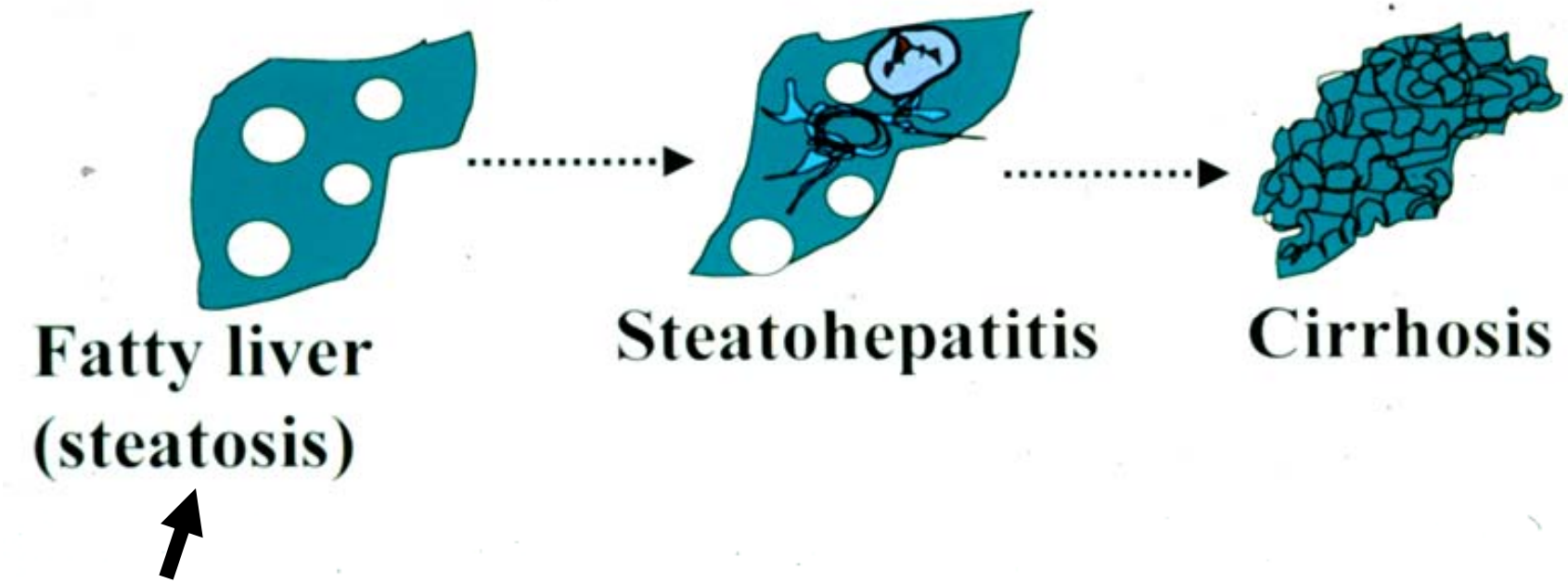
1. **Fatty Liver: AFLD & NAFLD**
2. **Drug hepatitis**
3. **Iron overload disorders**
   - **-hemosiderosis**
   - **-hereditary hemochromatosis**
4. **Copper overload—Wilson disease**
5. **Alpha-1-antitrypsin deficiency**

Fatty liver and possible sequelae



AFLD (alcoholic fatty liver dis.)

