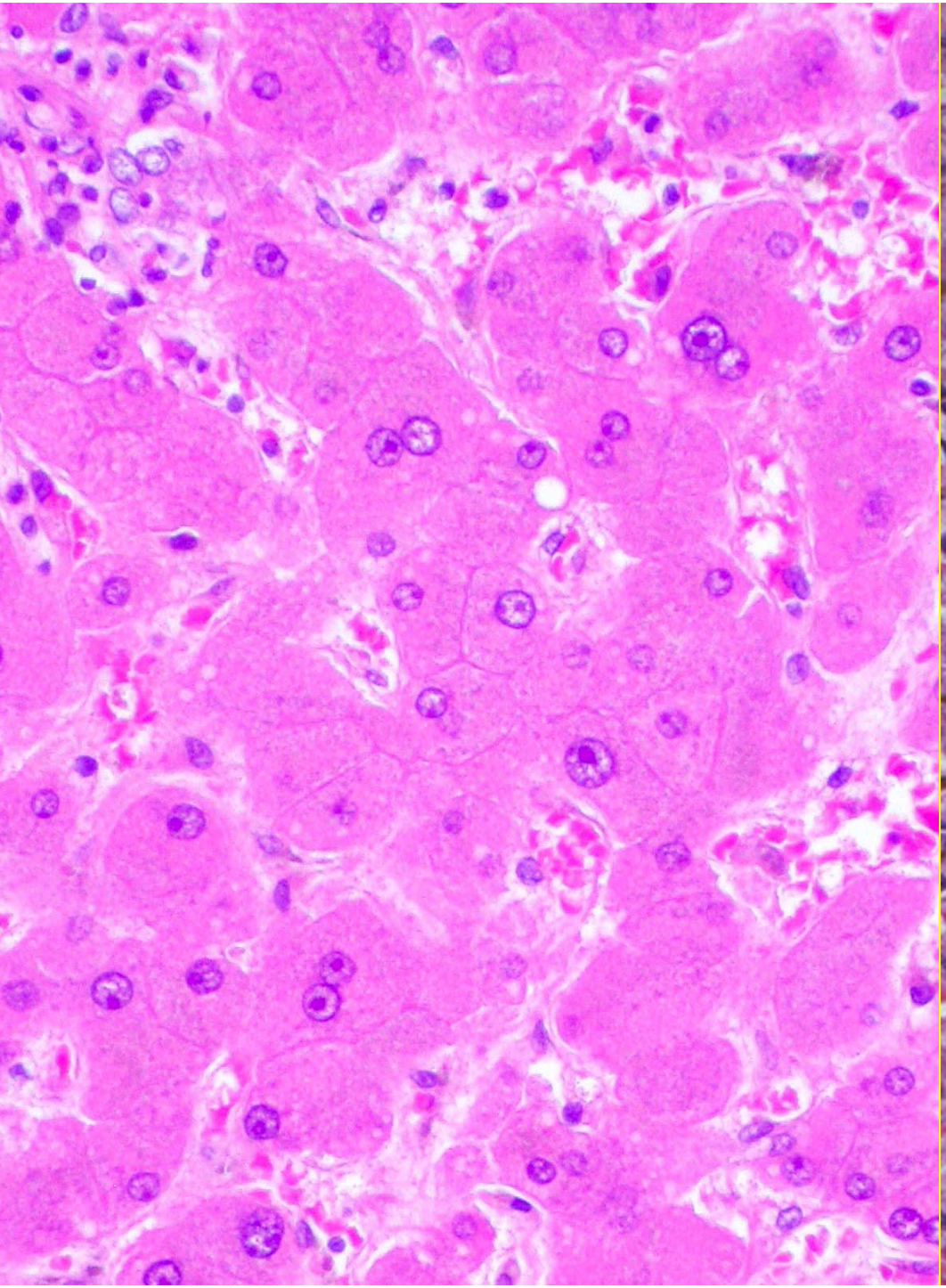


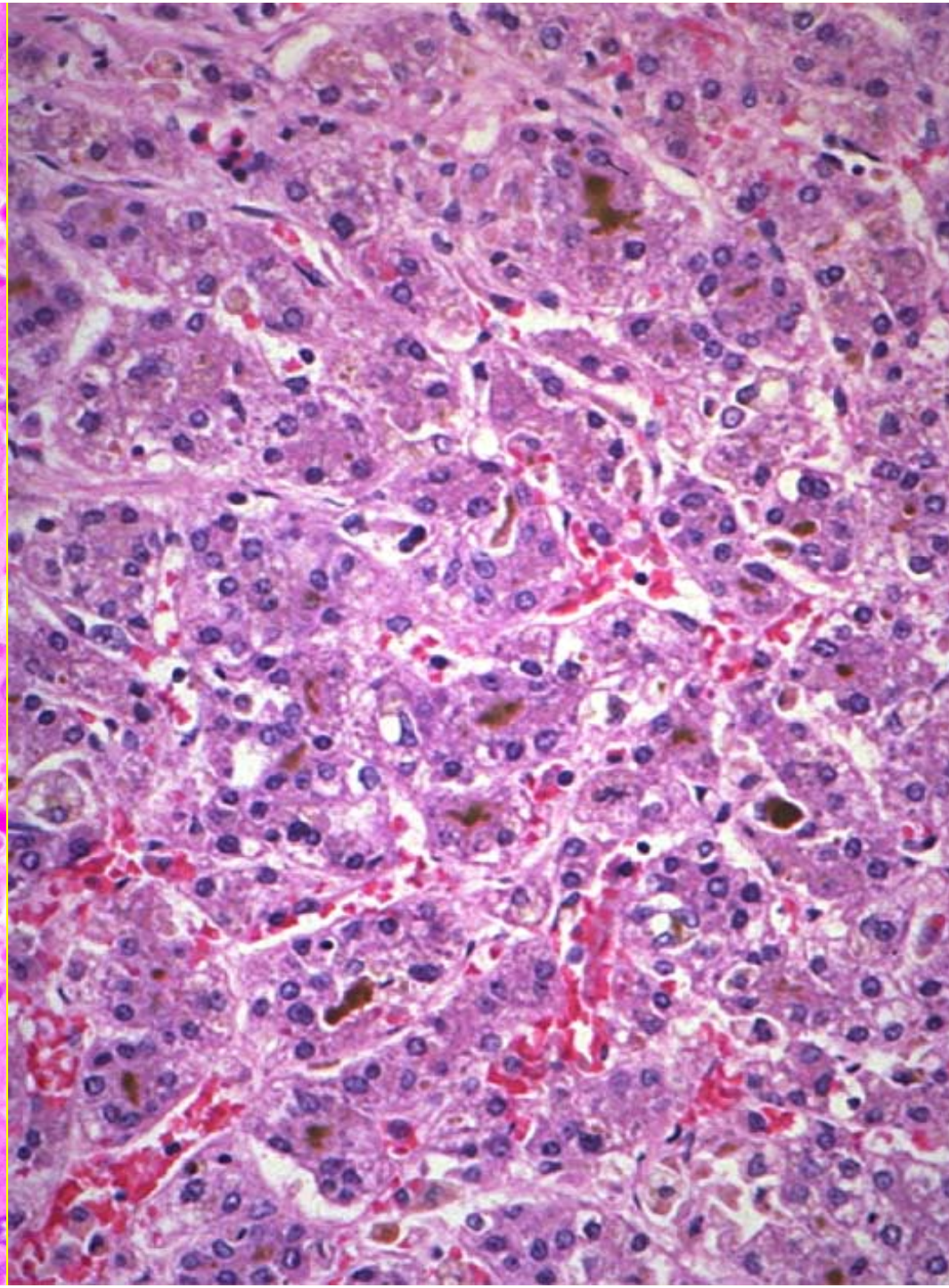




Hepatotoxicity of Metals
Arsenic (1)

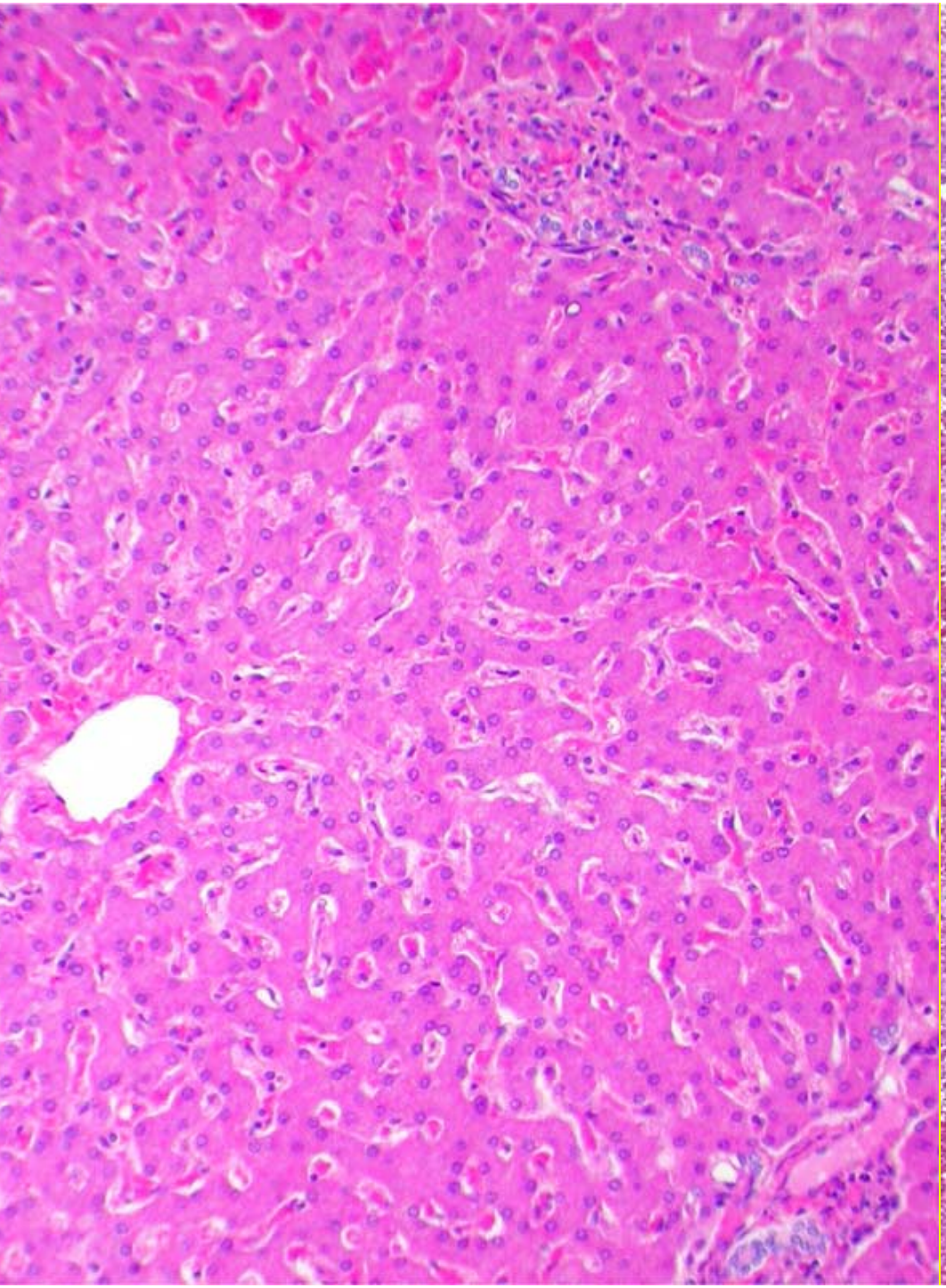
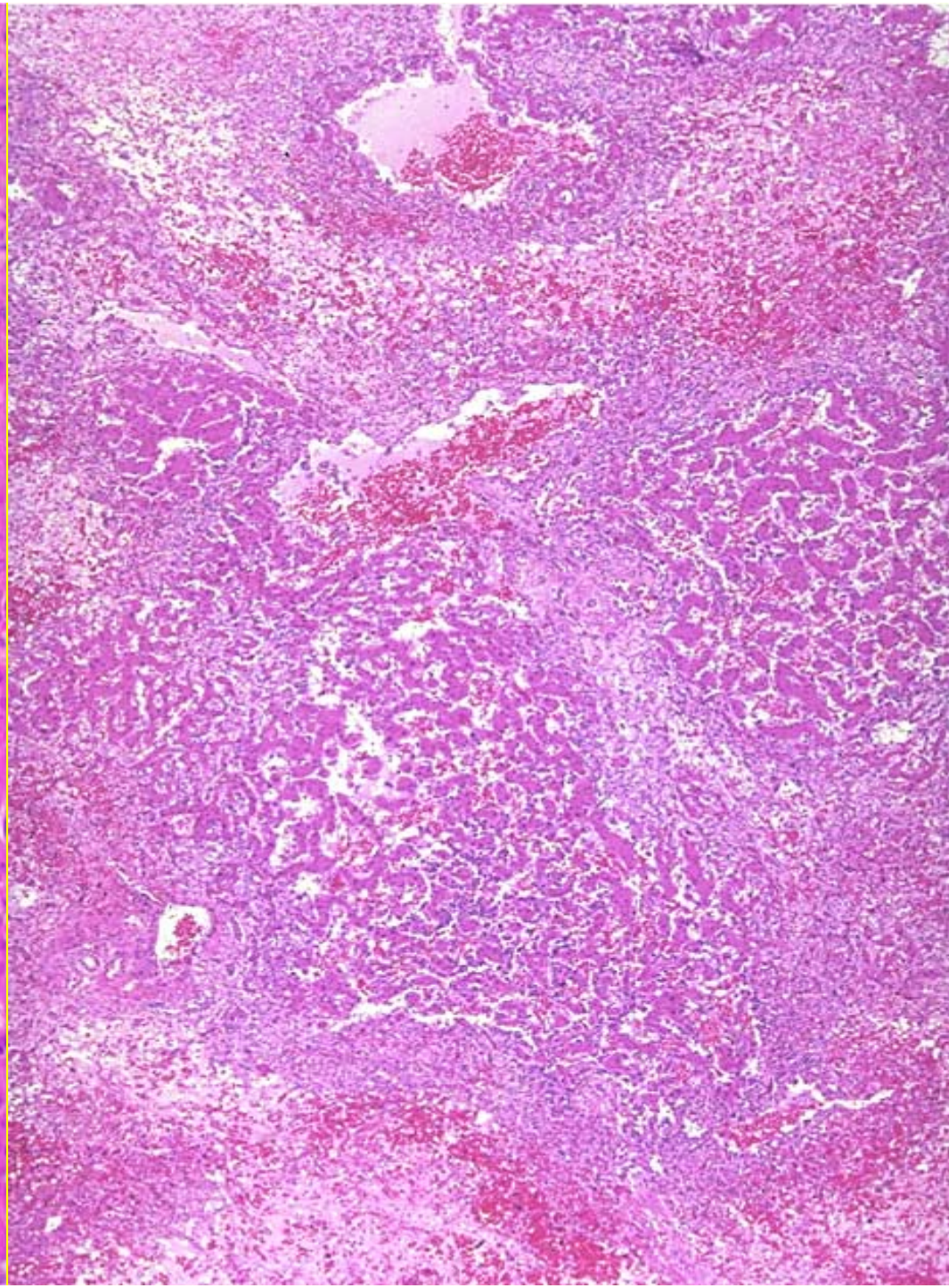
- Acute Toxicity
  - Intrahepatic cholestasis
  - Steatosis
  - Zone 3 necrosis
  - ↑ Mitotic activity
  - Venocclusive disease

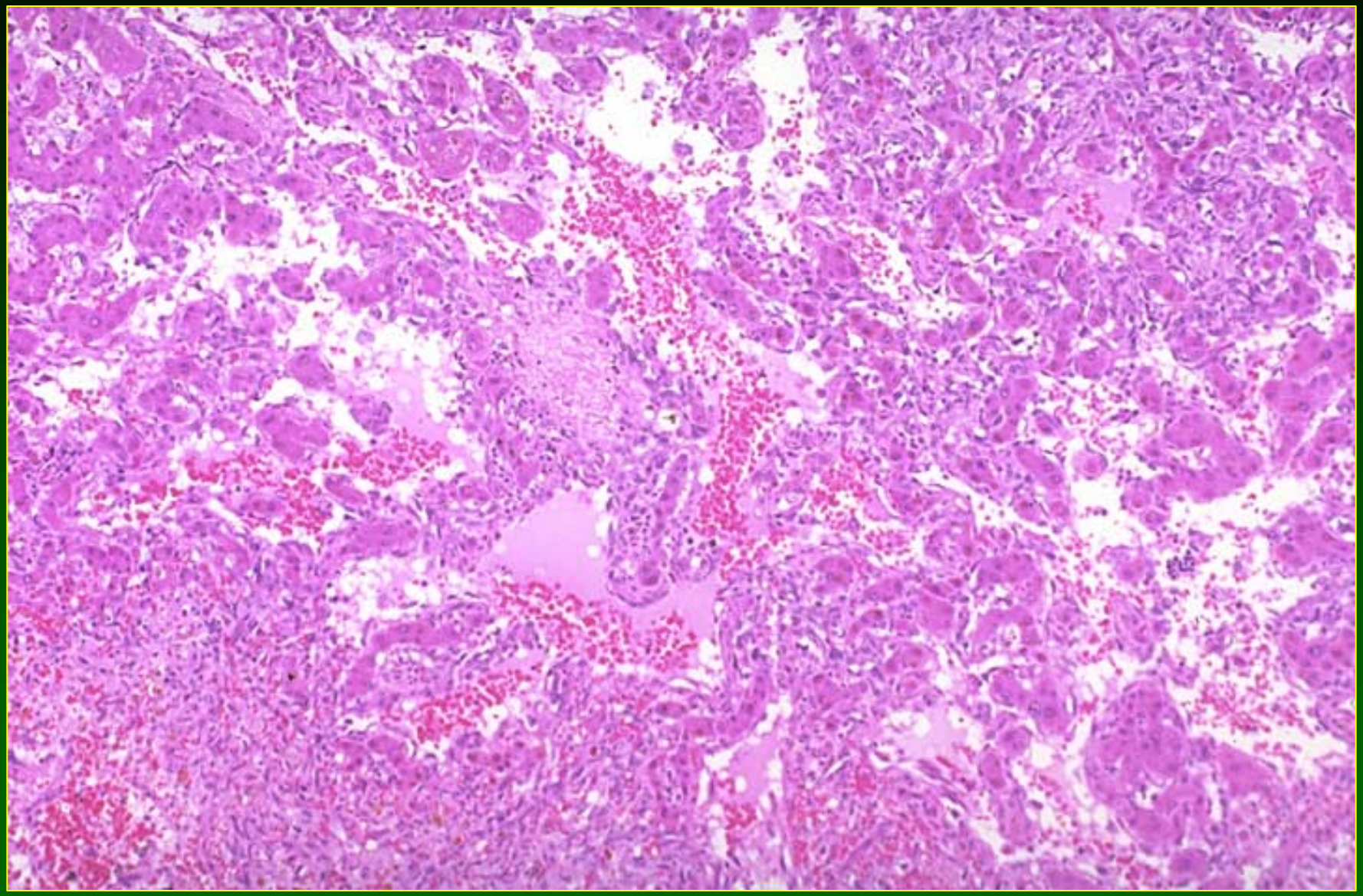


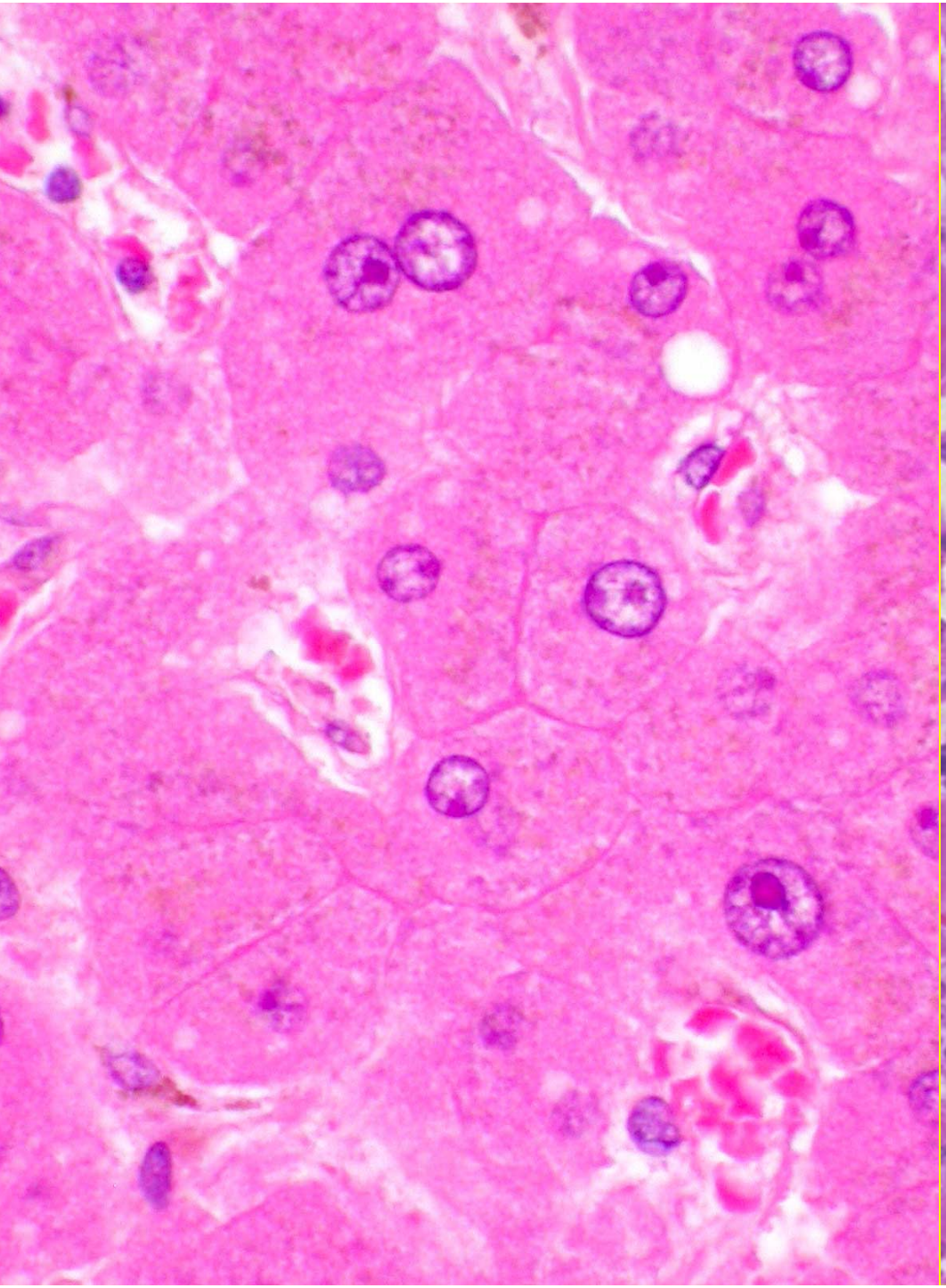


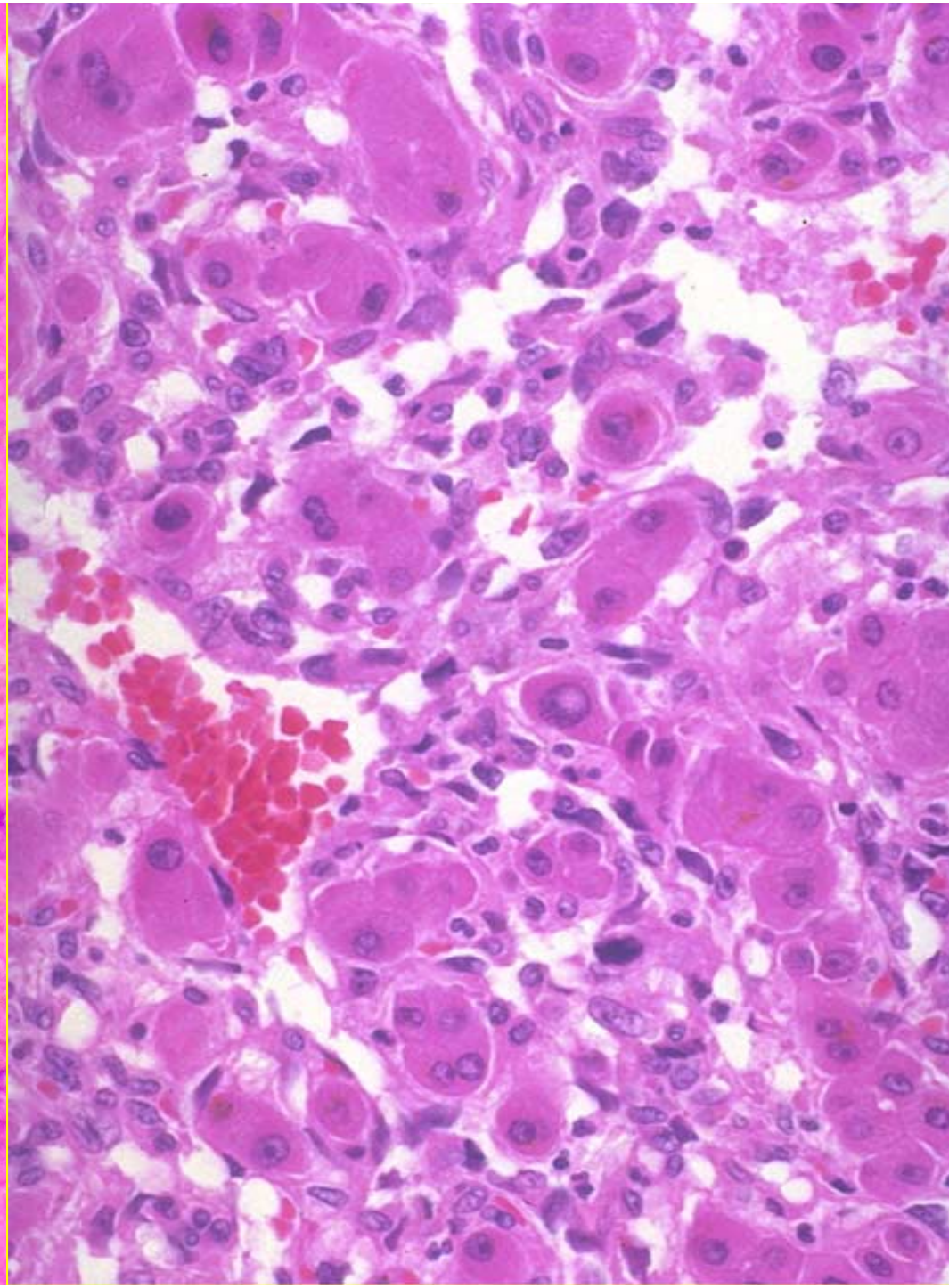
Hepatotoxicity of Metals
Arsenic (2)

- Chronic Toxicity
  - Hepatoportal sclerosis
  - Systemic arterial disease
  - Cirrhosis
  - Angiosarcoma
  - Hepatocellular carcinoma

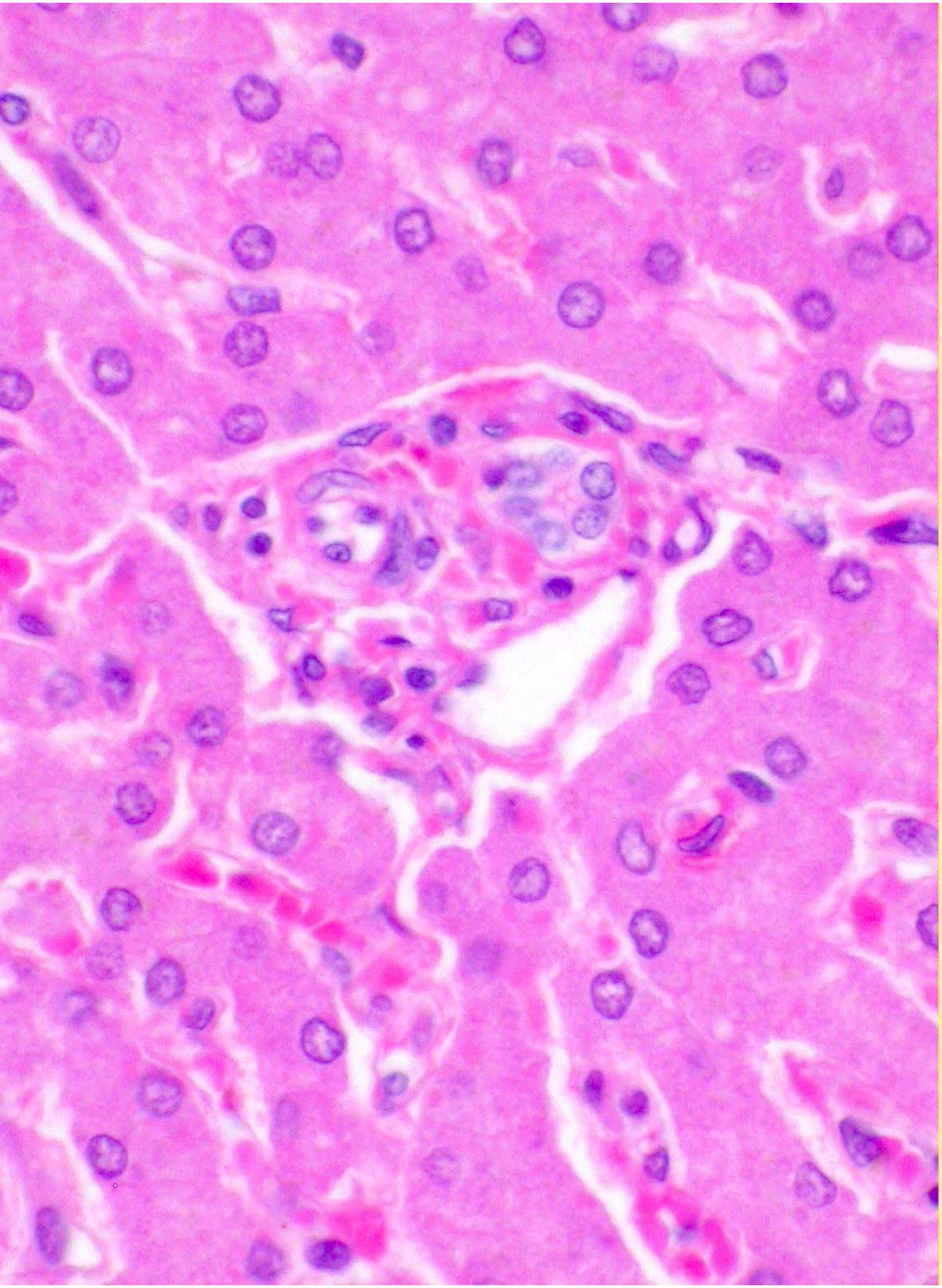


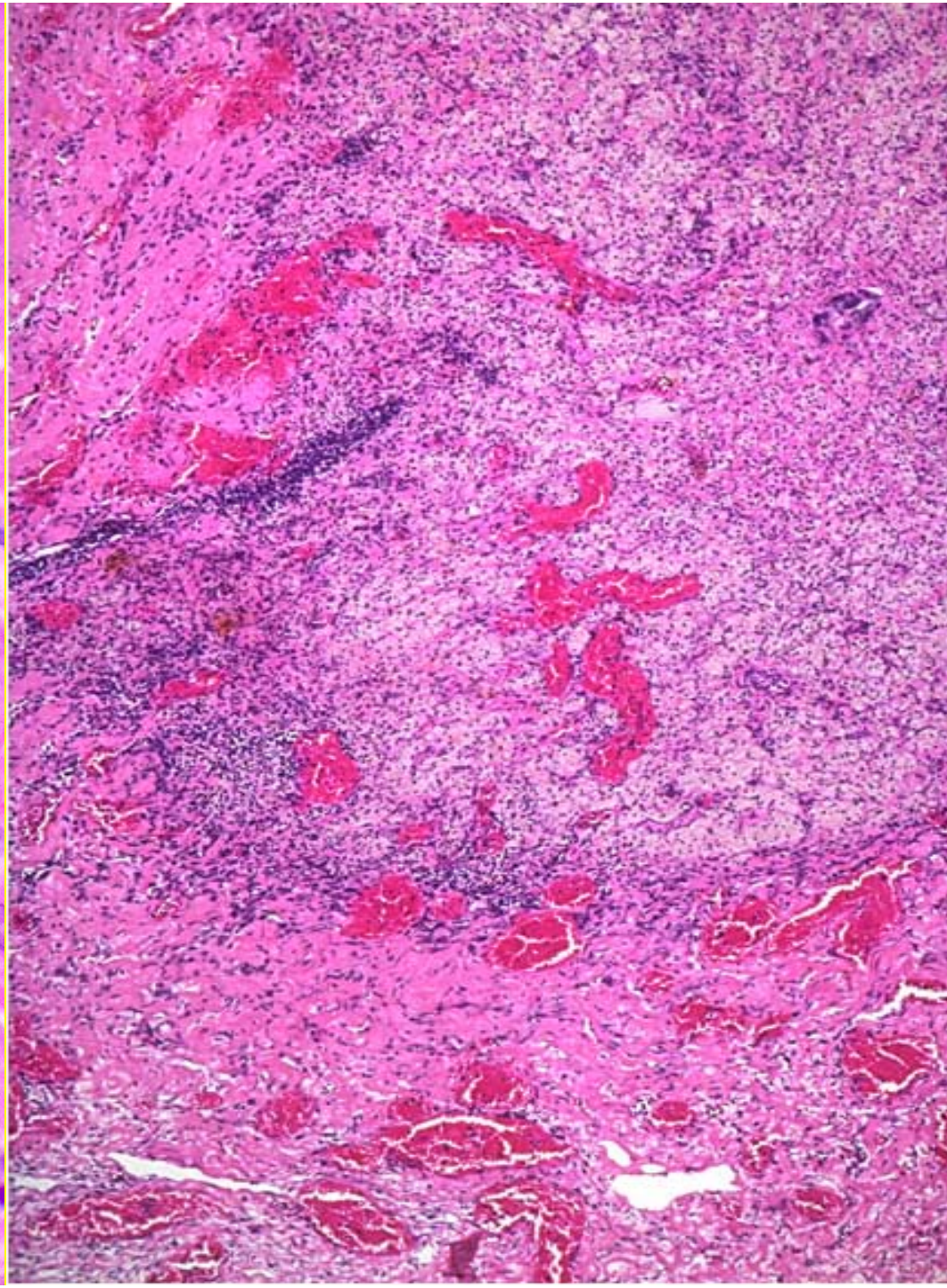


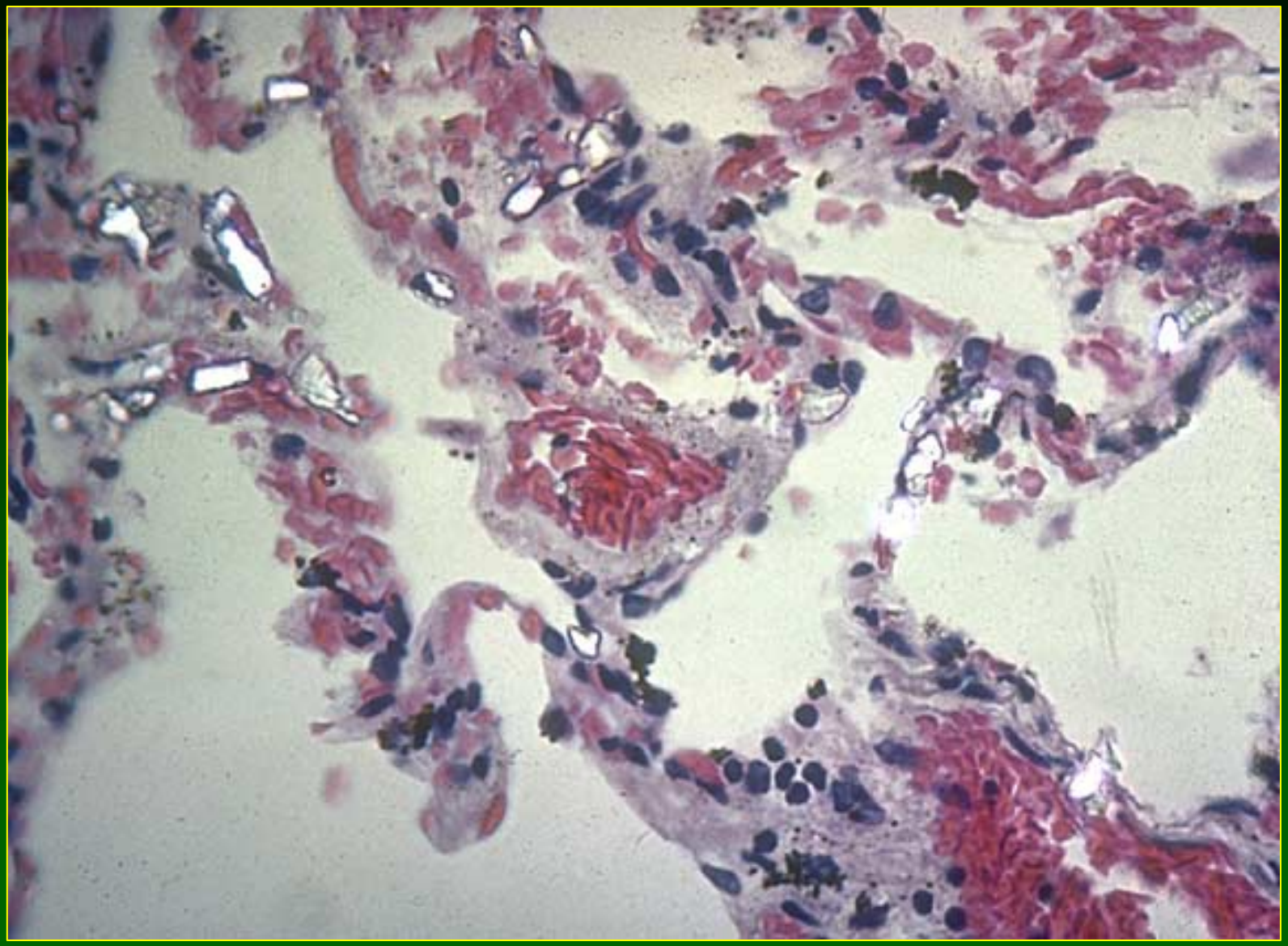


Hepatotoxicity of Metals
Barium

- Intravasation of $BaSO_4$ enema into portal venous system $\rightarrow$portal pylephlebitis or liver abscess