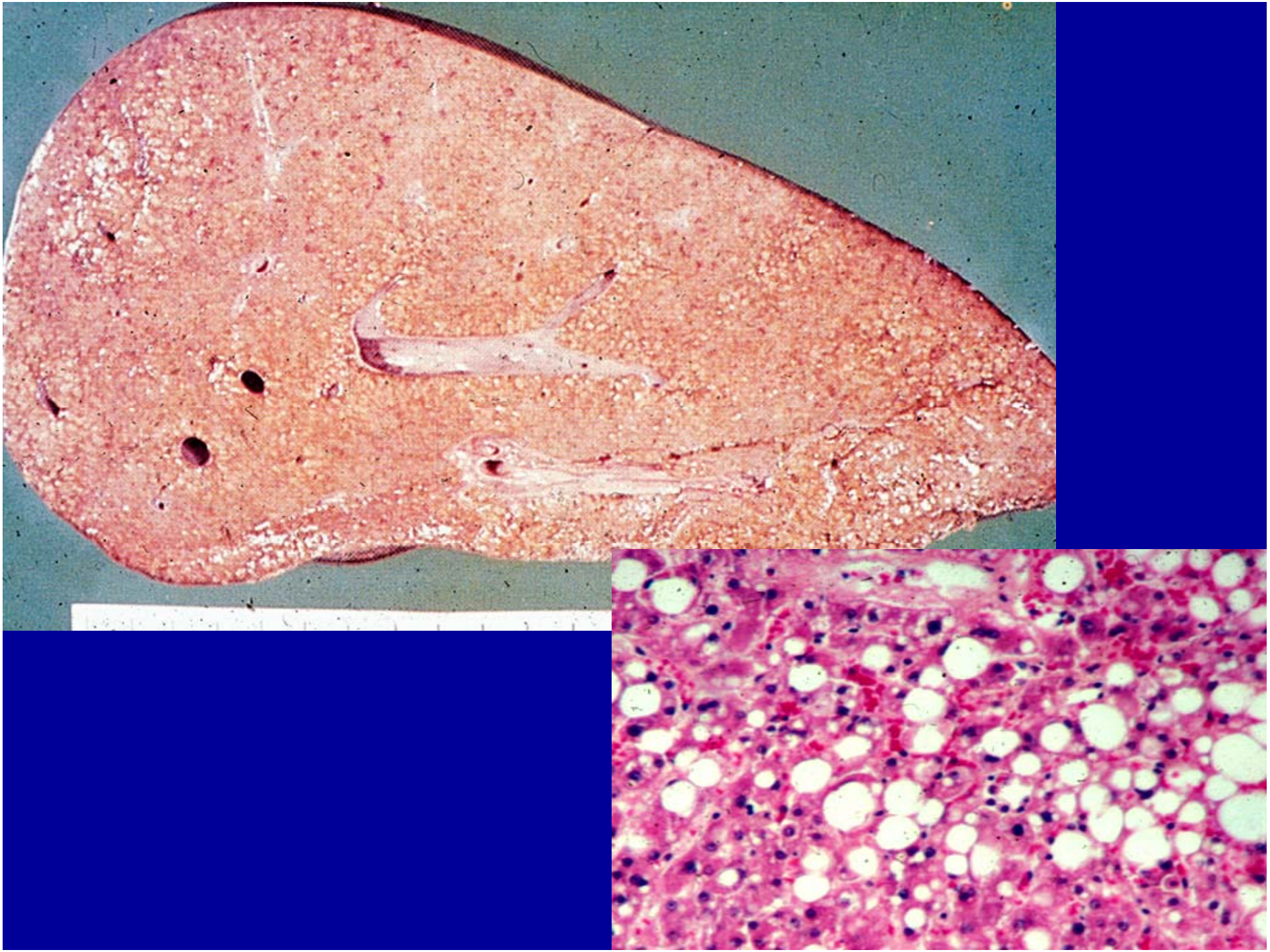
ASH alcoholic steatohepatitis

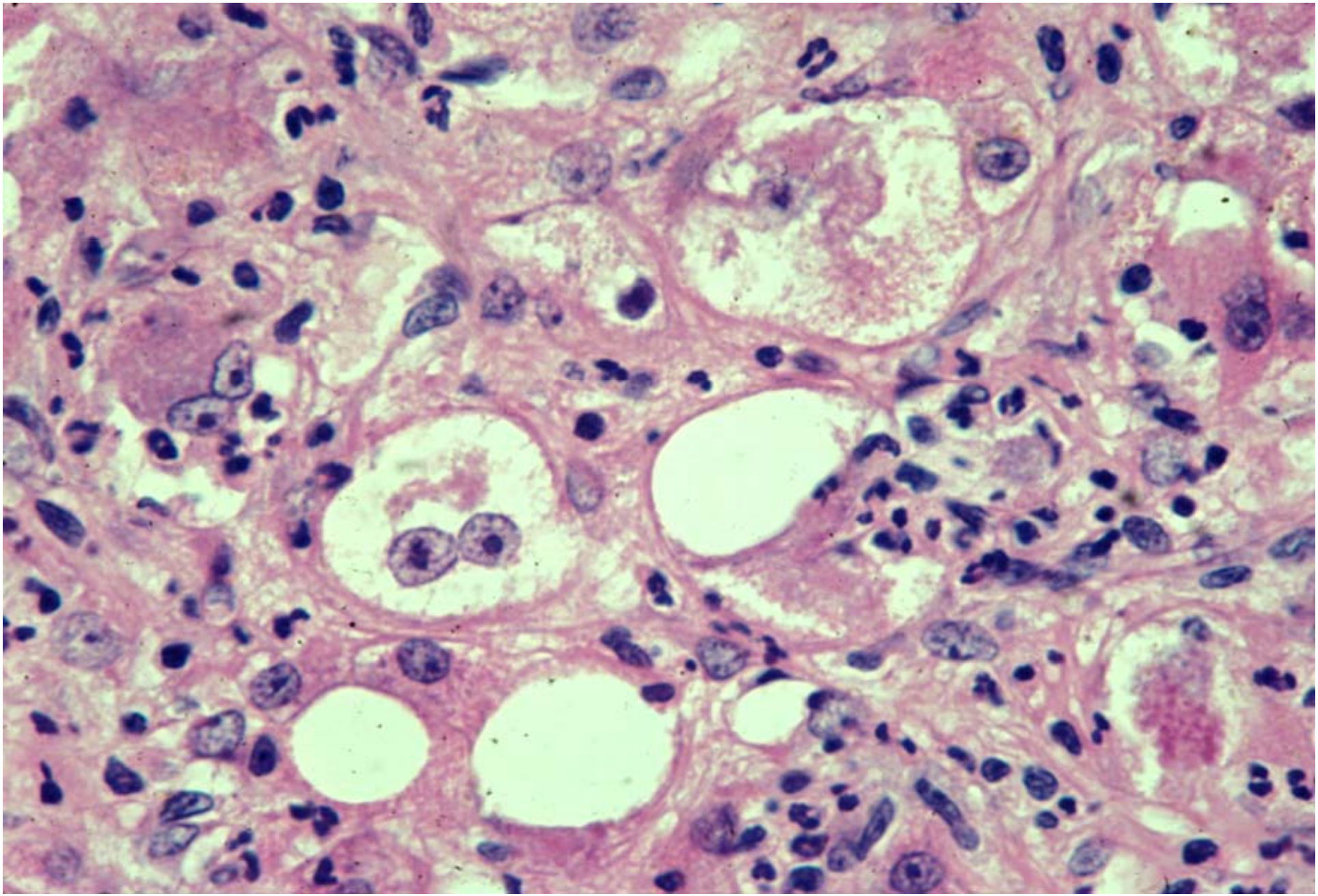