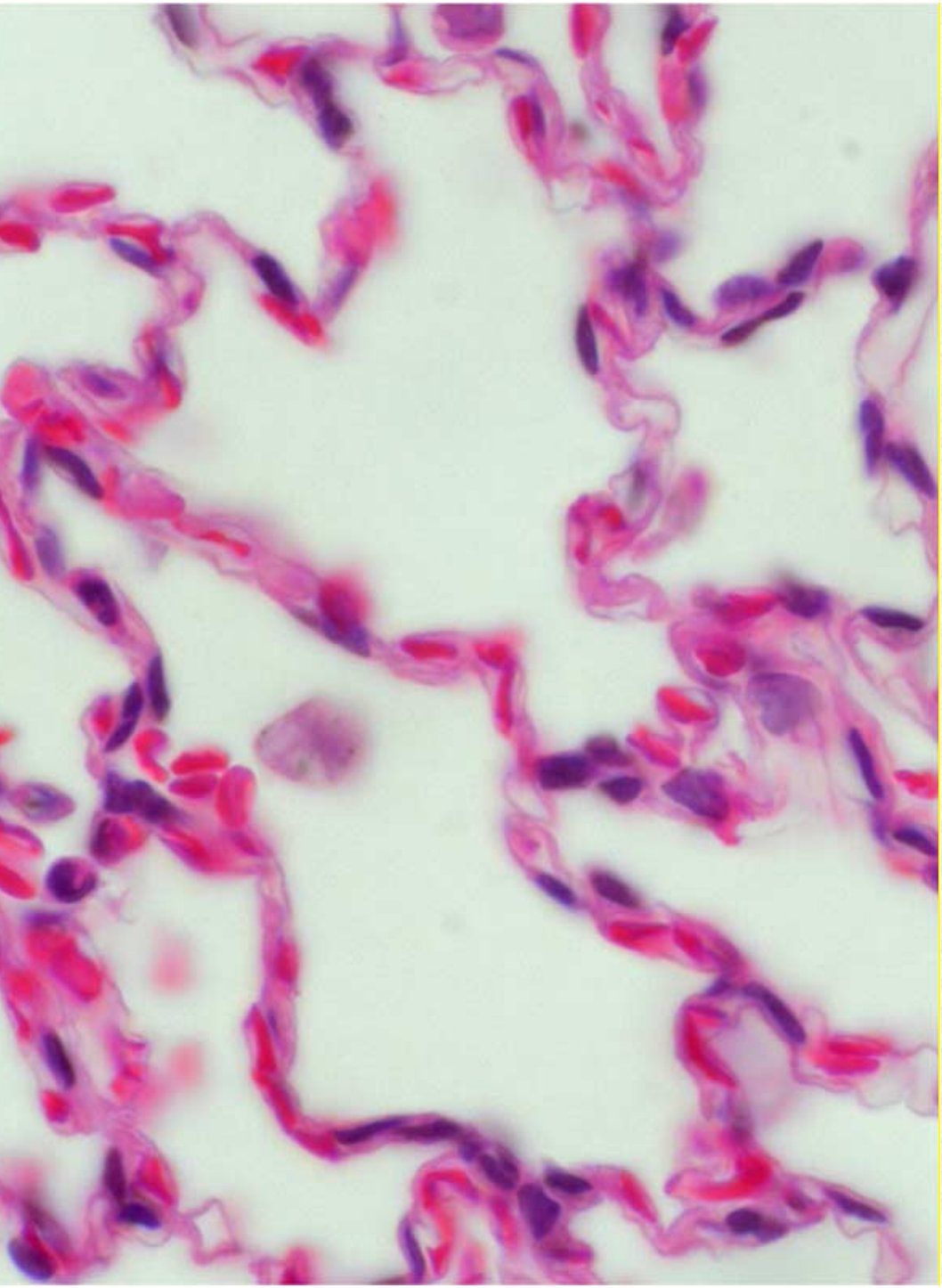


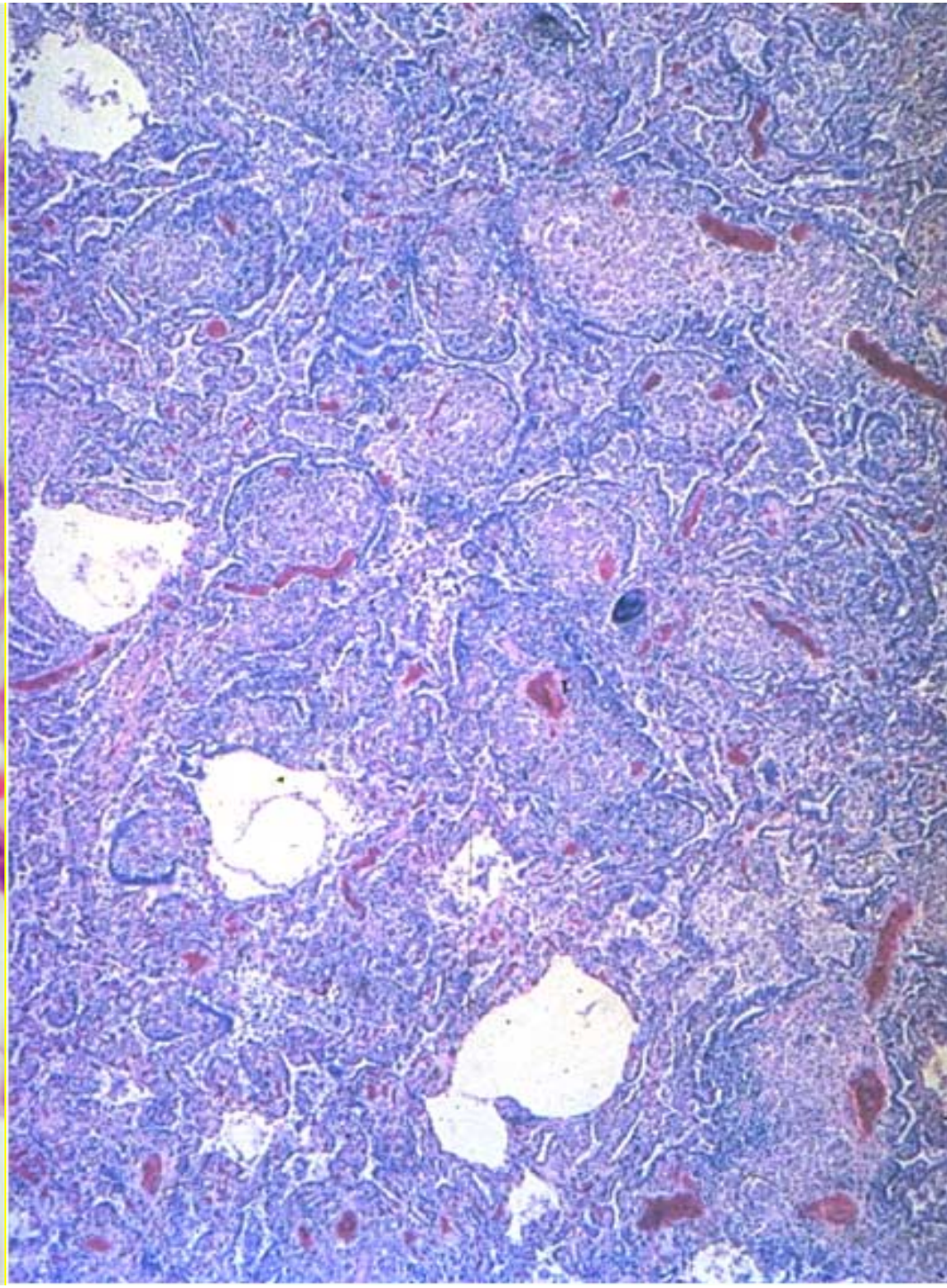


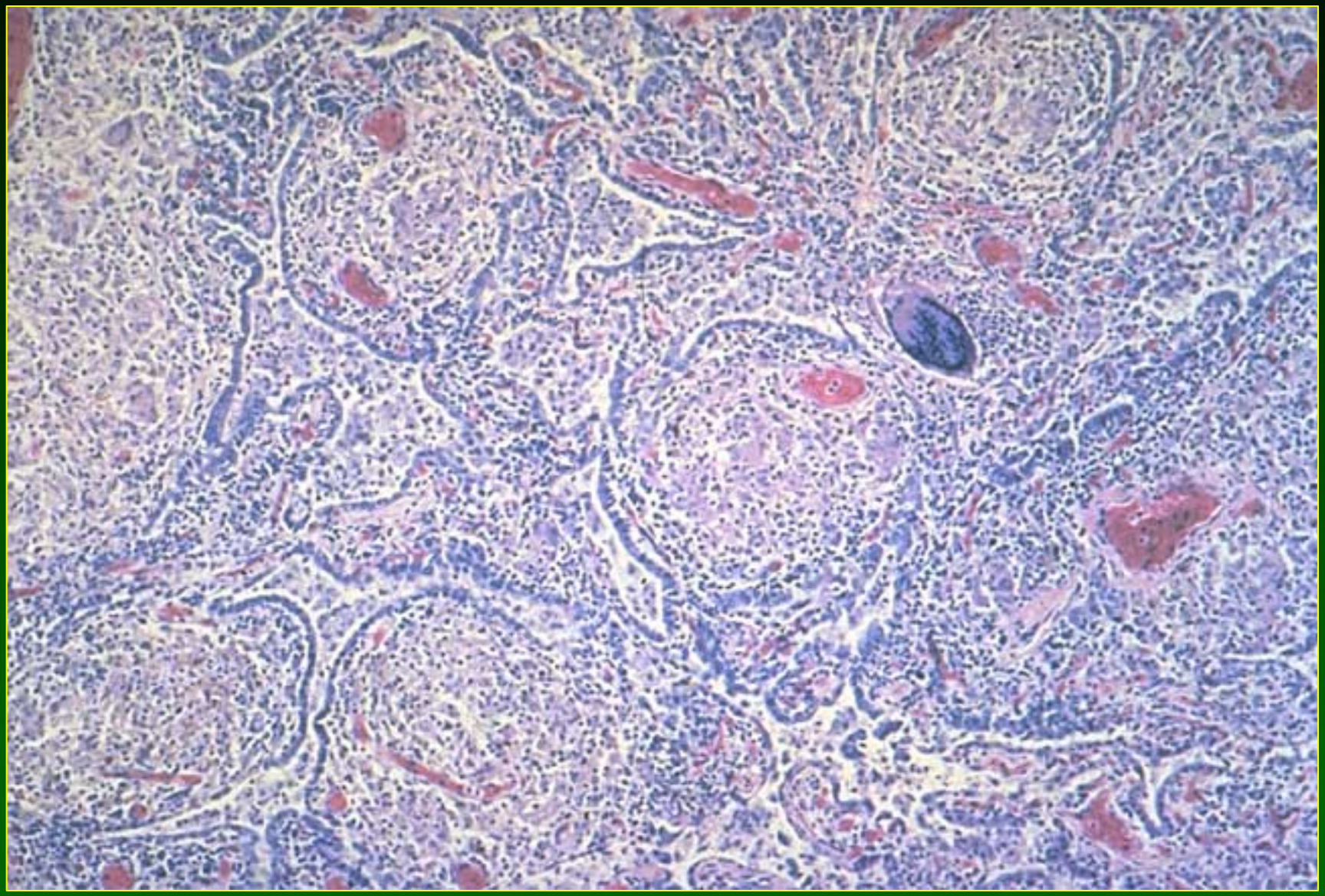
Hepatotoxicity of Metals
Beryllium

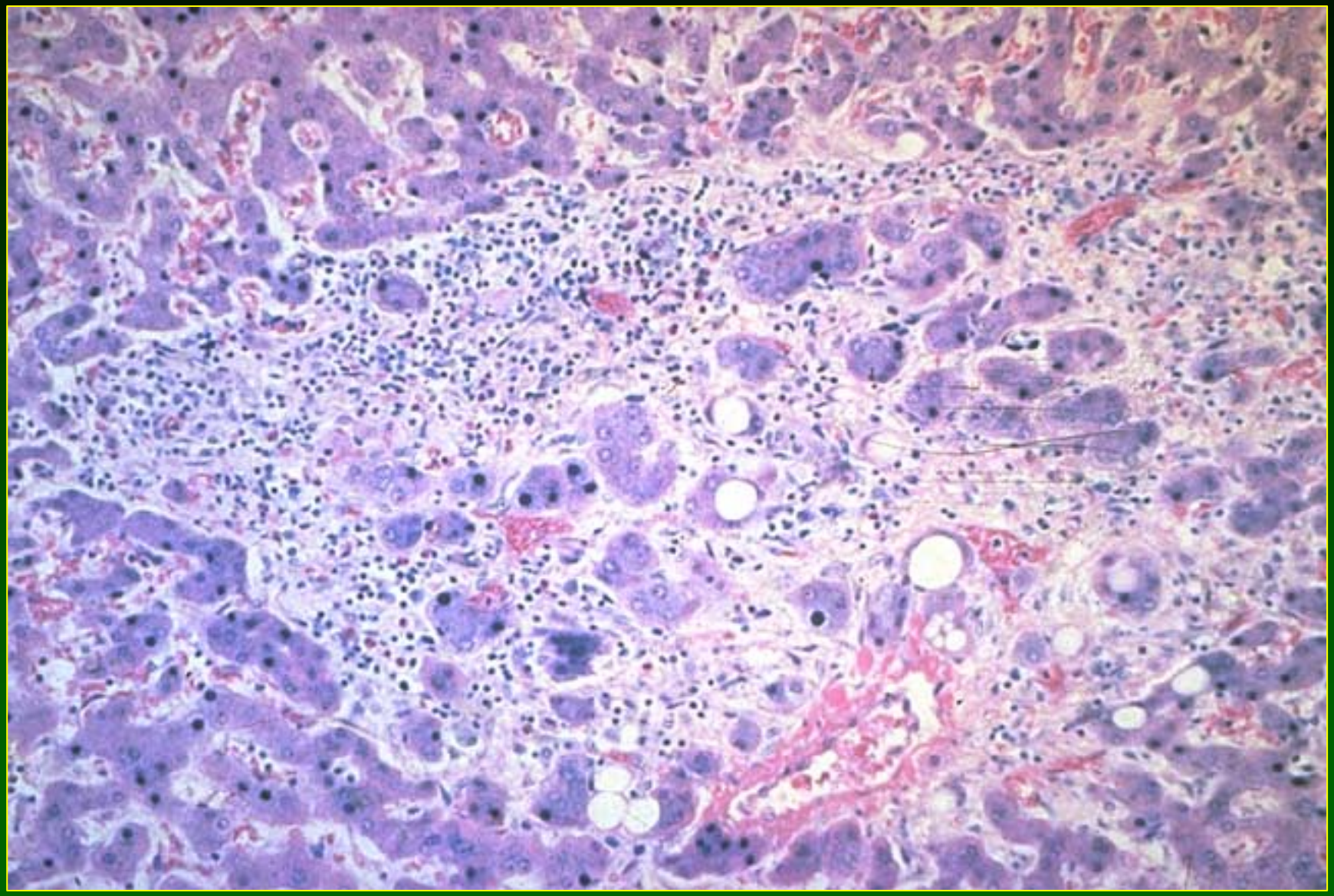
- Noncaseating, epithelioid granulomas in chronic beryllium disease (berylliosis)
- Midzonal hepatic necrosis (exp.)

- Male, age 28 years
- Occupation chemist
- Exposure:Beryllium and other materials during schooling and employment. 15 pound loss and shortness of breath. Died one year later. Lung and liver showed granulomas and focal necrosis respectively.





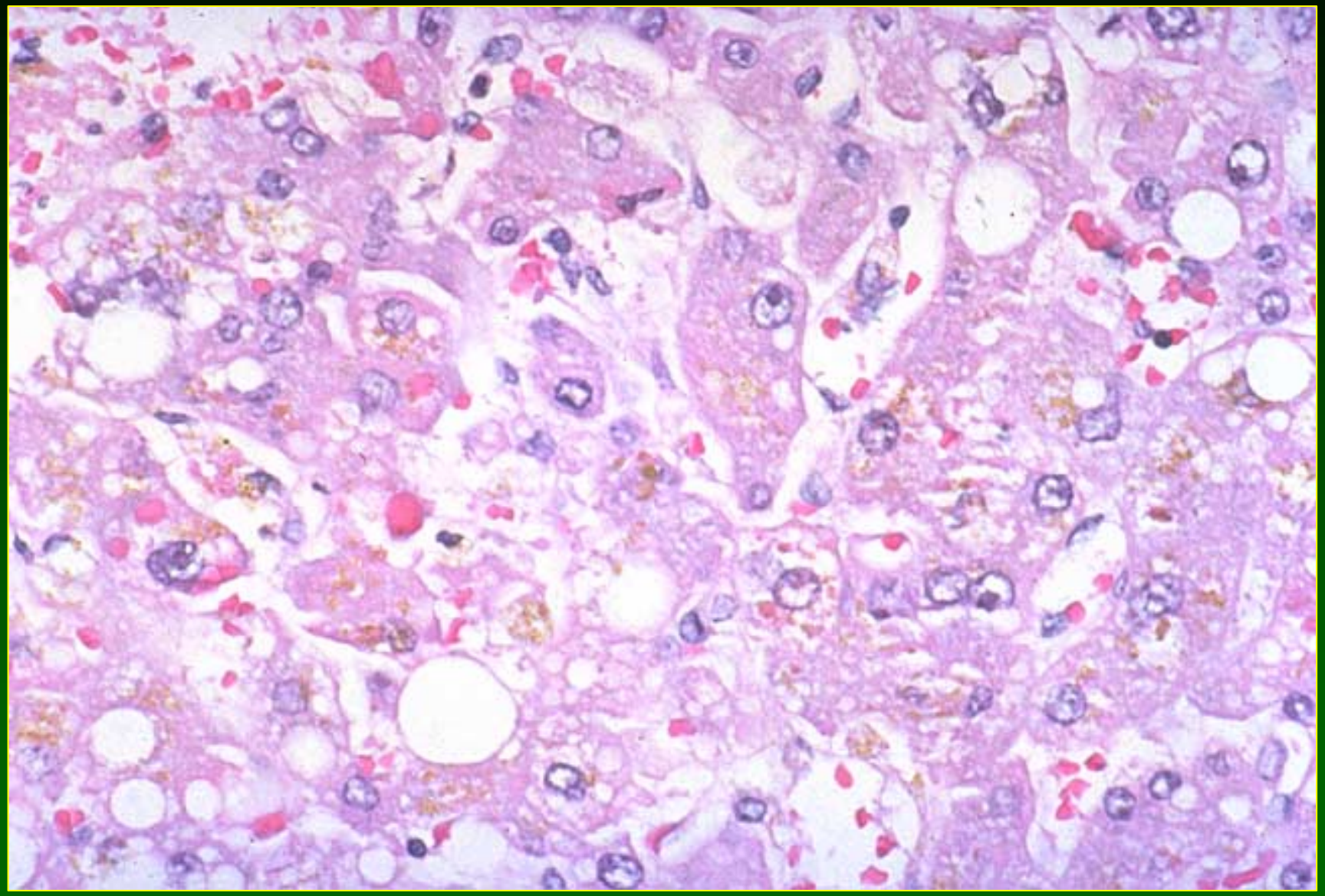


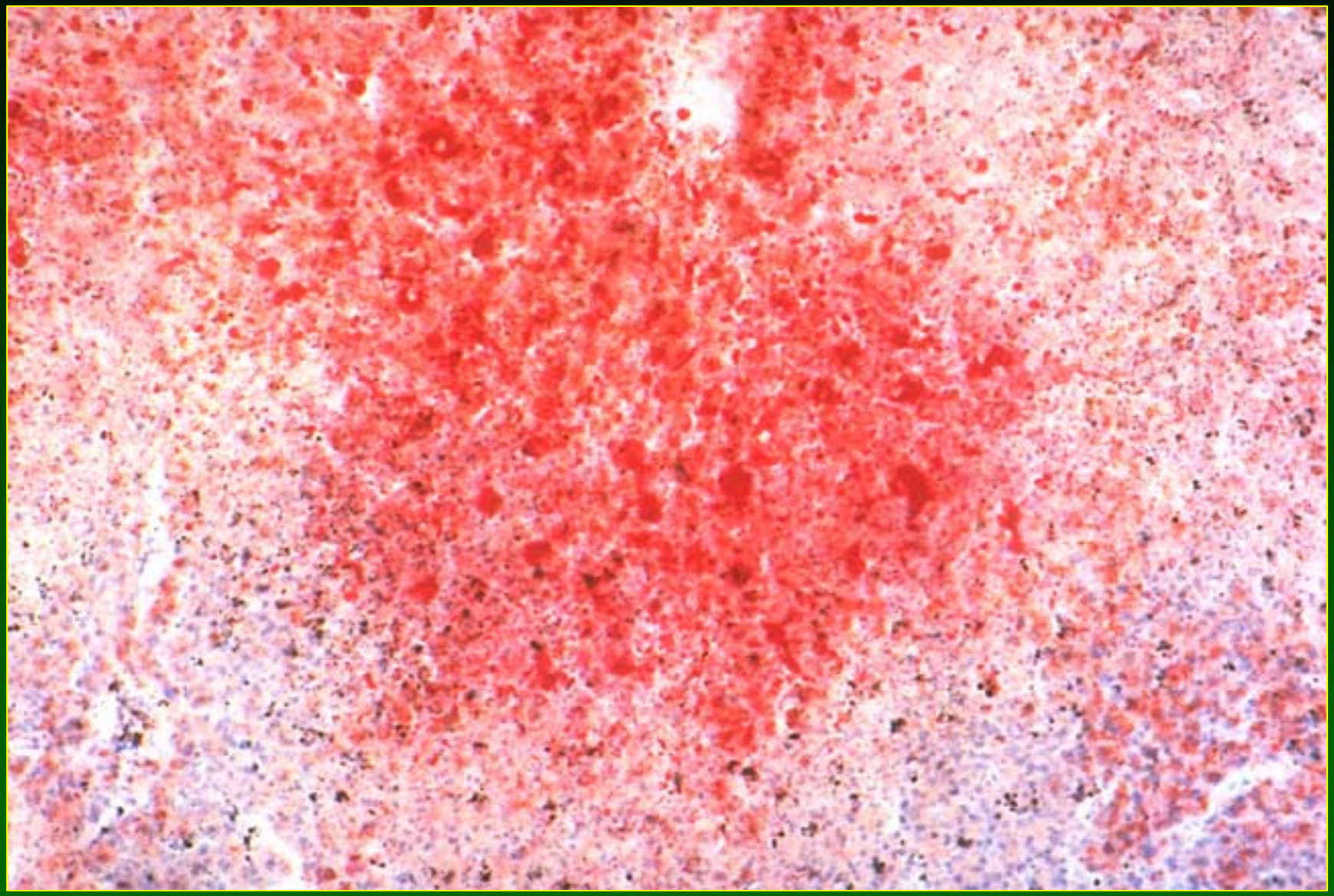


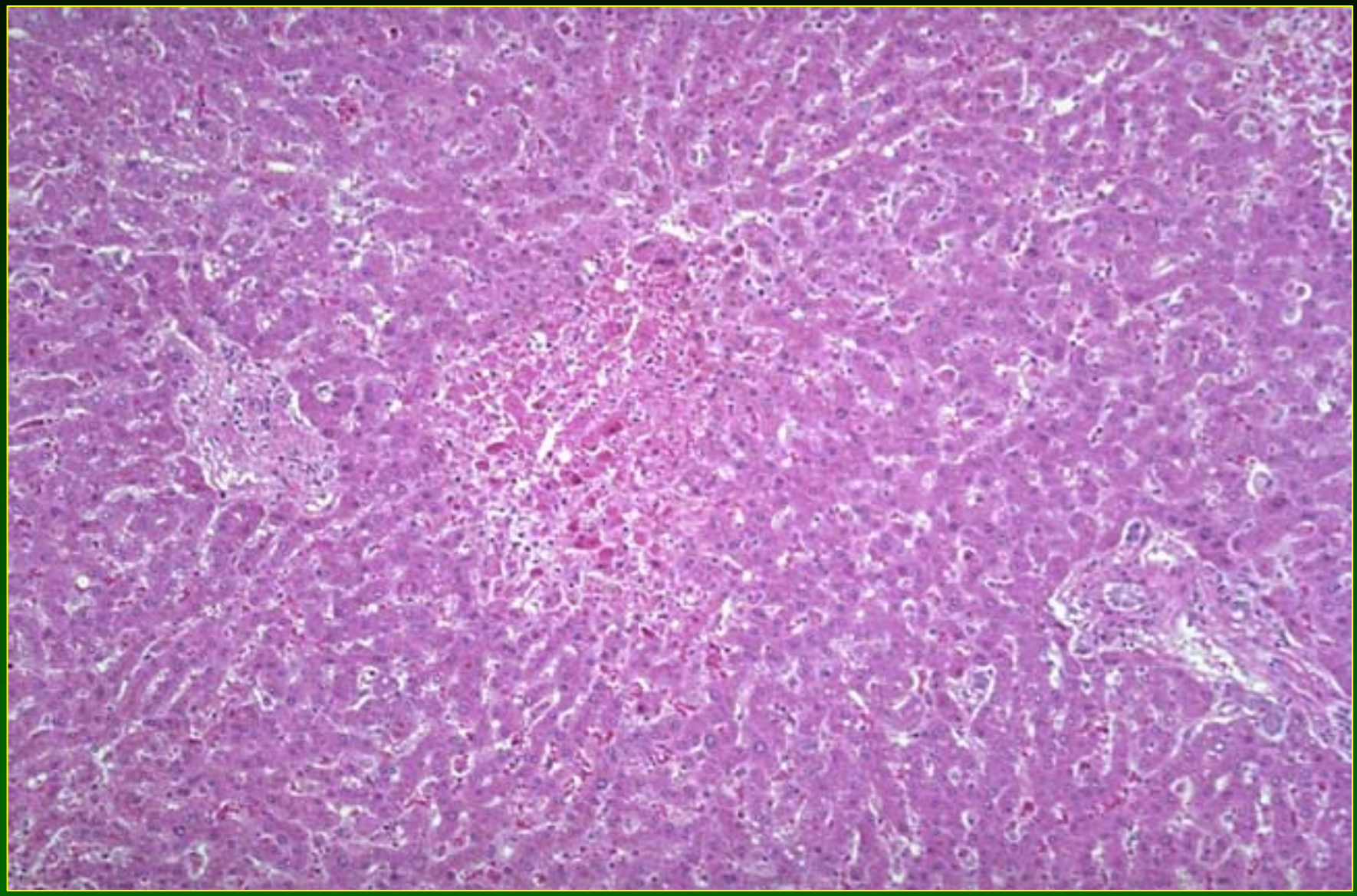
Hepatotoxicity of Metals
Copper (1)