Cirrhosis

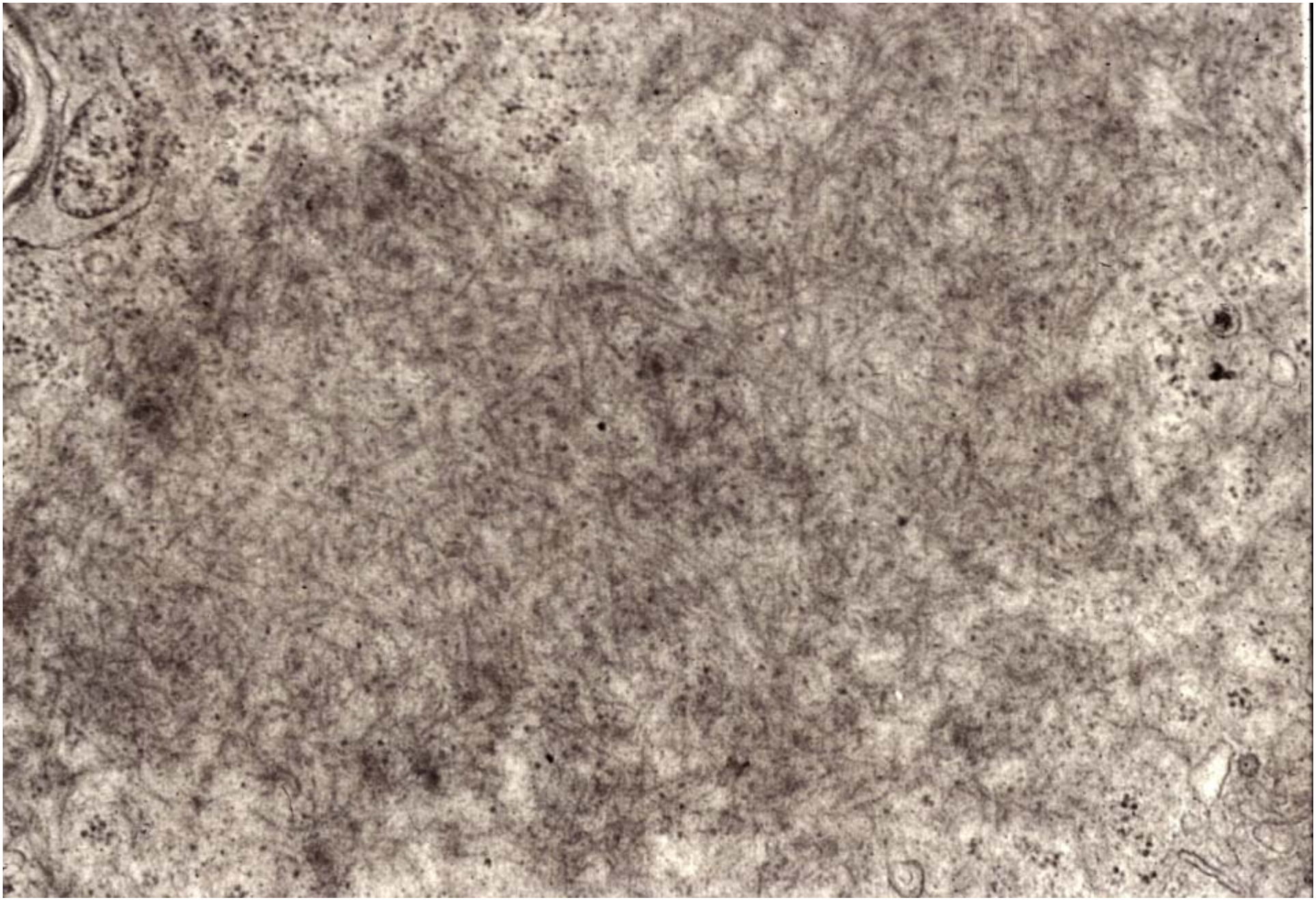
NAFLD (non-alcoholic fatty liver disease)