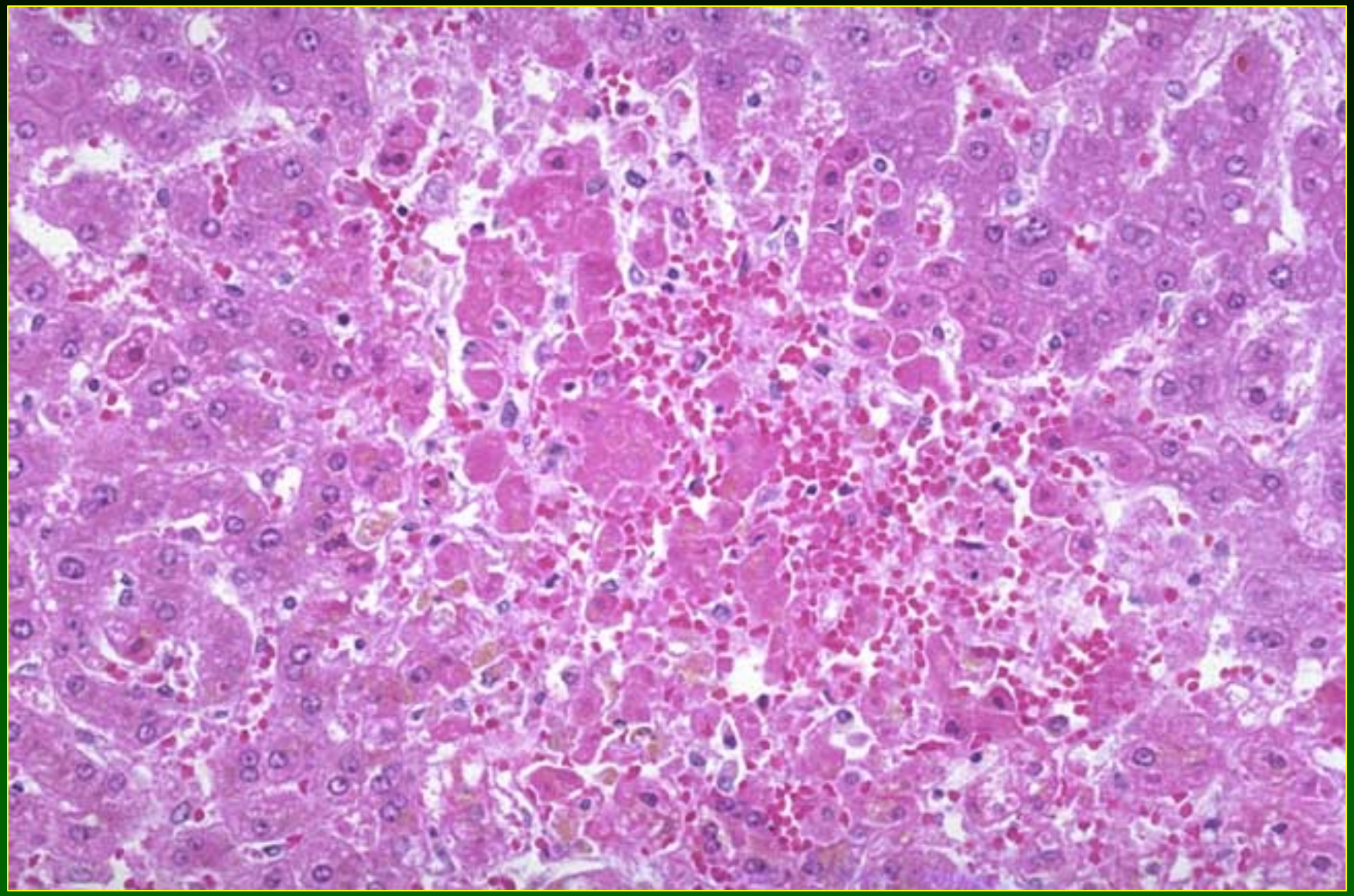
- Acute Toxicity: Zone 3 necrosis; cholestasis; hypertrophy of Kupffer cells with erythrophagocytosis; copper accumulation in Kupffer cells (sheep)

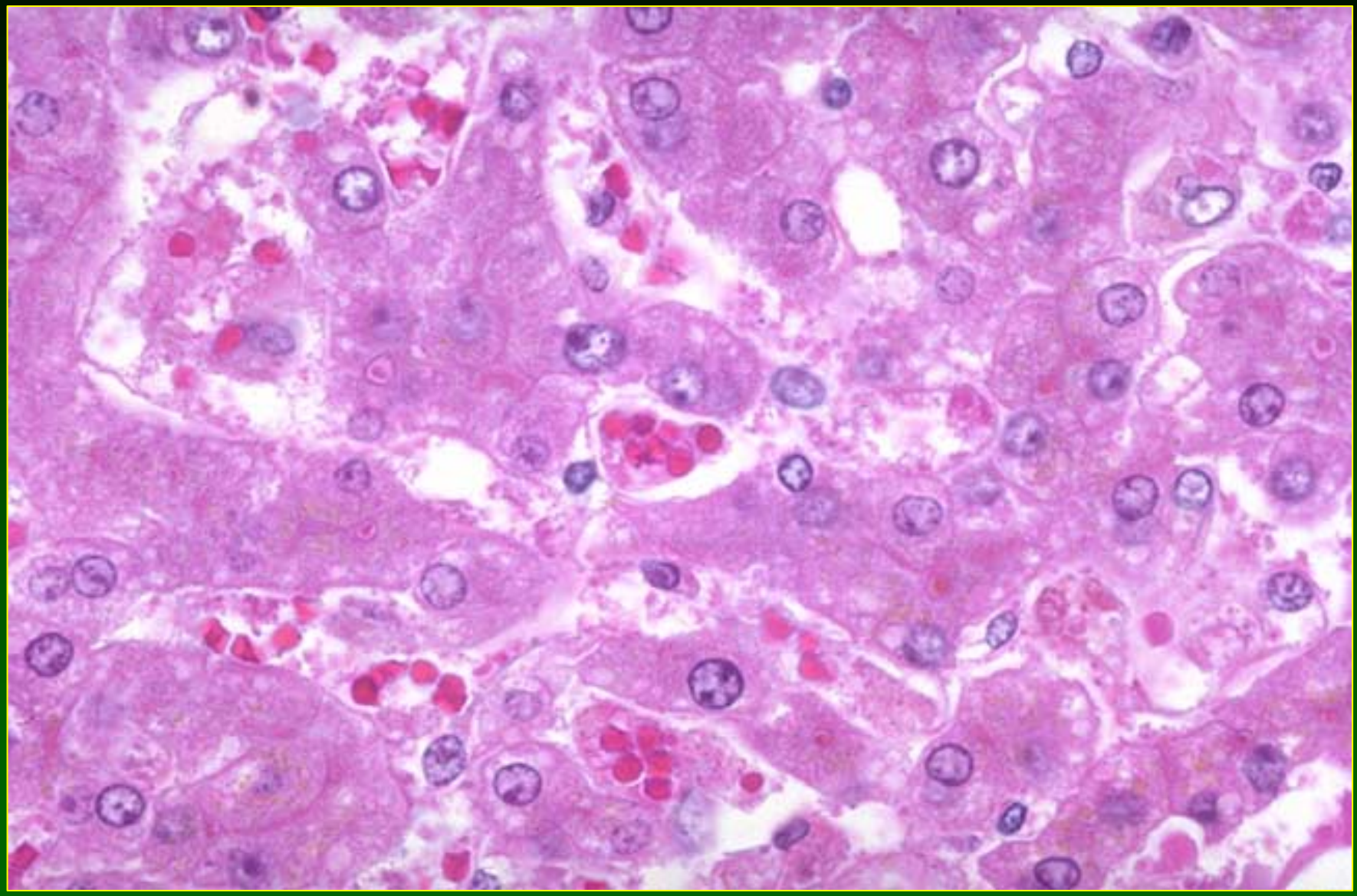
- A 44-year old woman with a history of having ingested a large amount of valium and alcohol. She was treated with Copper Sulfate to induce emesis. High levels of serum copper found and also high copper levels in liver tissue. Liver shows cholestasis and fat confirmed by Oil red o stain.





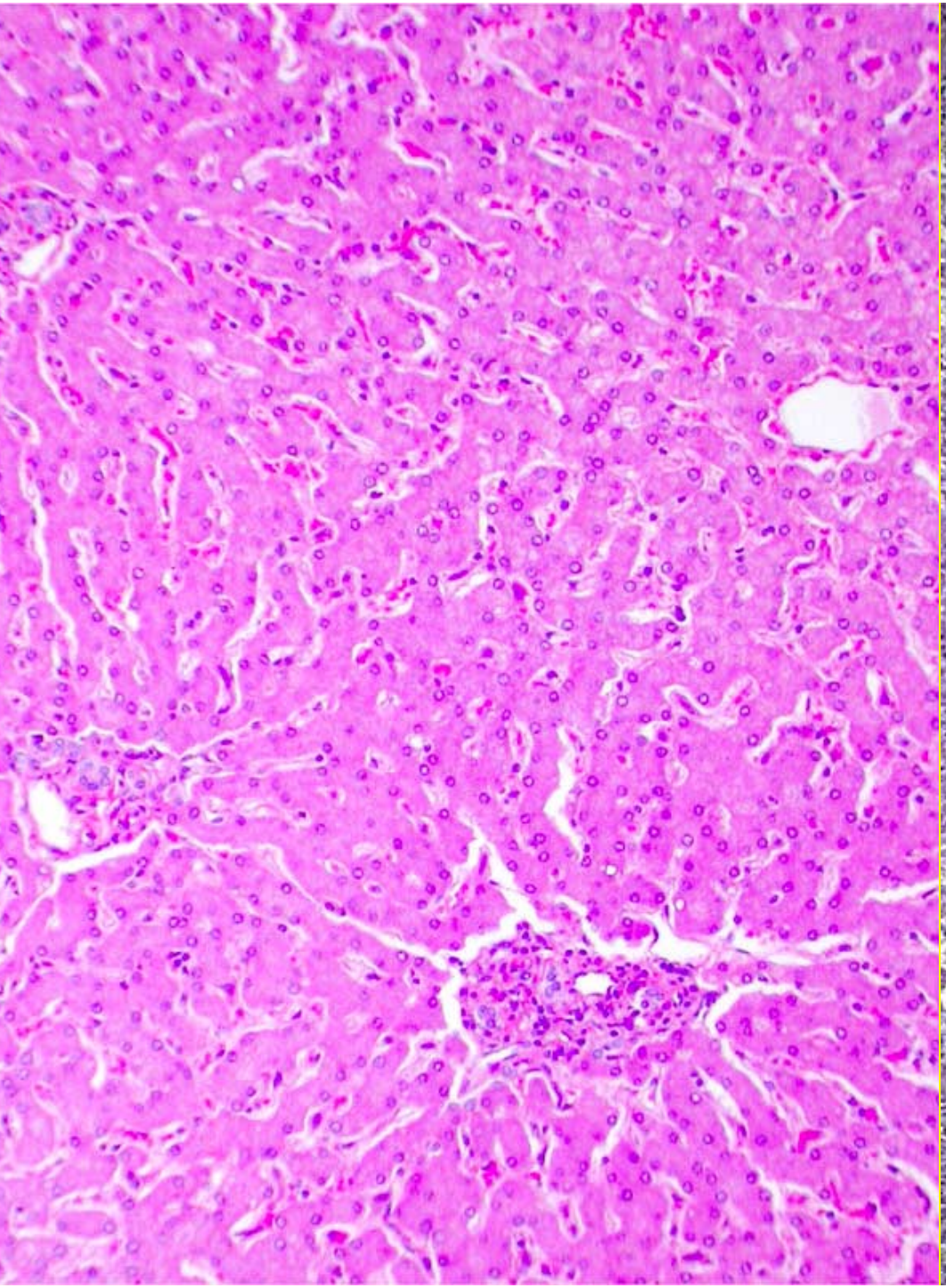


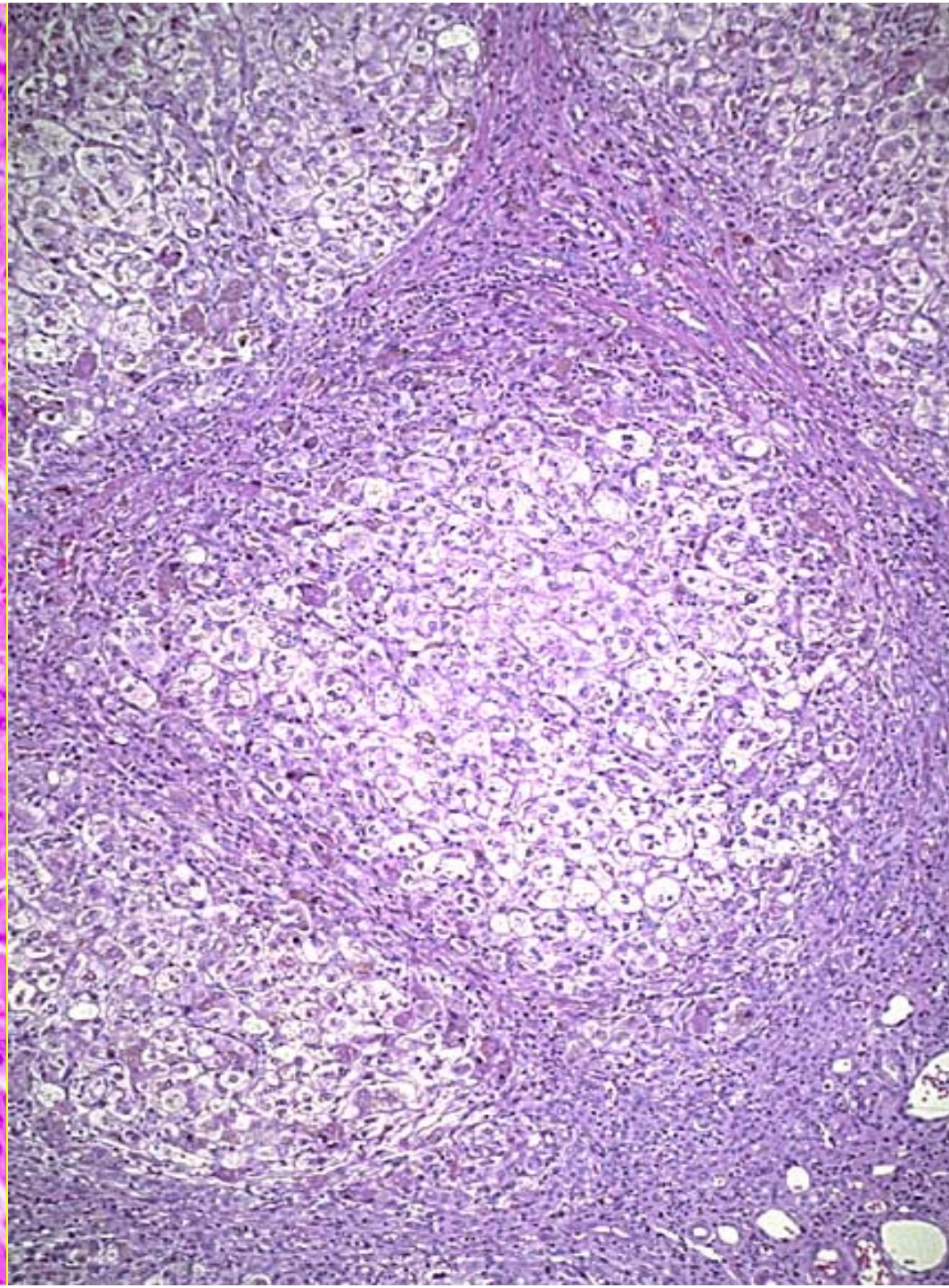


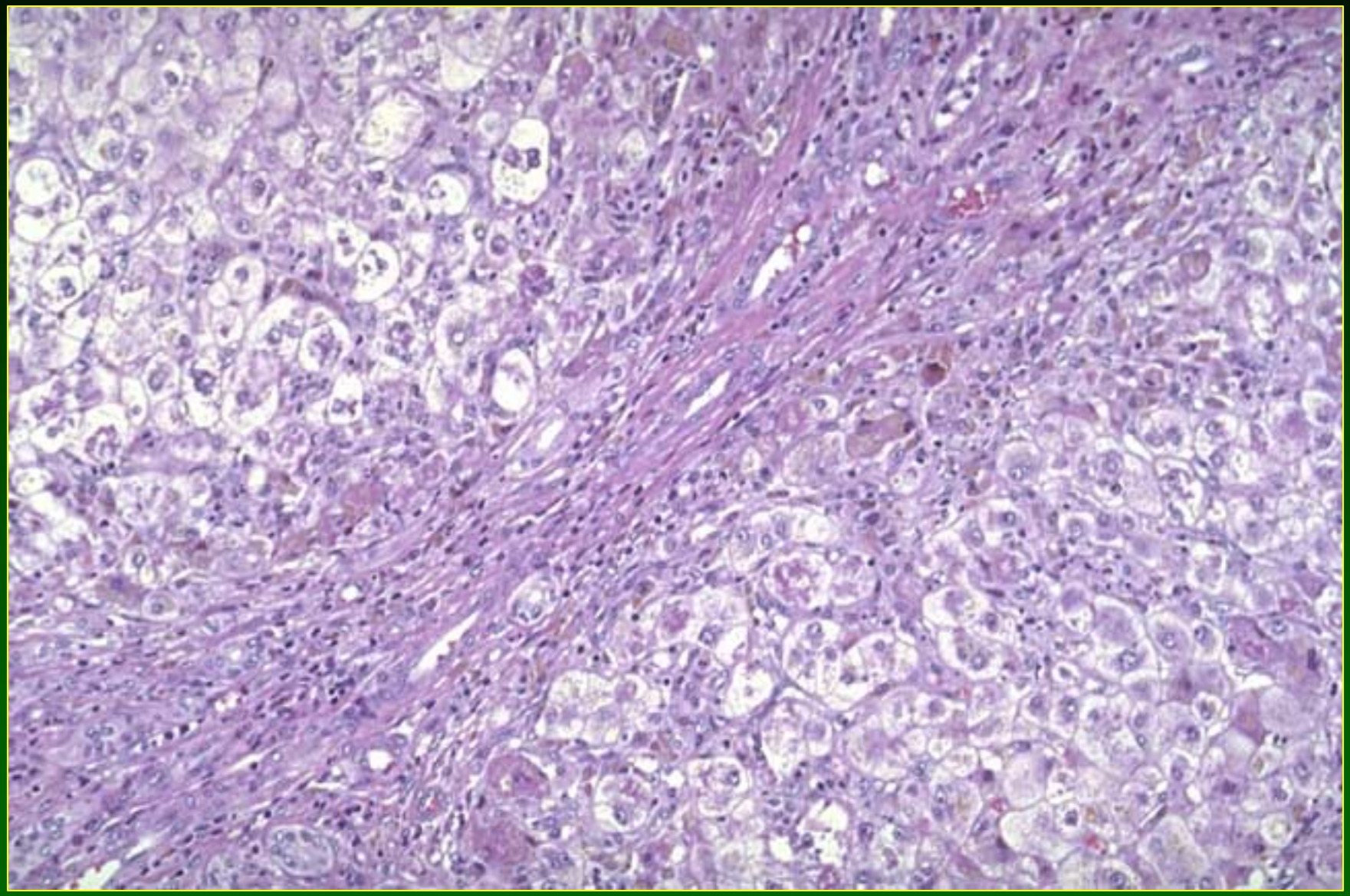


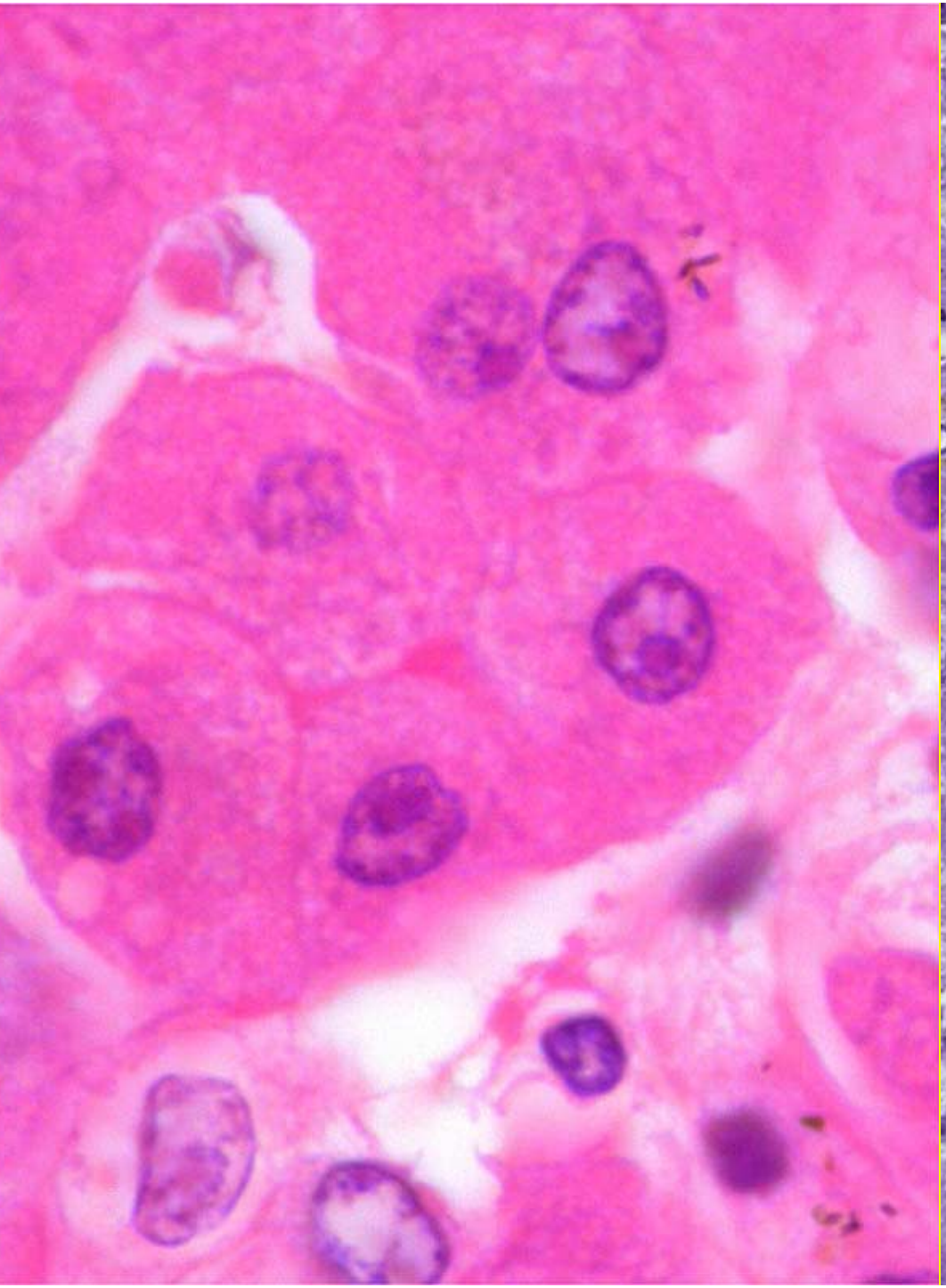
Hepatotoxicity of Metals
Copper (2)