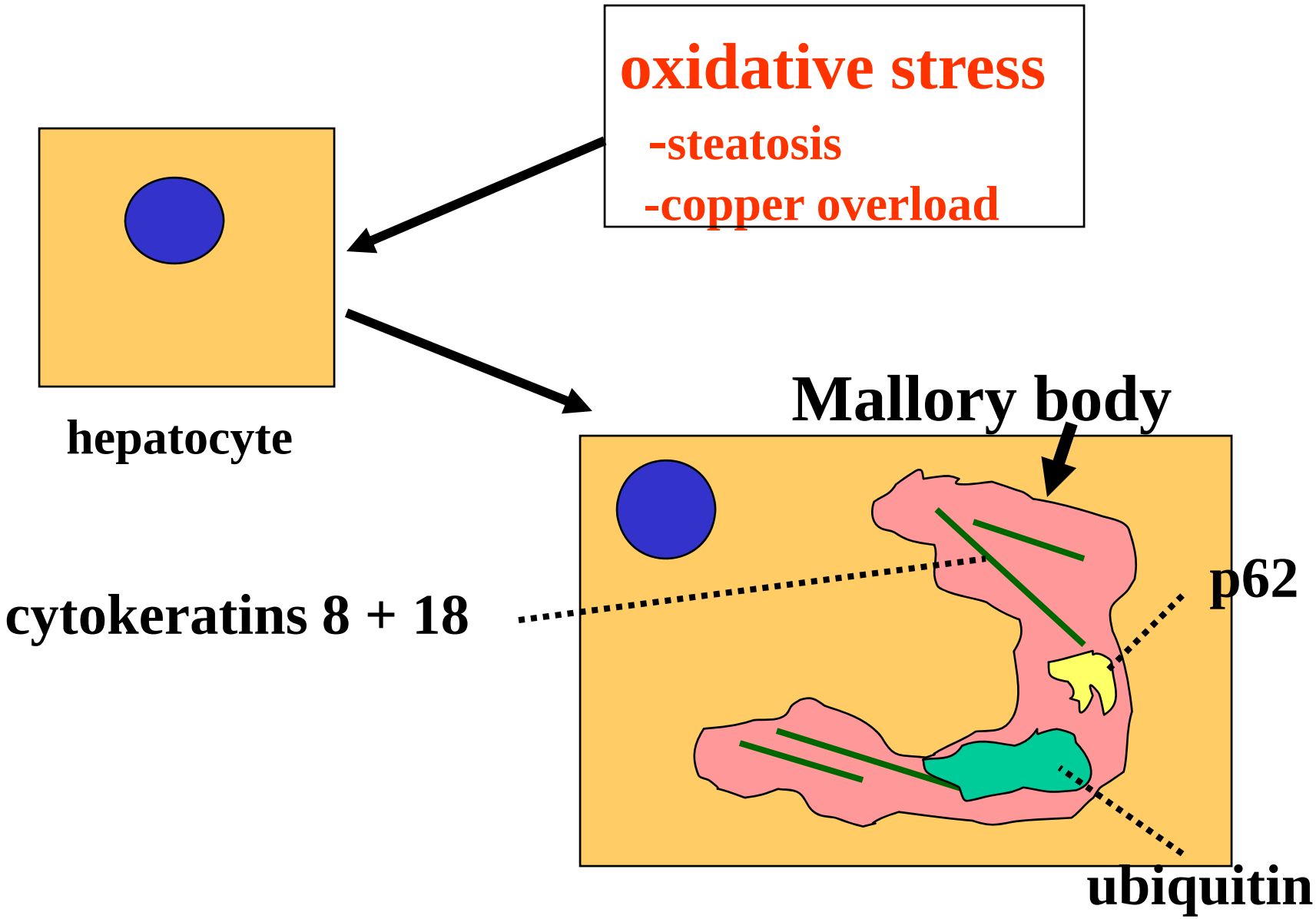
NASH non-alcoholic steatohepatitis

Cirrhosis

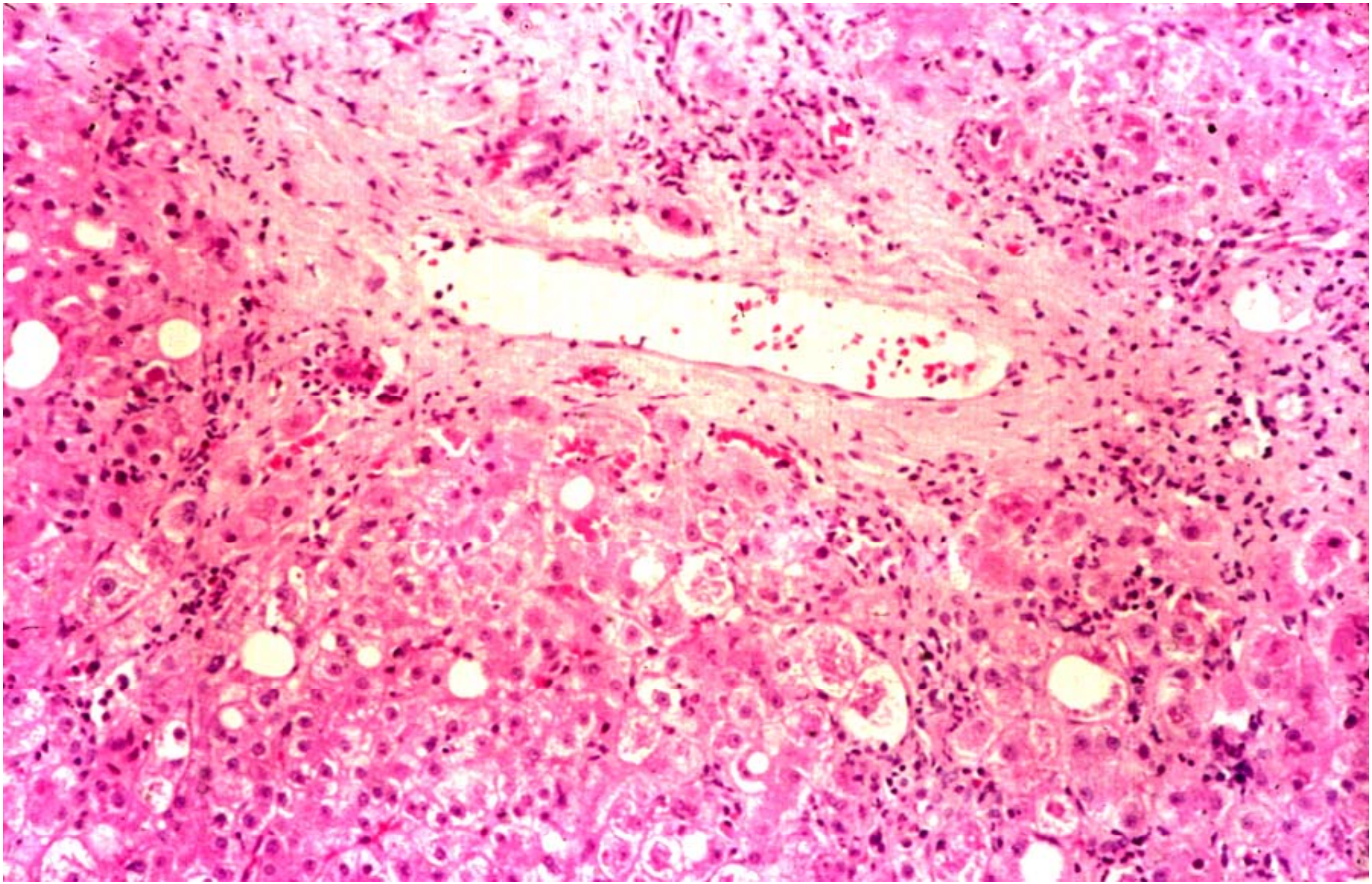


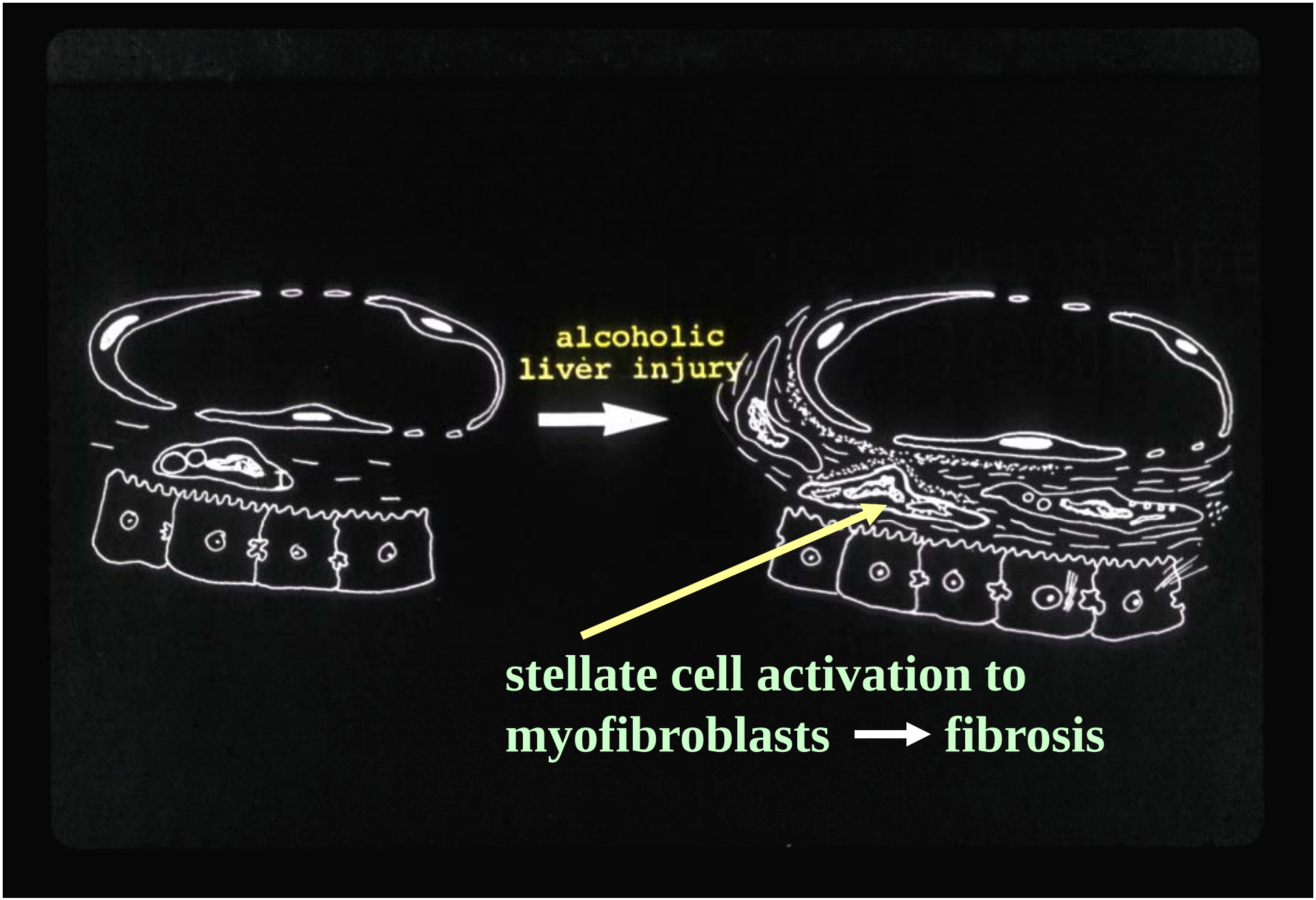


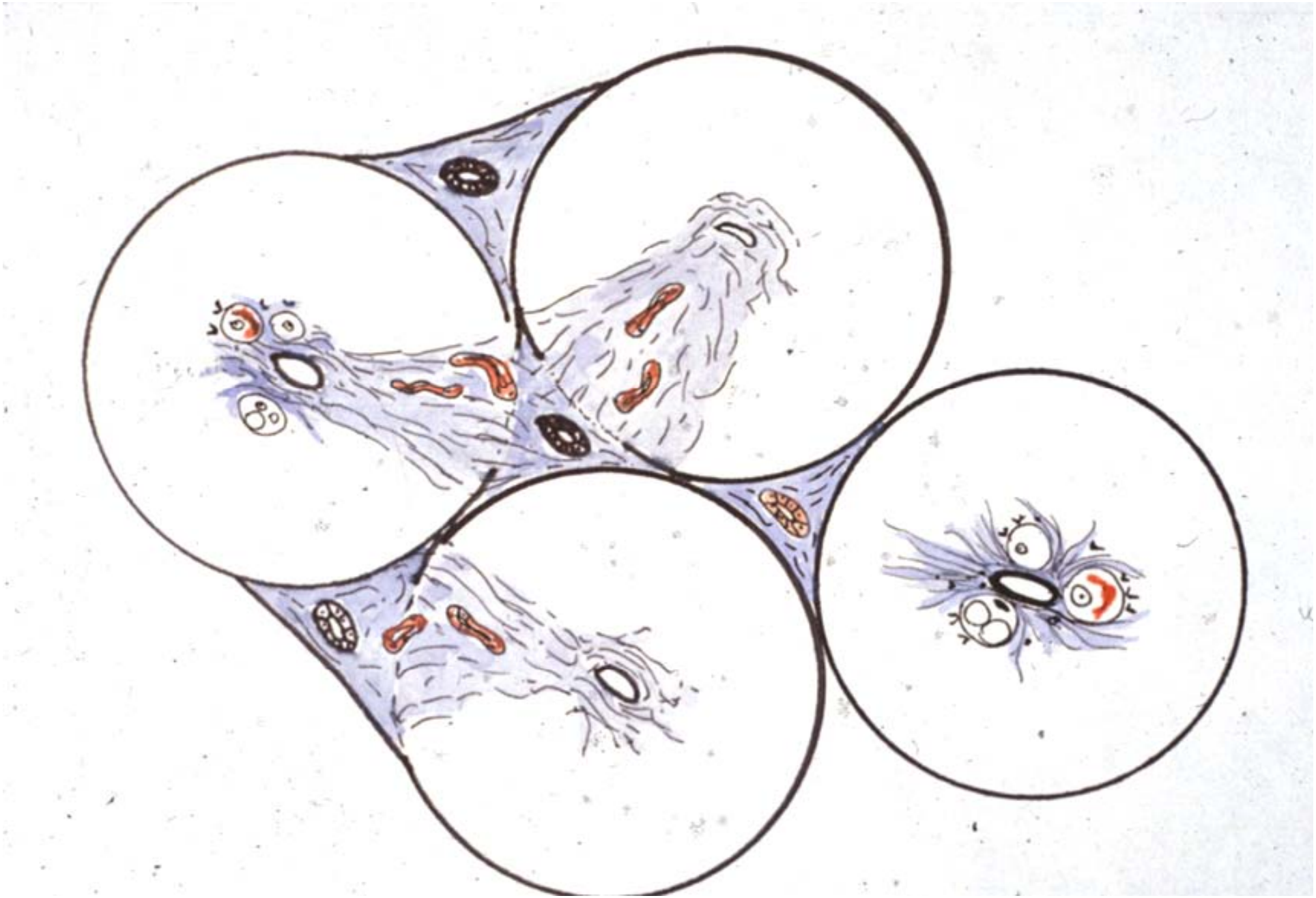


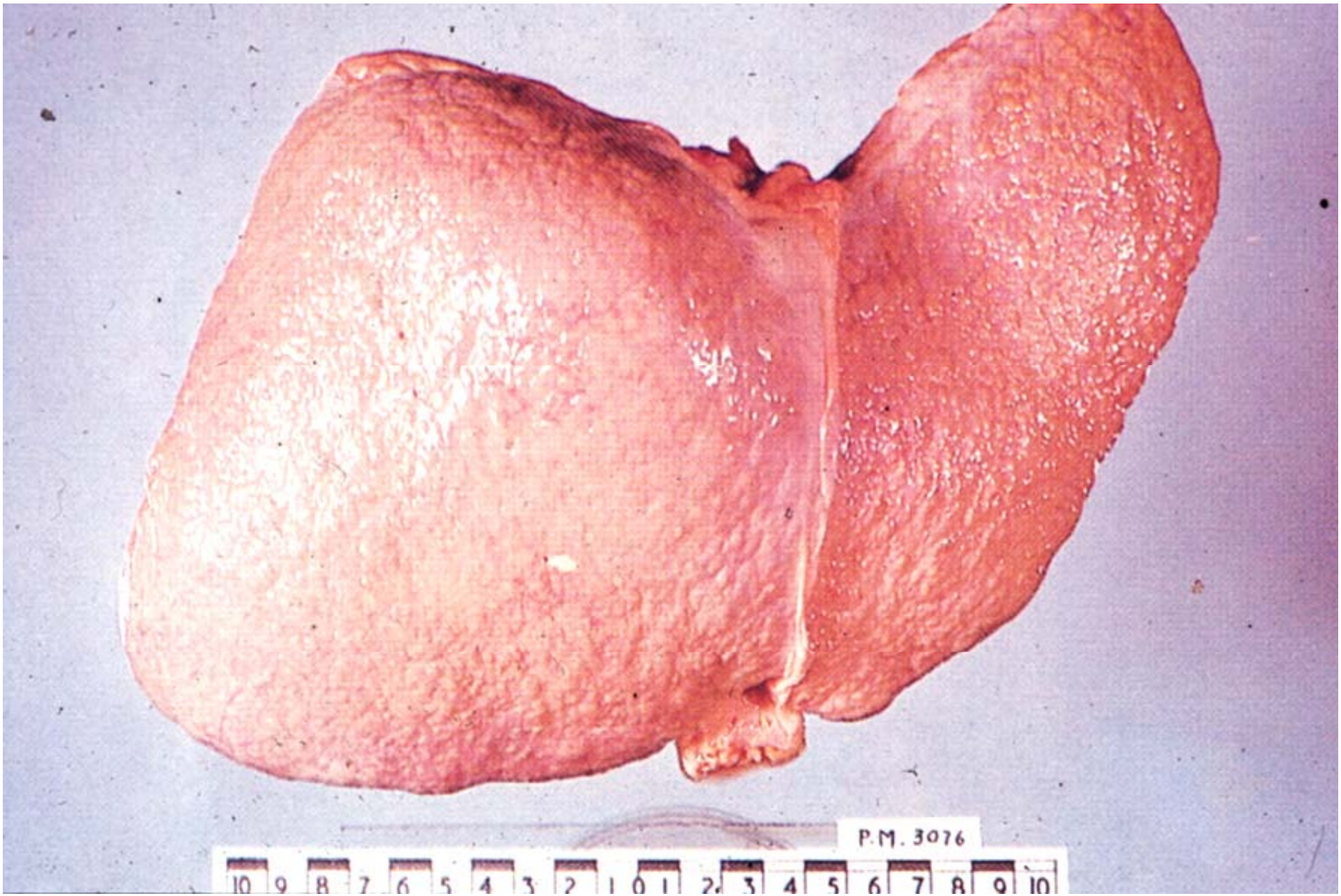


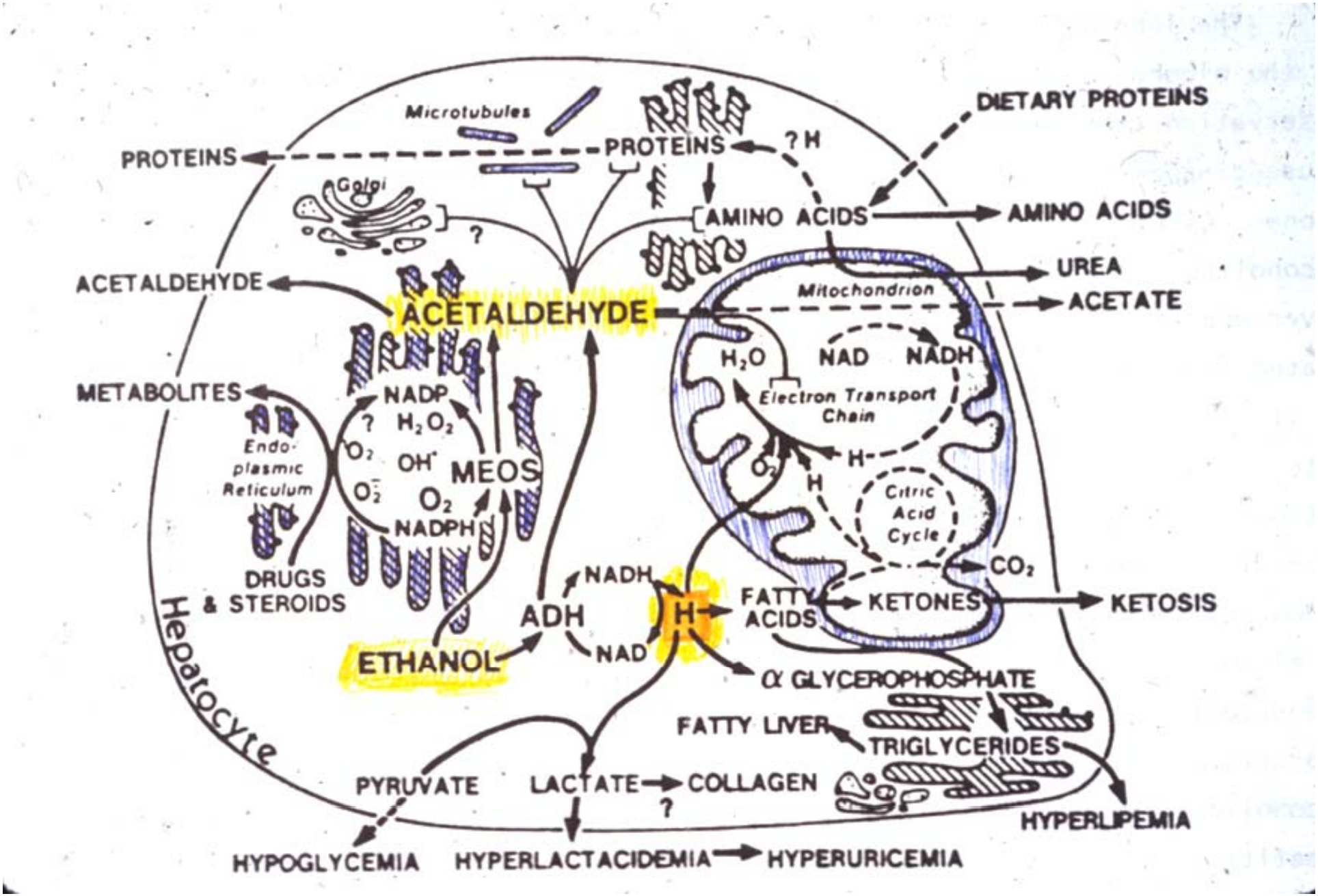