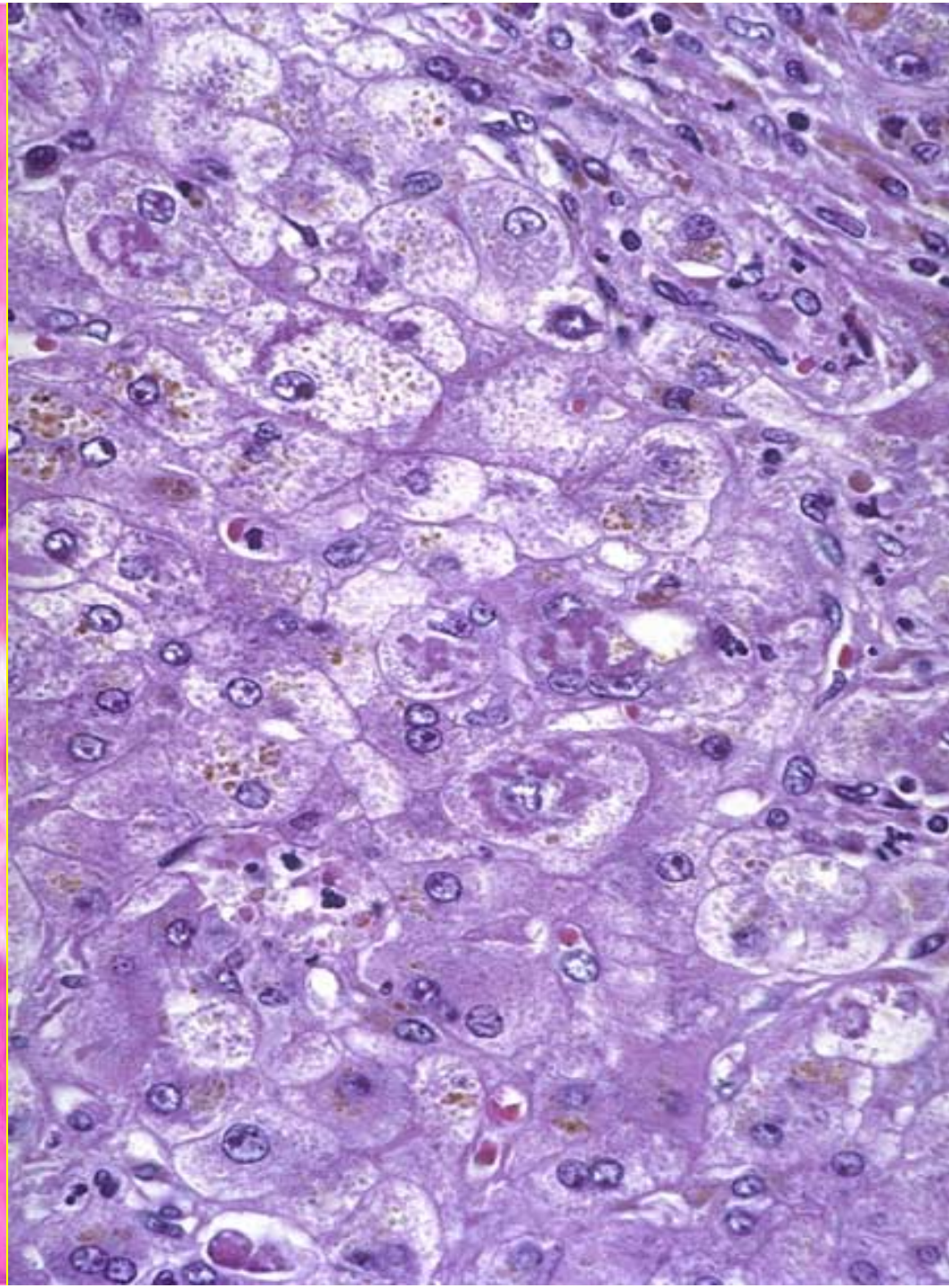
- Chronic Toxicity:
  - Epithelioid granulomas
  - Cirrhosis with Mallory bodies resembling Indian childhood cirrhosis
  - Angiosarcoma

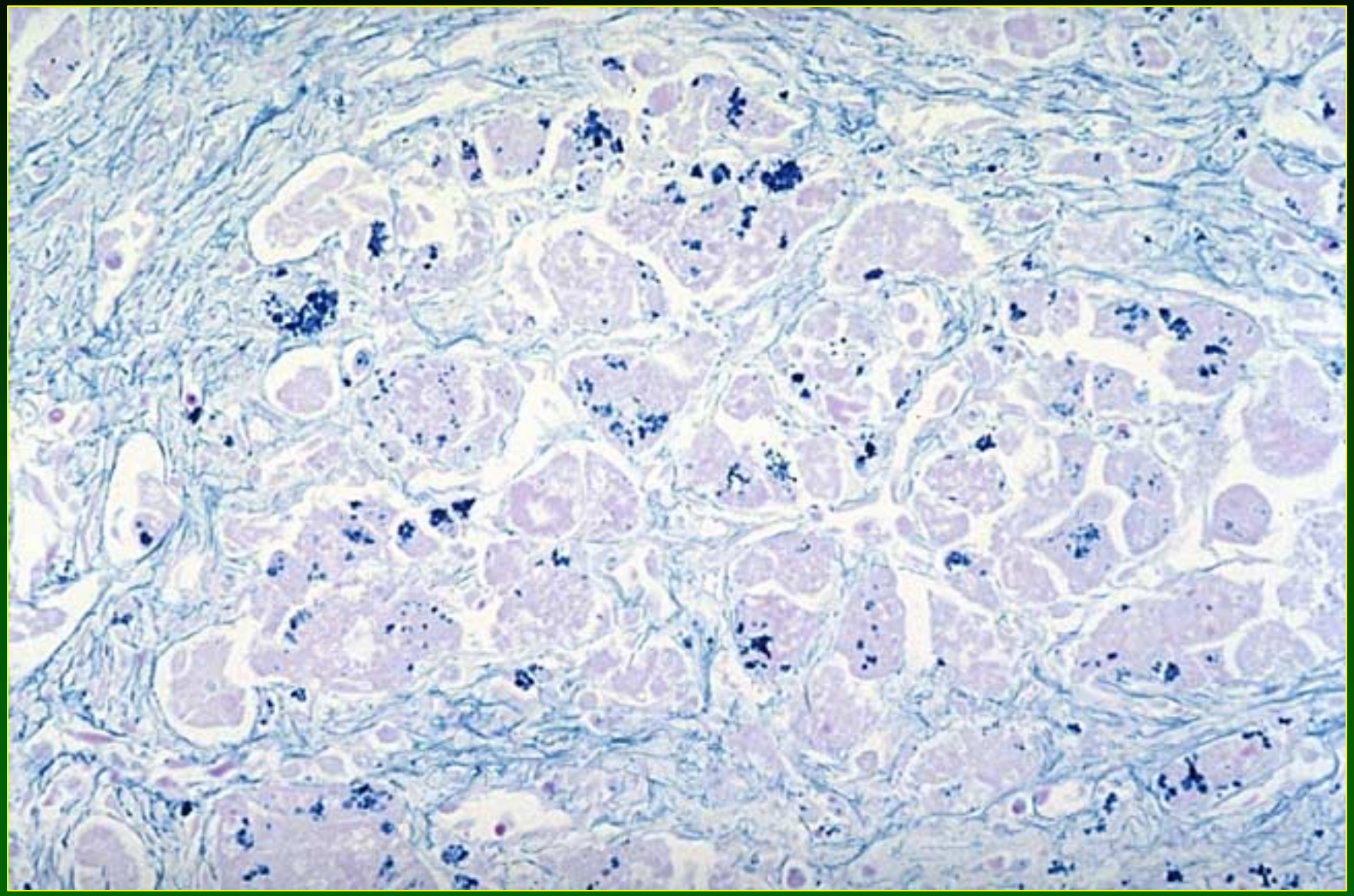












Iron Poisoning
General

- Leading cause of poisoning deaths in children < 6 years of age in U.S.
- > 110,000 reports to U.S. poison control centers since 1986
- 17% of children reported to poison control centers (1980-1992)

Iron Poisoning
General

- Rarely reported in adults*
- Fatalities can occur after as little as 400 mg elemental iron in children (600-5000mg in adults)

*Manoguerra: Am J Hosp Pharm 1976;33:1088-1090

Iron Poisoning
Elemental Iron Content of Products

Product	Elemental Iron
Ferrous sulfate 325 mg tablets	60
Ferrous gluconate 325 mg tablets	40
Ferrous fumarate 325 mg tablets	105
Prenatal vitamins with iron	40-60
Adults vitamins with iron	10-100
Children’s vitamins	3-25

Stage of Iron Poisoning*

Stage	Onset	Symptoms
I	<6 hours	GI bleeding, vomiting diarrhea, shock, lethargy, coma
II	6-24 hours	Apparent improvement
III	12-24 hours	Metabolic acidosis, fever, leukocytosis, liver and renal failure
IV	Weeks	Intestinal scarring with possible obstruction

*After Manoguerra, 1976

Iron Poisoning
Diagnosis

- History
- Presence of tablets in vomitus or lavage fluid
- Abdominal radiography
- Serum Fe determination:
  - >500 ug/dl (severe poisoning)
  - <300 ug/dl (moderate/severe)

Iron Poisoning
Treatment

- Sodium bicarbonate (oral, lavage, enema)
- X-ray of abdomen to assess removal of tablets
- Serum iron determination
- I.V. fluids for shock and acidosis
- Deferoxamine
- Treatment of liver and/or renal failure

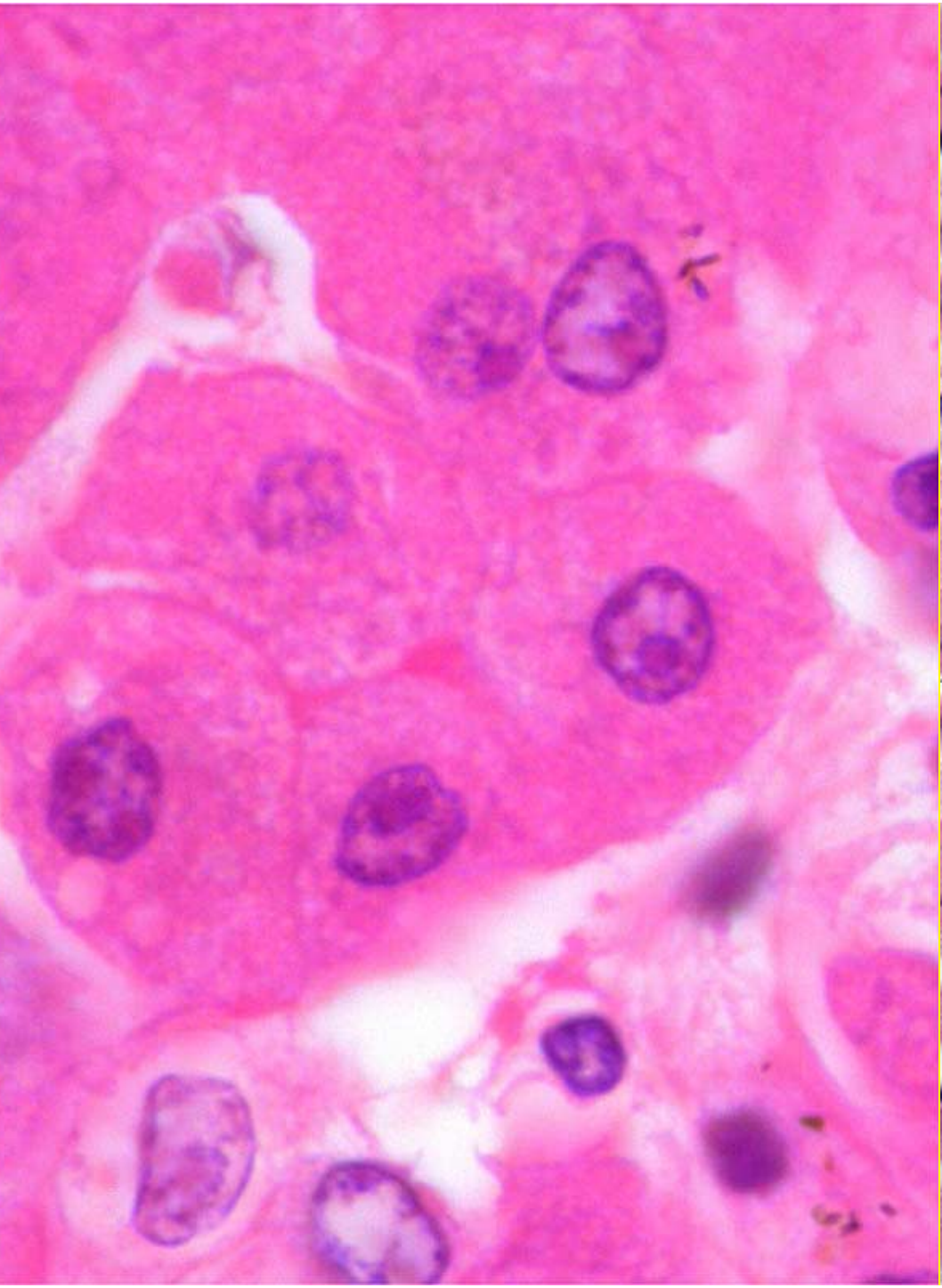
Iron Toxicity

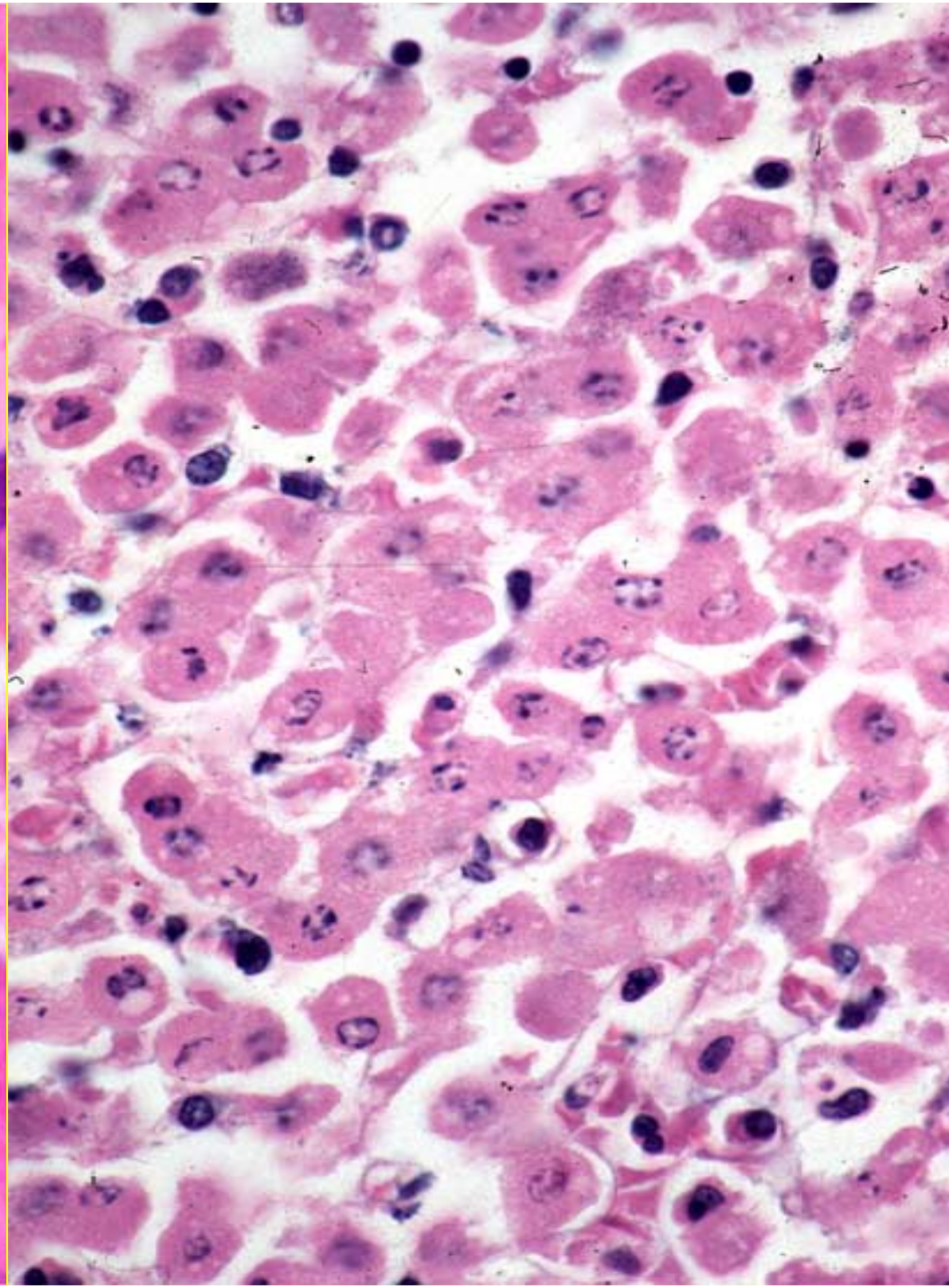
- Acute: Children > adults
- Acute/Subacute: Ulcers/strictures of esophagus or stomach caused by iron tablets in adults*

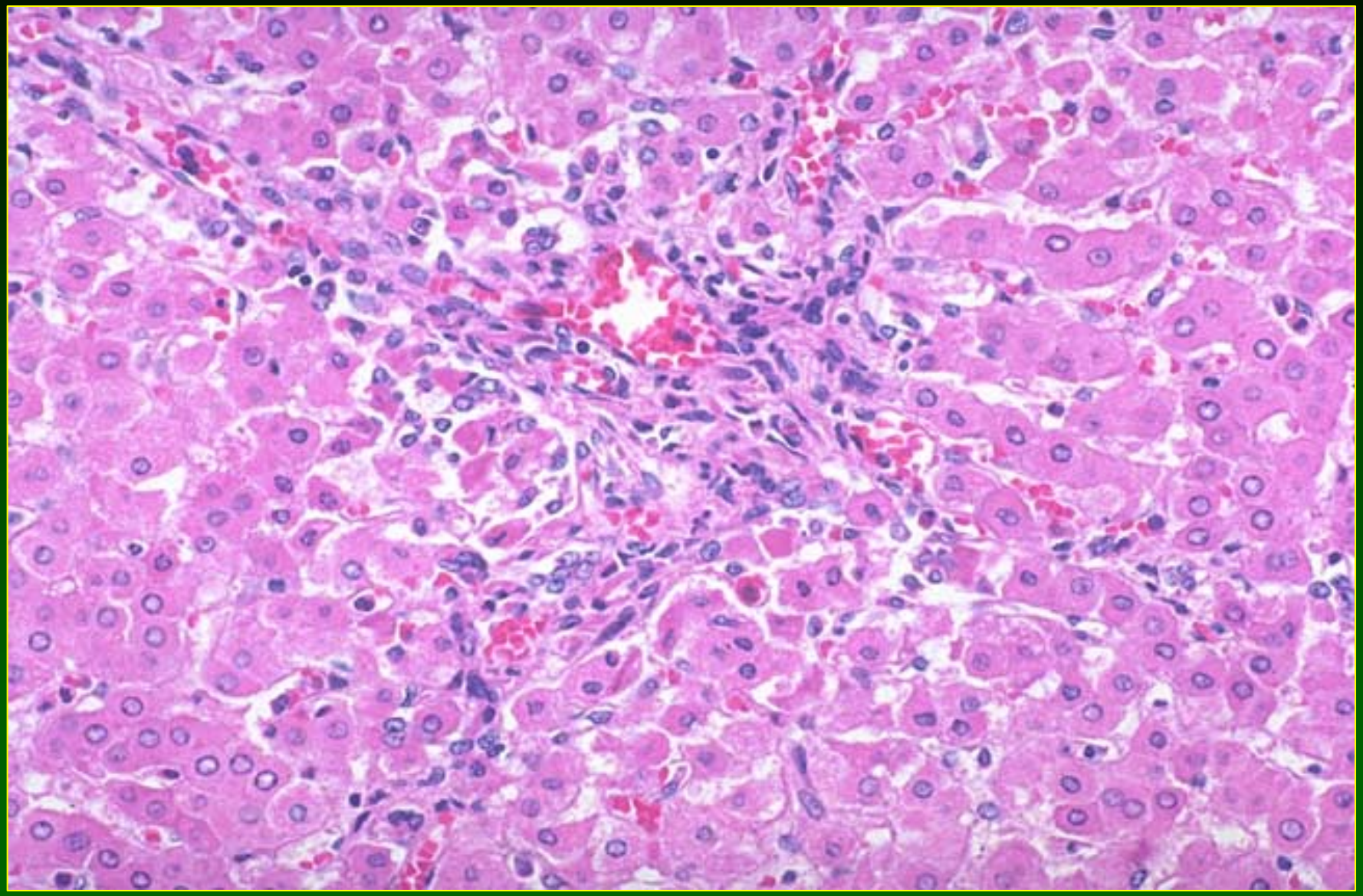
*Eckstein & Symons: Pathology 1996;28:142

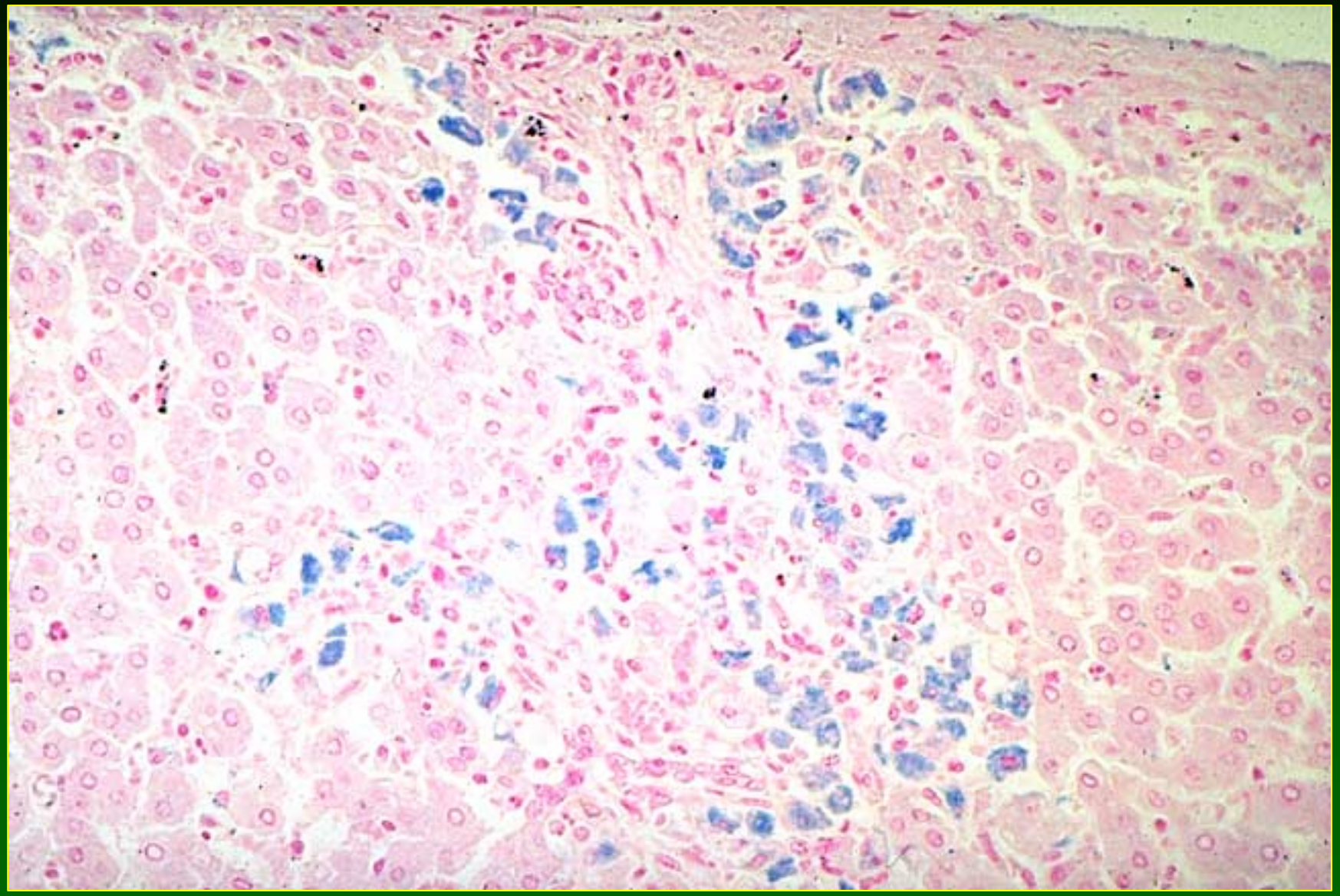
Iron Toxicity
Pathology - Acute

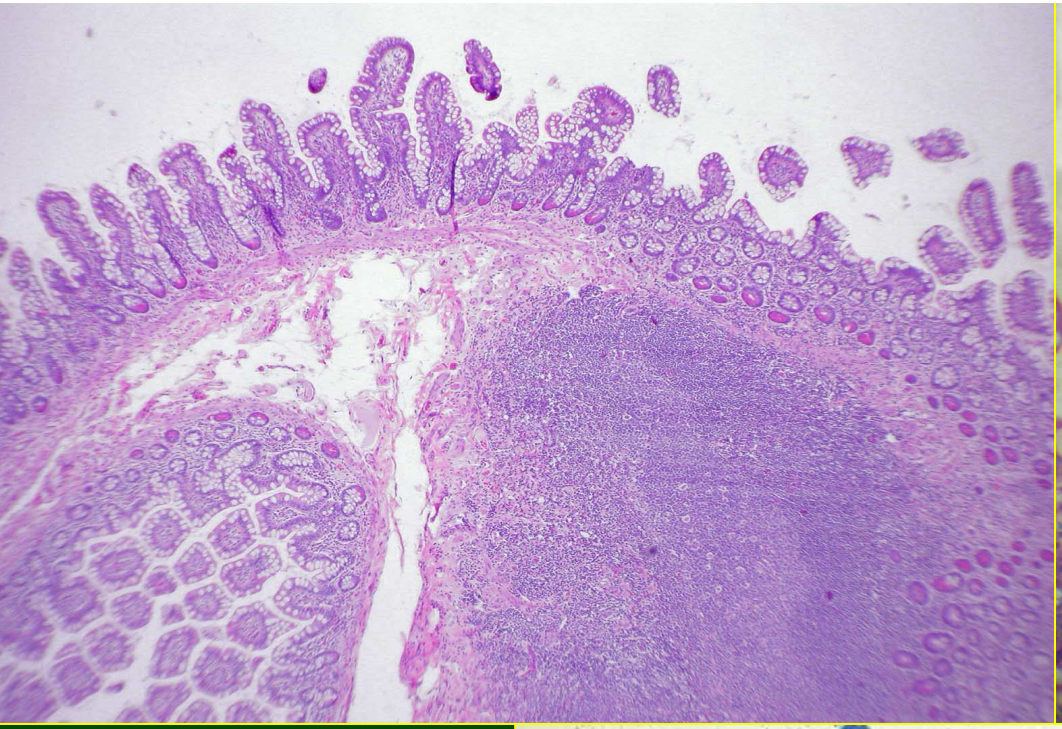
- Stomach/Intestine: Congestion, necrosis, neurtrophilic infiltration, impregnation of mucosa and vessels with iron
- Liver; Zone 1 coagulative necrosis; iron impregnation of necrotic cells and sinusoidal endothelium

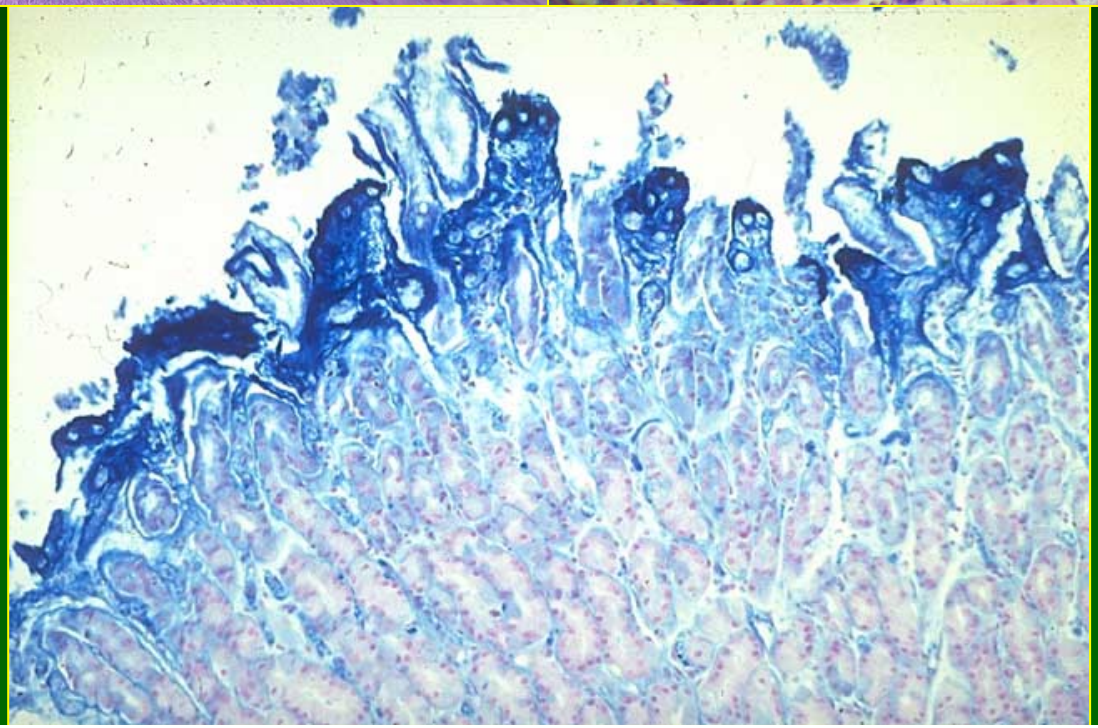


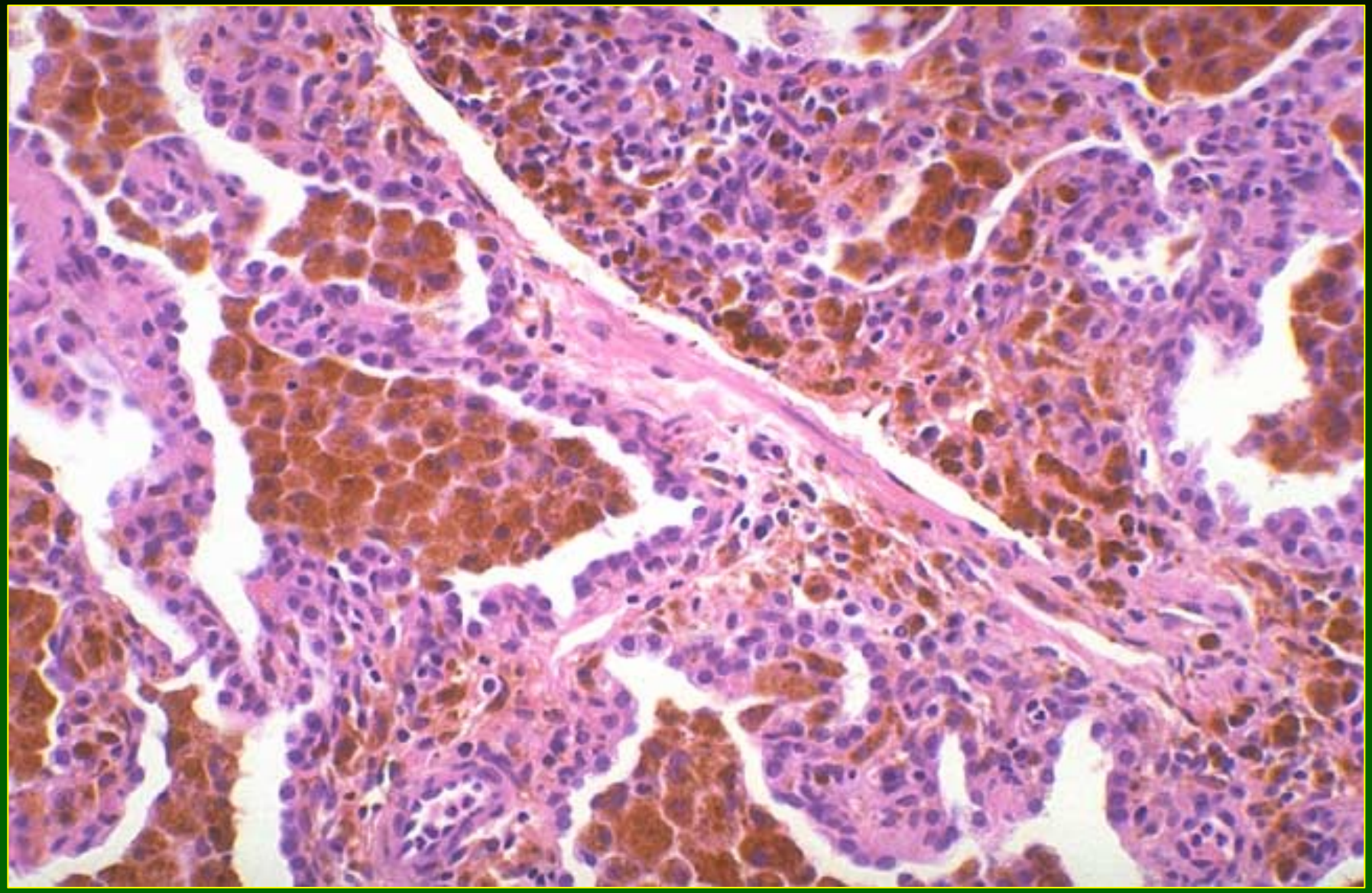


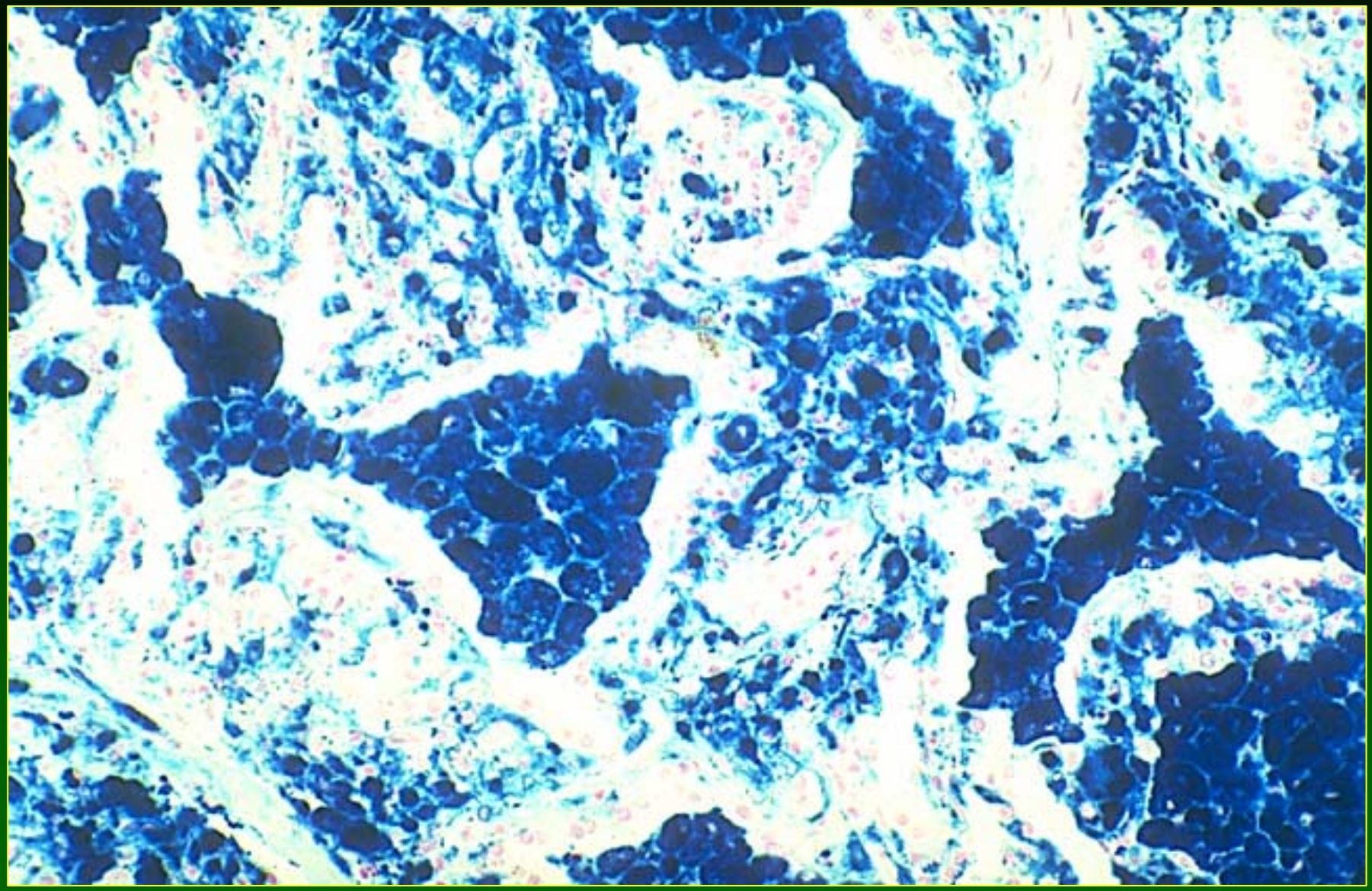












Iron Toxicity
Pathology - Chronic

- Hemosiderosis
- Fibrosis
- Cirrhosis - rarely

Iron Toxicity
Chronic

- Iron overload in children on prolonged parenteral nutrition
- Hemosiderosis in hemodialysis patients given parenteral iron
- Portacaval shunt hemosiderosis
- Hemosiderosis from chronic Fe ingestion
- Transfusional hemosiderosis

Hepatotoxicity of Metals
Acute Phosphorus Poisoning

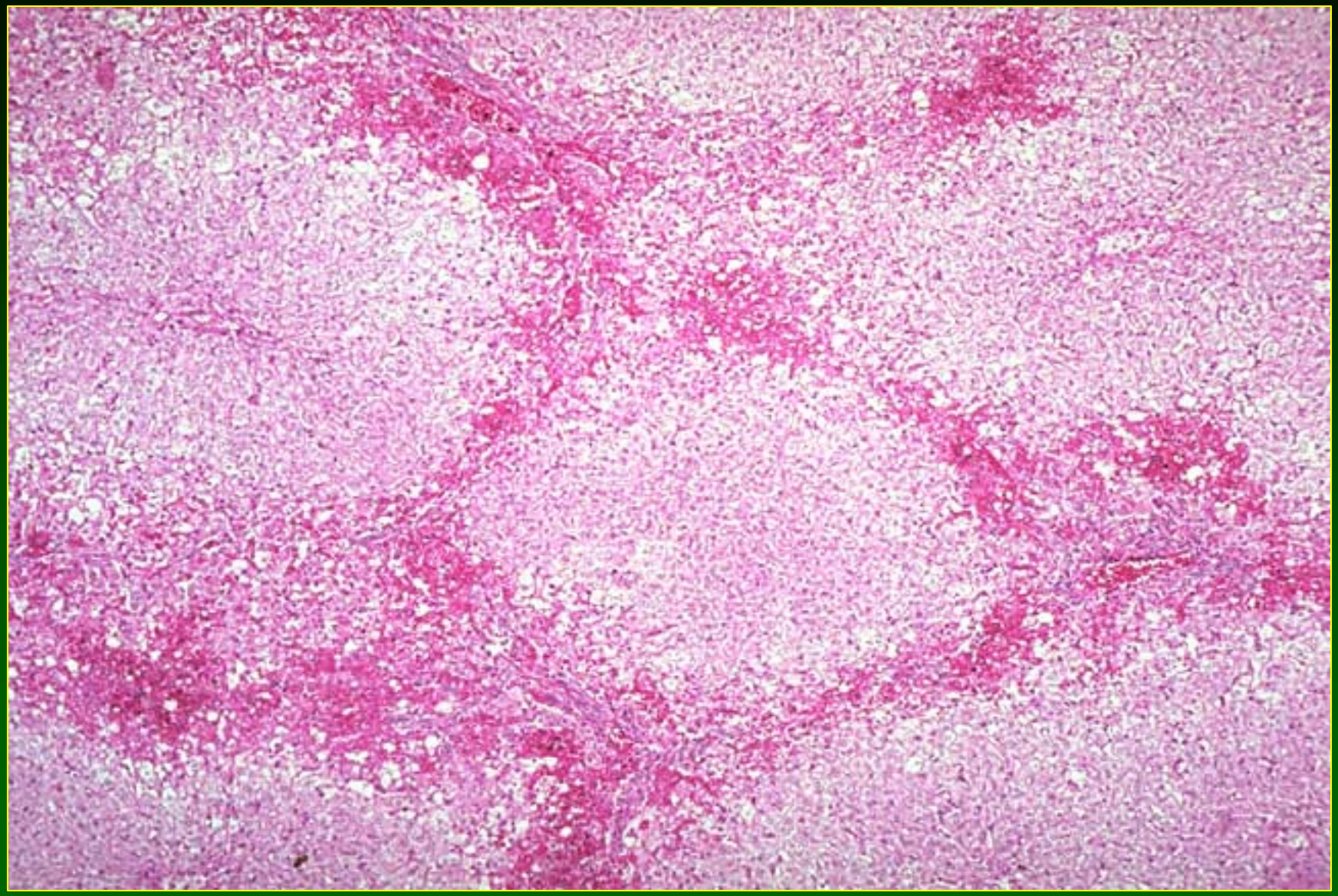
- Accidental or suicidal ingestion of rodenticides, roach paste or fire crackers
- Minimum dose 15mg; lethal dose 60mg or more
- Mortality rate 27% and 48% in two series

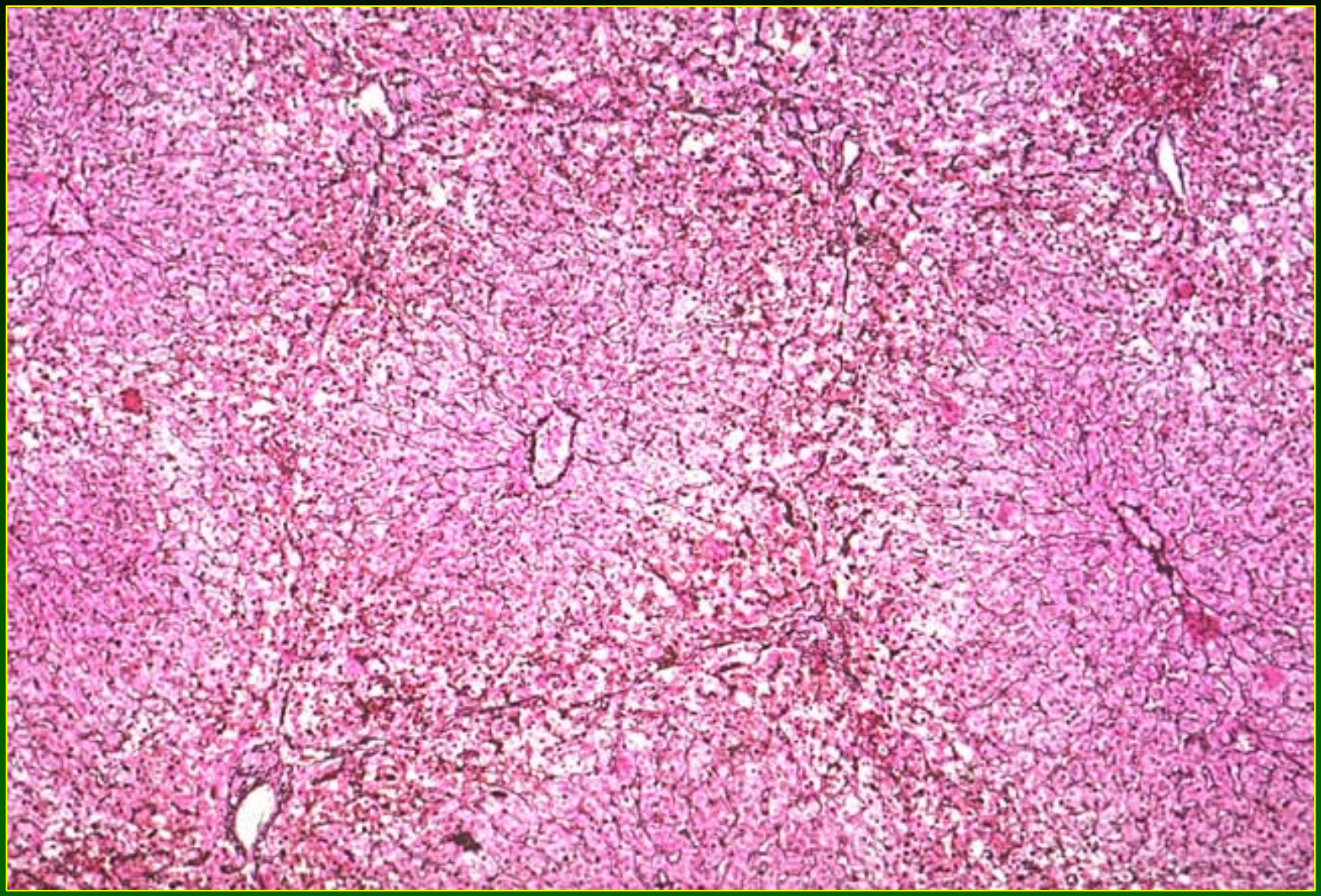
Hepatotoxicity of Metals
Acute Phosphorus Poisoning