PATHOGENESIS OF MALLORY BODIES




alcoholic
liver injury
stellate cell activation to
myofibroblasts → fibrosis




P.M. 3076


Microtubules
PROTEINS
PROTEINS
?H
DIETARY PROTEINS
Golgi
?
AMINO ACIDS
AMINO ACIDS
ACETALDEHYDE
UREA
Mitochondrion
ACETATE
ACETALDEHYDE
H_2O
NAD
NADH
METABOLITES
NADP
Electron Transport Chain
H_2O_2
Endo-plasmic Reticulum
O_2
OH·
MEOS
H
O_2^-
O_2
Citric Acid Cycle
NADPH
CO_2
DRUGS & STEROIDS
NADH
FATTY ACIDS
KETONES
KETOSIS
ADH
H
NAD
ETHANOL
α GLYCEROPHOSPHATE
FATTY LIVER
TRIGLYCERIDES
Hepatocyte
PYRUVATE
LACTATE
COLLAGEN
?
HYPERLIPEMIA
HYPOGLYCEMIA
HYPERLACTACIDEMIA
HYPERURICEMIA

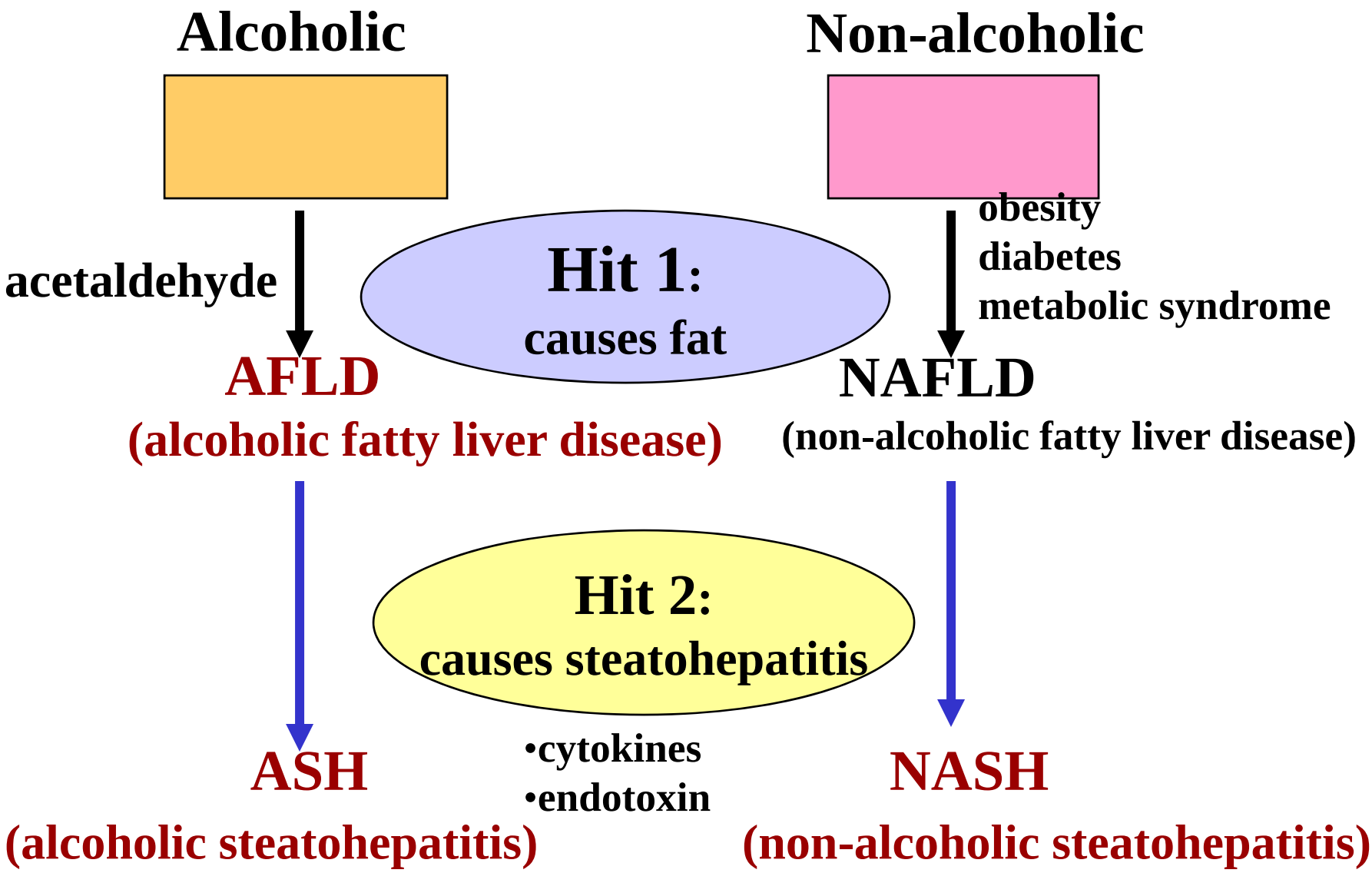
	Drink	Grams of Alcohol
Beer:	1 can (12 oz.)	10
Bourbon:	1 jigger	15 - 17
	1 pint	160-190
	1 fifth	226-305
White wine	1 oz.	2.6
	1 fifth	66
Port	1 fifth	115
Double martini (mixed at home)		40