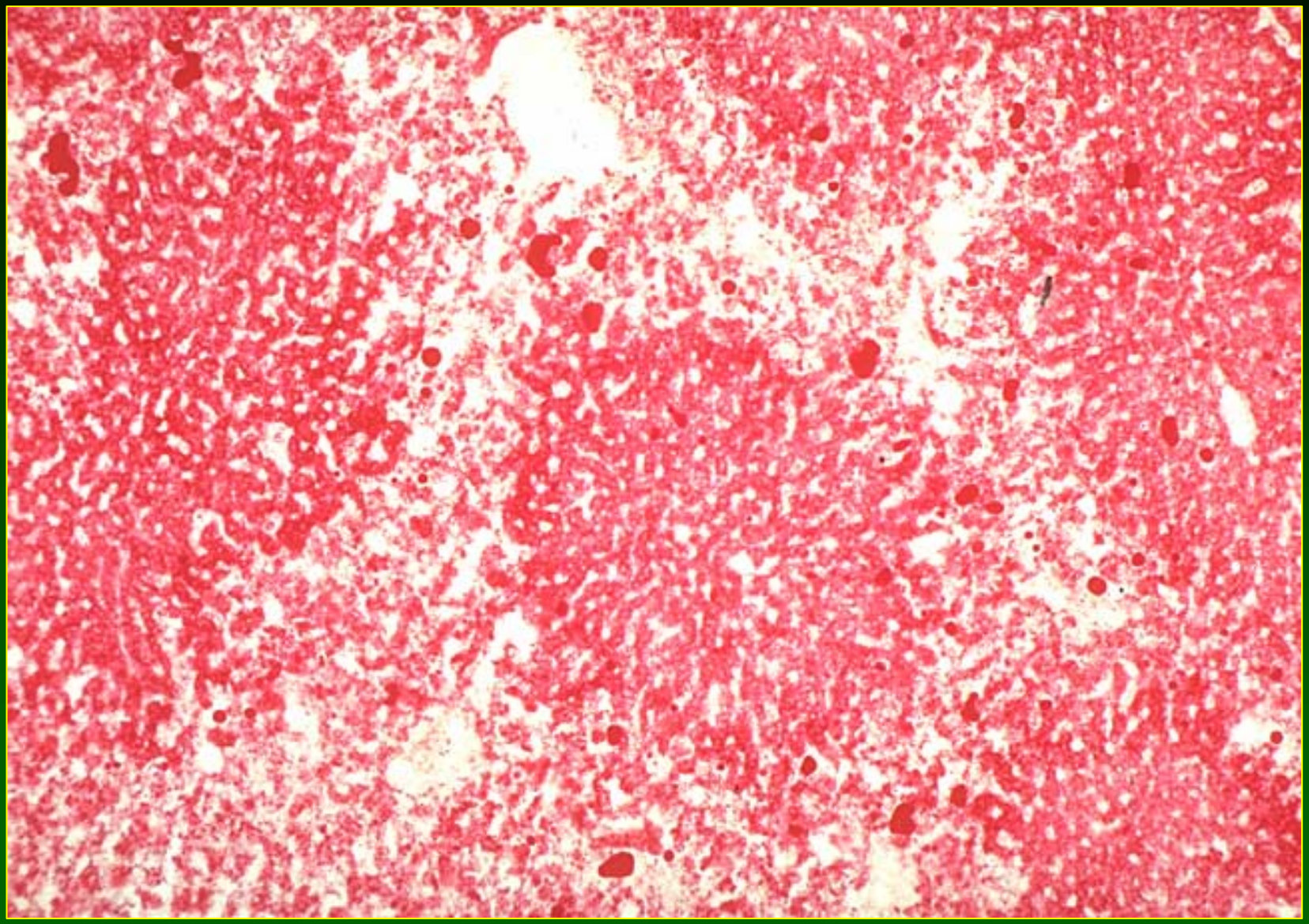
- Cutaneous burns, garlic odor and luminescence of vomitus or feces
- 6-8 hours: Nausea, vomiting, diarrhea, abdominal pain
- 1-3 Days: Symptom-free period
- > 3 Days: Same as first stage + hematemesis, hepatomegaly, jaundice, multiorgan failure and death

Hepatotoxicity of Metals
Phosphorus

- Acute Toxicity: Zone 1 necrosis +/- microvesicular steatosis; massive necrosis rare
- Chronic Toxicity: None







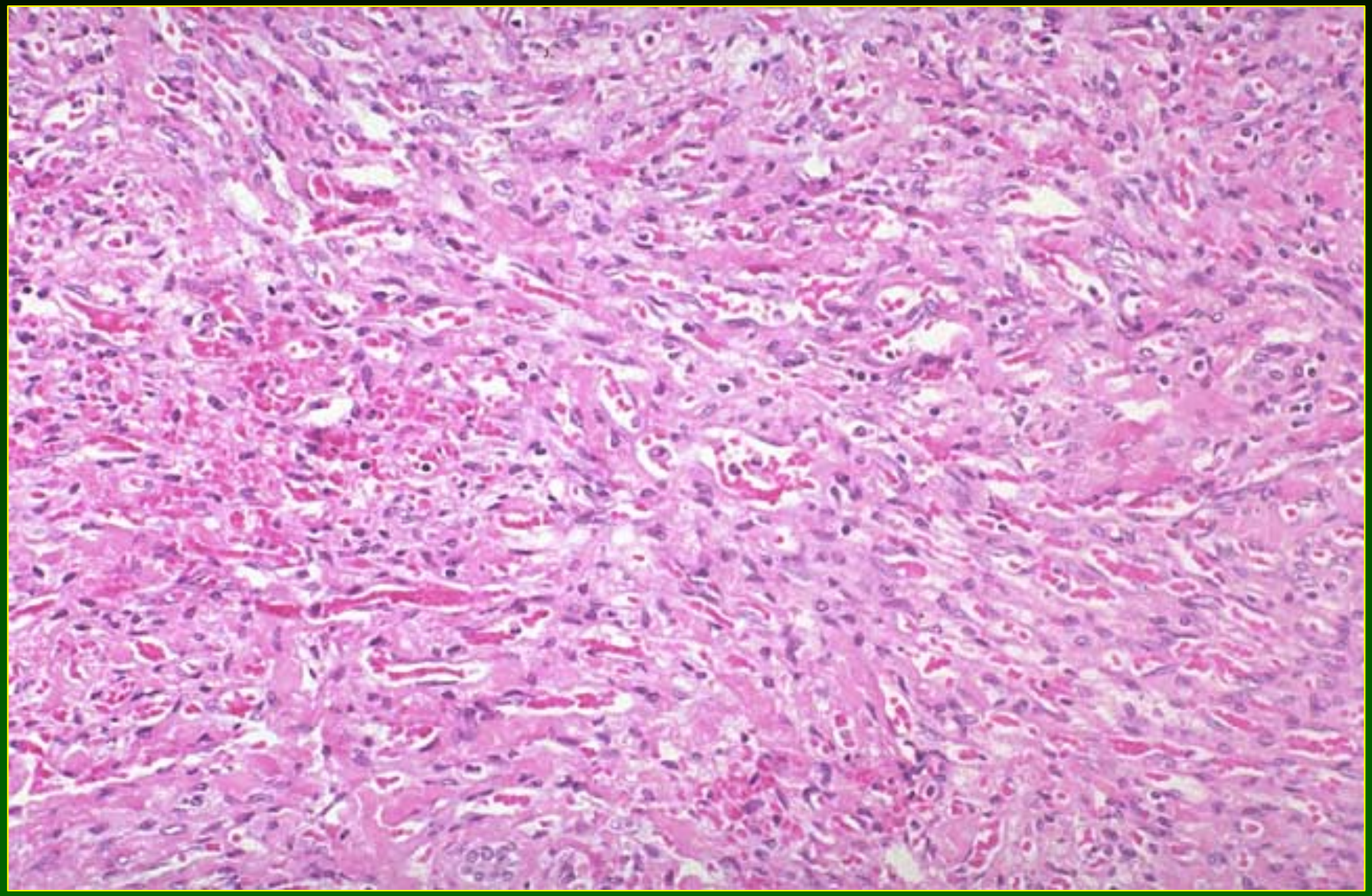
Hepatotoxicity of Metals
Thorium (1)

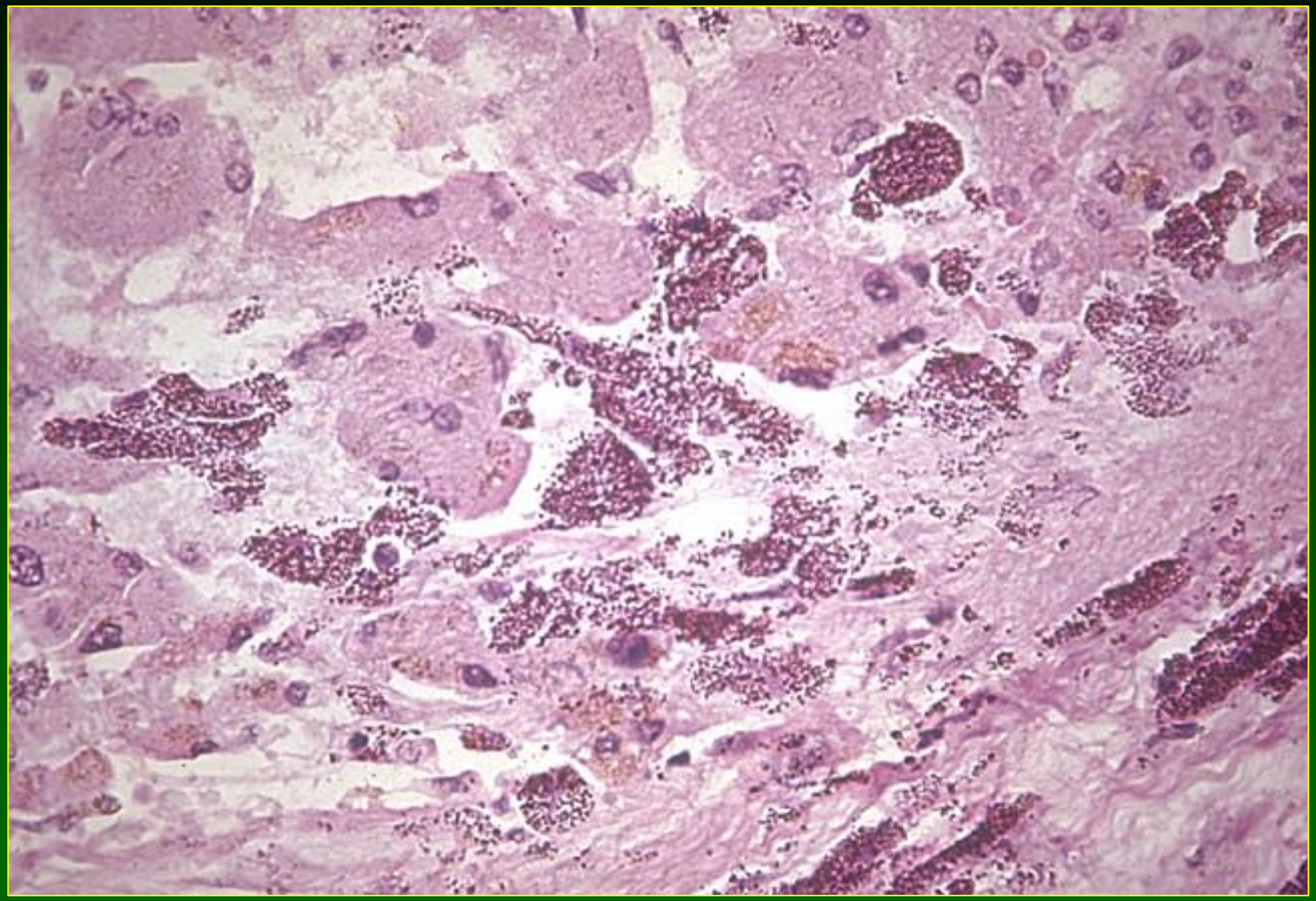
- Thorotrast, a colloidal suspension of thorium dioxide was used for radiographic opacification in 30s-50s
- Injected material accumulated in reticuloendothelial cells of the liver, spleen lymph nodes and bone marrow
- Half life: 400 years

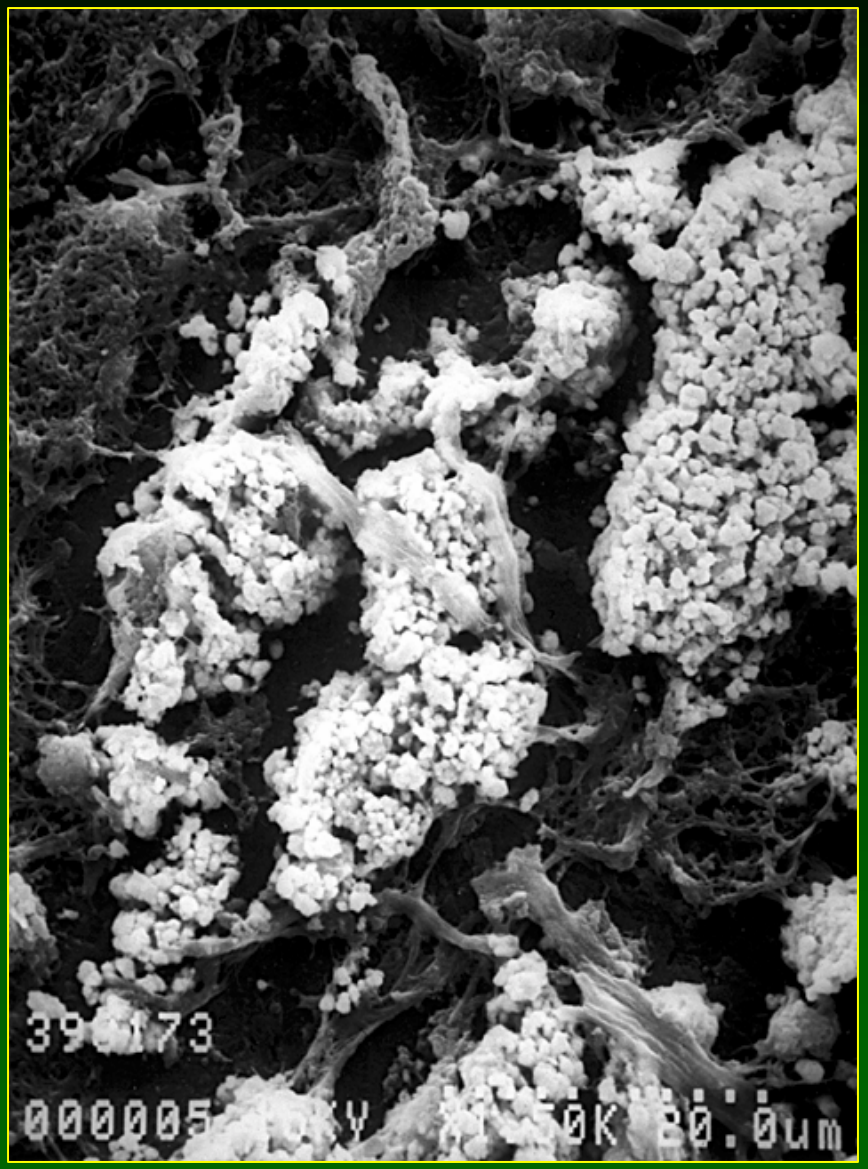
Hepatotoxicity of Metals
Thorium (2)

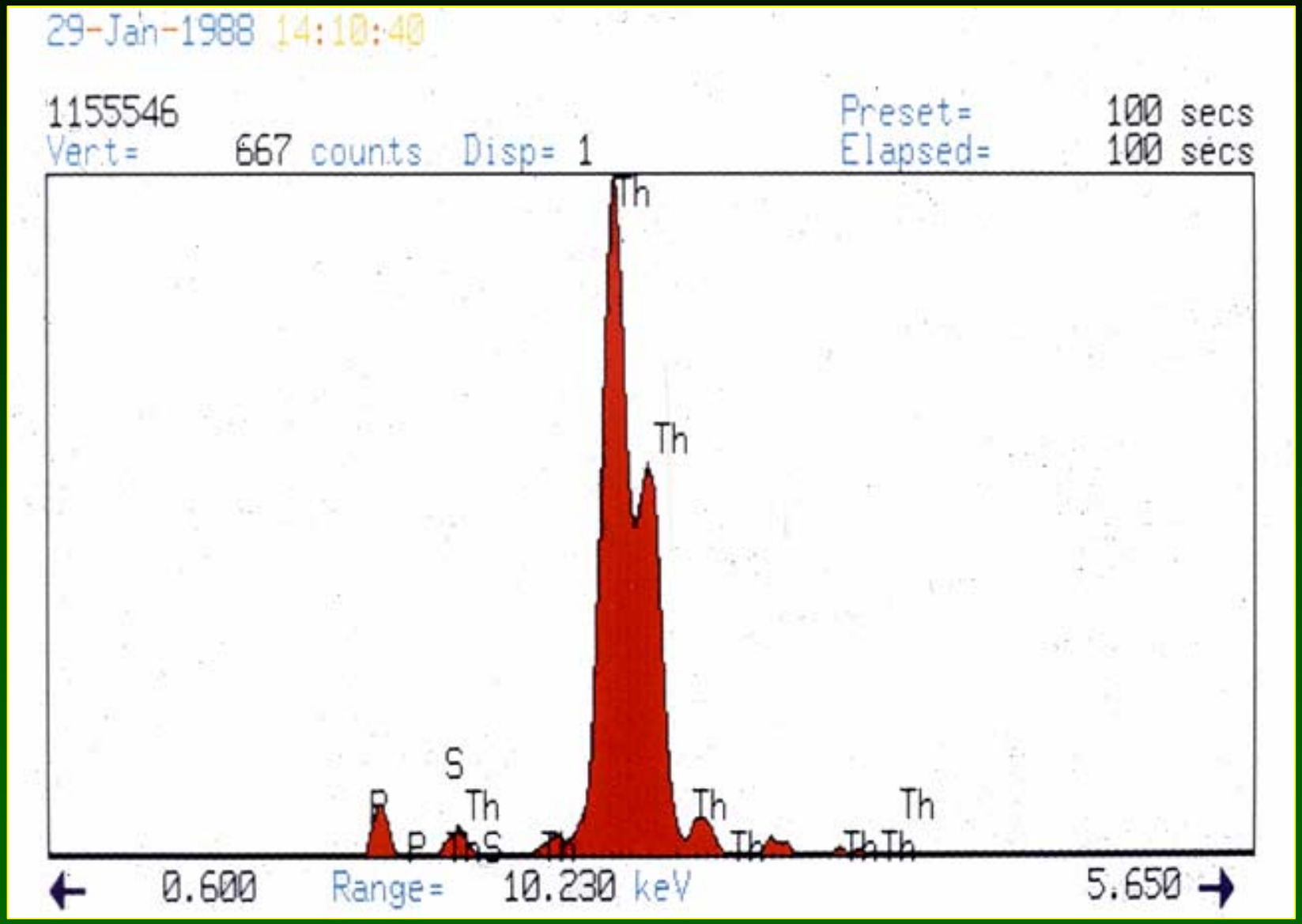
- Extensive fibrosis associated with Thorotrast deposits; cirrhosis (very rare)
- Venocclusive disease, granulomas (rare)
- Major complication is induction of malignant tumors--angiosarcoma, cholangiocarcinoma, hepatocellular carcinoma (latent period > 14 years)

- A 54 year old white male with right upper quadrant pain of two months duration. Sixteen years earlier the patient received 75cc of 2 1/2%thorium dioxide IV and radiographs of liver and spleen were made.



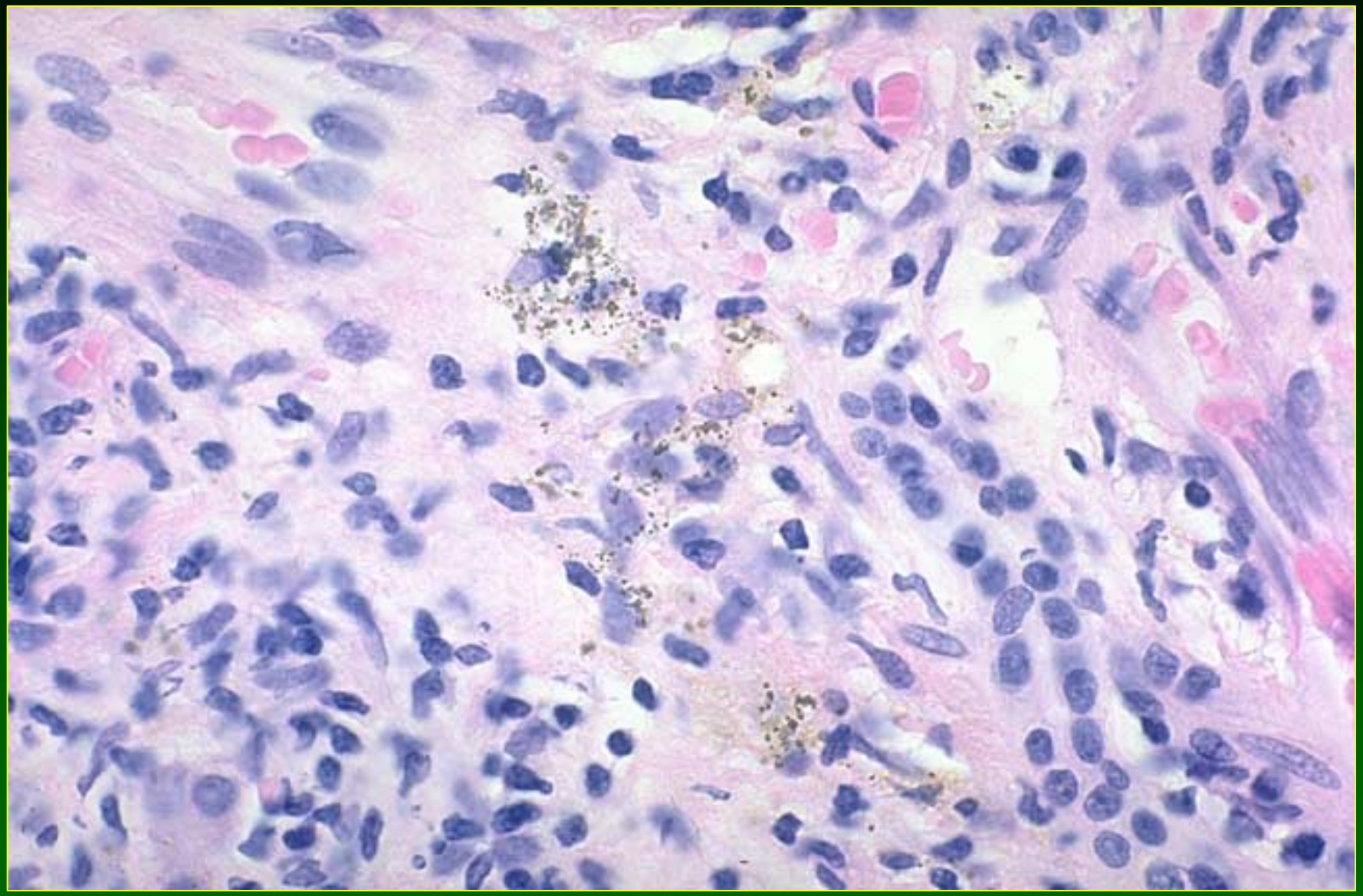


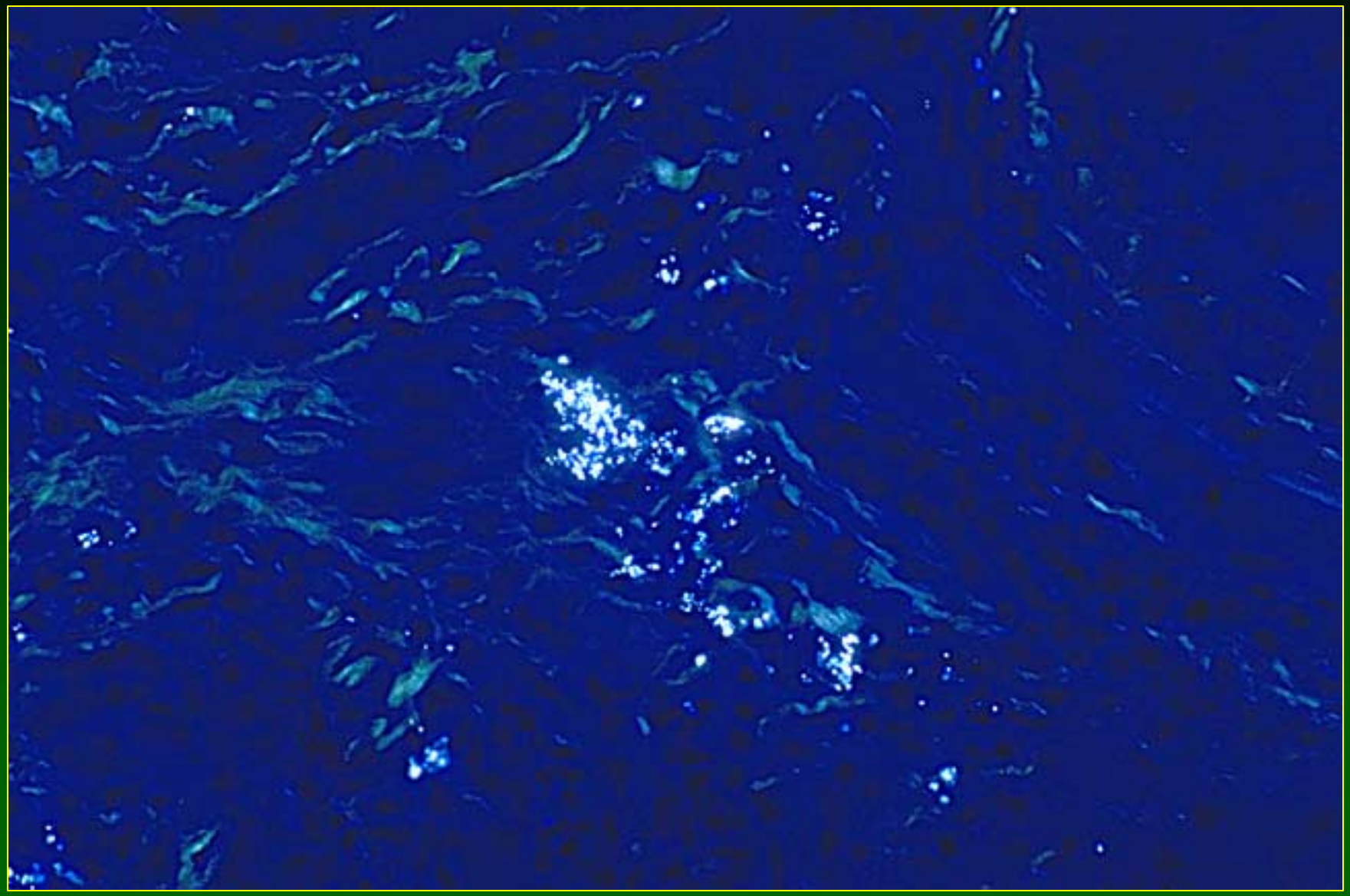

39 173
000005
0K 30.0um

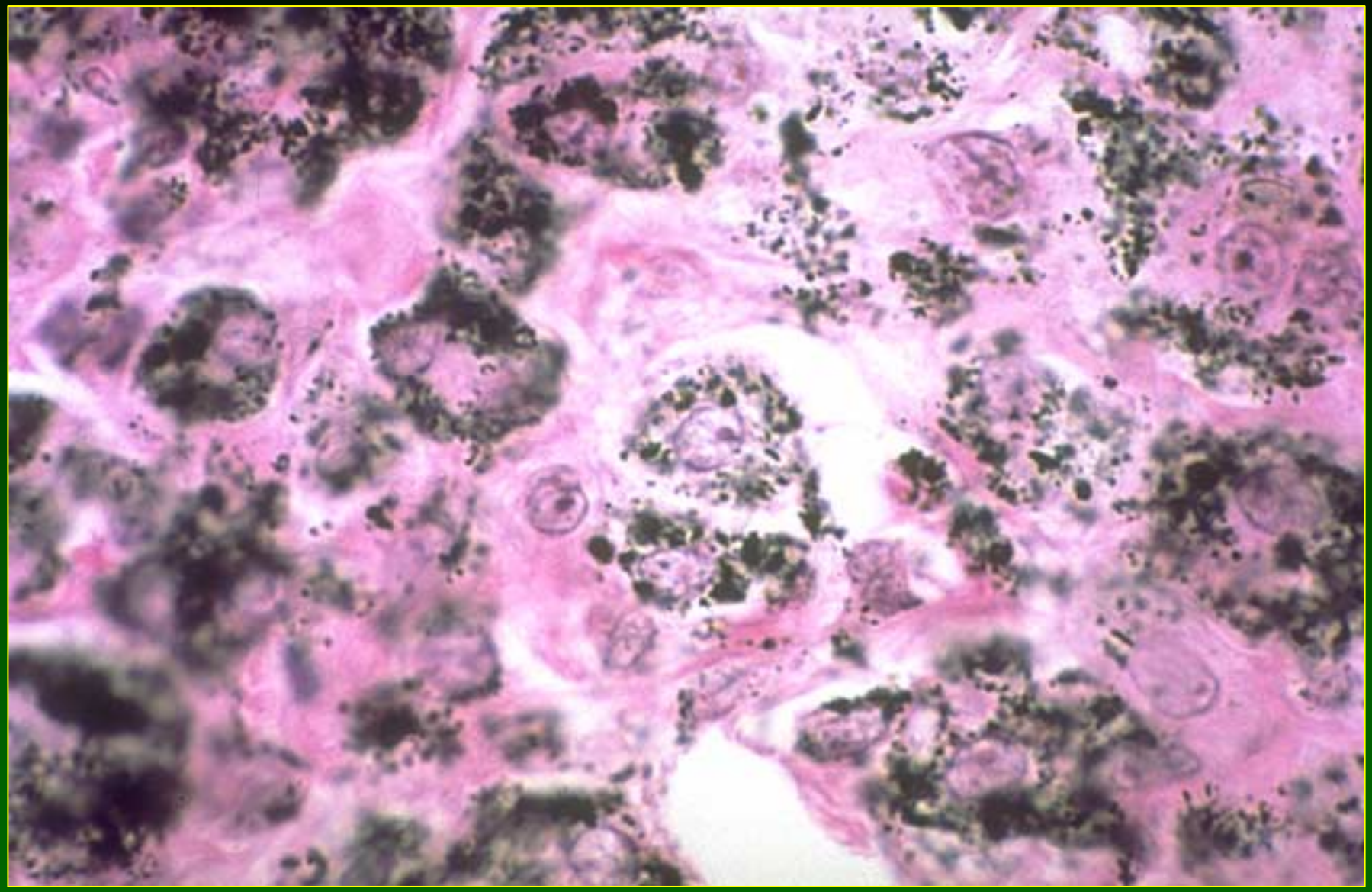

29-Jan-1988 14:10:40
1155546
Vert= 667 counts Disp= 1
Preset= 100 secs
Elapsed= 100 secs
Th
Th
S
P
Th
Th
Th
Th
0.600
Range= 10.230 keV
5.650

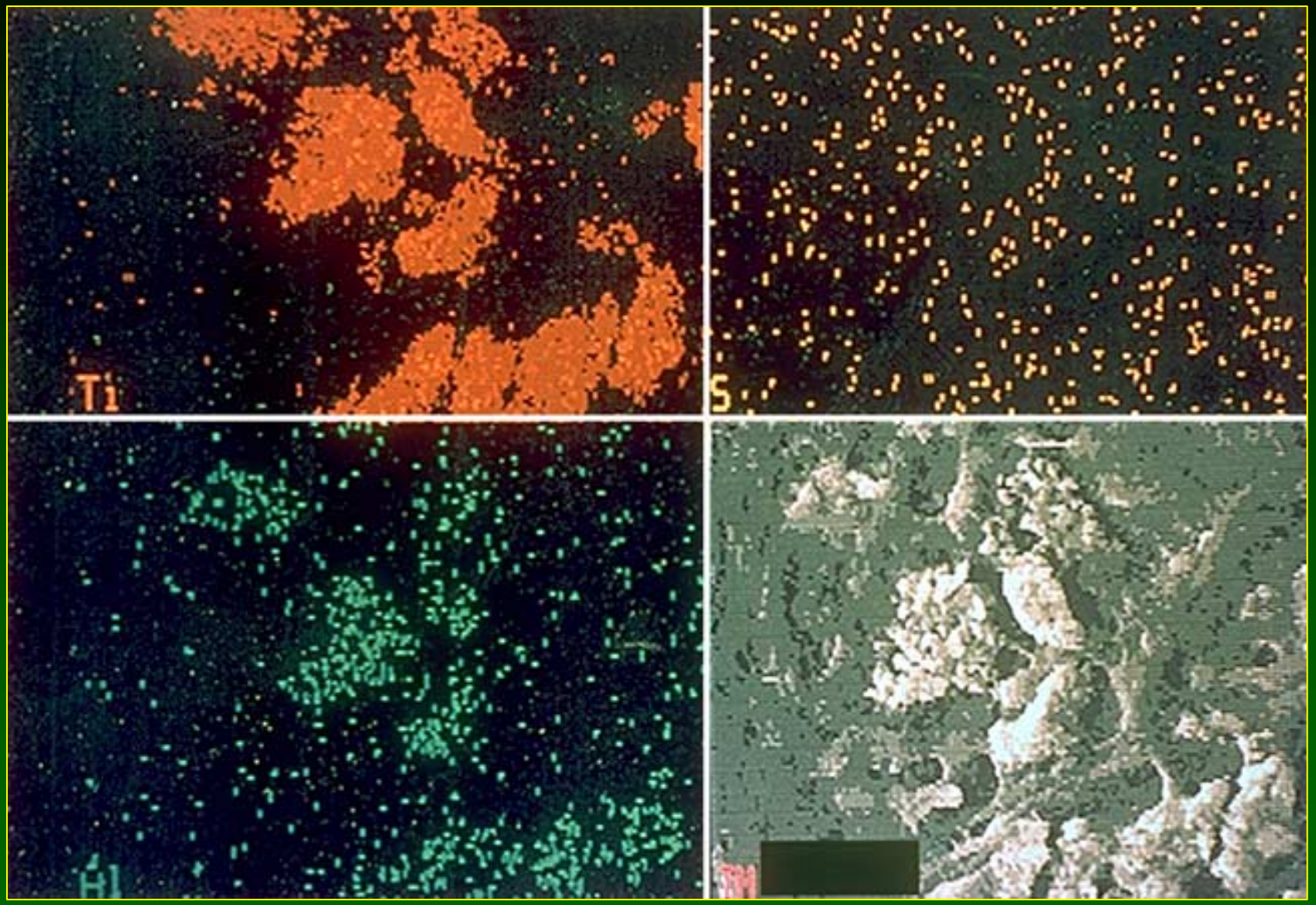
Hepatotoxicity of Metals
Titanium

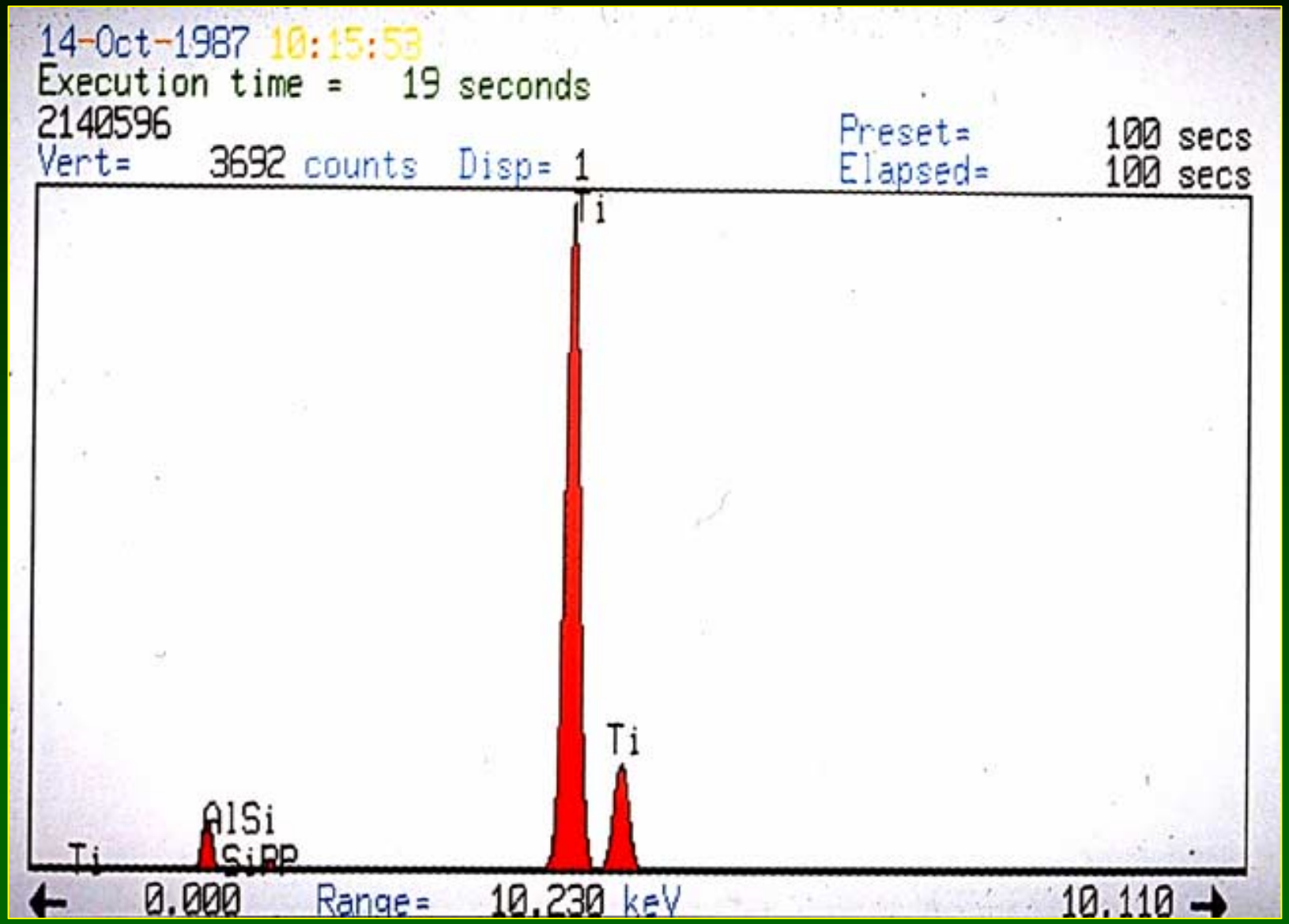
- Accumulation of black, granular pigment in Kupffer cells and portal macrophages, together with talc in Kupffer cells and portal macrophages, of intravenous abusers of drugs

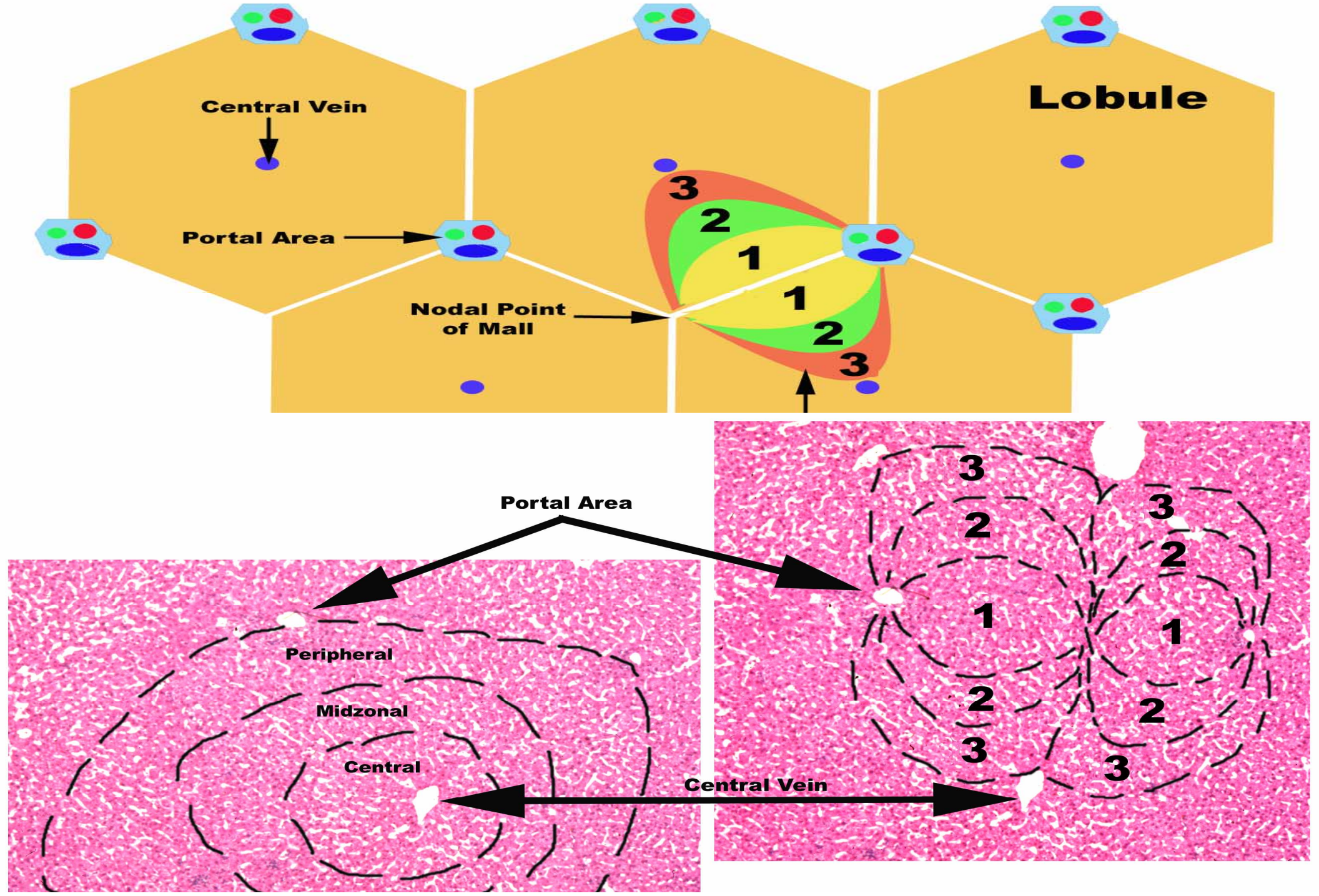







Ti
S
Al


14-Oct-1987 10:15:53
Execution time = 19 seconds
2140596
Vert= 3692 counts Disp= 1
Preset= 100 secs
Elapsed= 100 secs
Ti
Ti
AlSi
SiPP
Ti
0.000
Range= 10.230 keV
10.110


Central Vein
Portal Area
Nodal Point
of Mall
Lobule
3
2
1
1
2
3
Portal Area
Peripheral
Midzonal
Central
Central Vein
3
2
1
2
3
3
2
1
2
3

Hepatotoxicity of Metals
Summary (1)

- Acute Effects:
  - Intrahepatic cholestasis
  - Submassive (e.g. zone 3 in Cu toxicity, zone 1 in phosphorus or iron toxicity)
  - Steatosis

Hepatotoxicity of Metals
Summary (2)

- Chronic Effects:
  - Granulomas
  - Fibrosis → cirrhosis
  - Vascular lesion, e.g. venocclusive disease
  - Malignancies, e.g. angiosarcoma, cholangiocarcinoma, hepatocellular carcinoma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