Liver Disease in 1000 Alcoholics

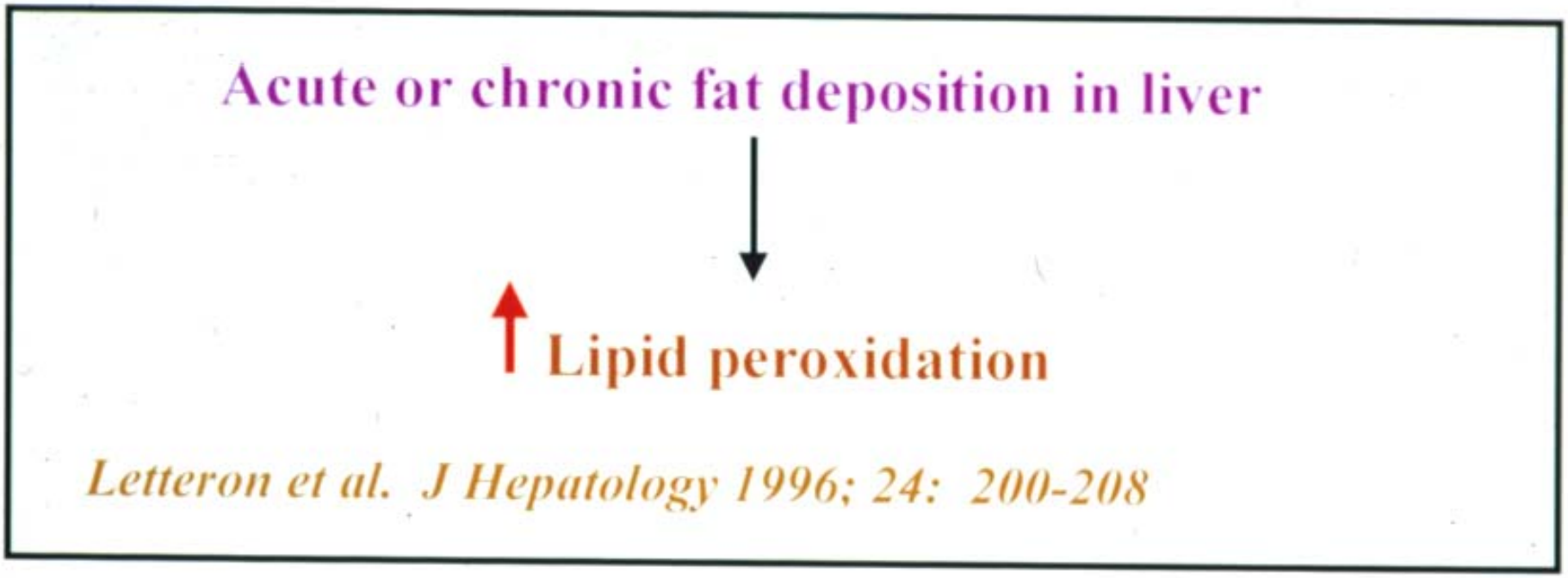
- 25% had normal livers
- 30% had uncomplicated fatty liver
- 20% had steatohepatitis without cirrhosis
- 25% had cirrhosis

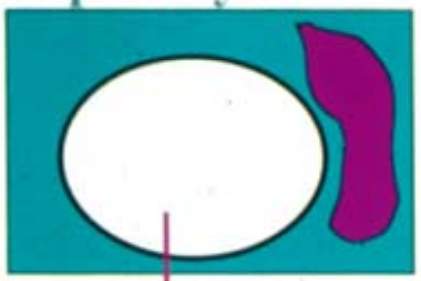
Steatohepatitis

- Alcoholic steatohepatitis (ASH)
- Non-alcoholic steatohepatitis (NASH)
  - -obesity
  - -diabetes
  - -hyperlipidemia
  - -drugs (e.g., amiodarone)



TWO-HIT HYPOTHESIS of STEATOHEPATITIS


Acute or chronic fat deposition in liver
Lipid peroxidation
Letteron et al. J Hepatology 1996; 24: 200-208



↑mobilization & availability of FFA's
↑hepatic synthesis of FFA's
↑esterification of FFA's into TG
↓export of TG from liver

Lipid peroxidation

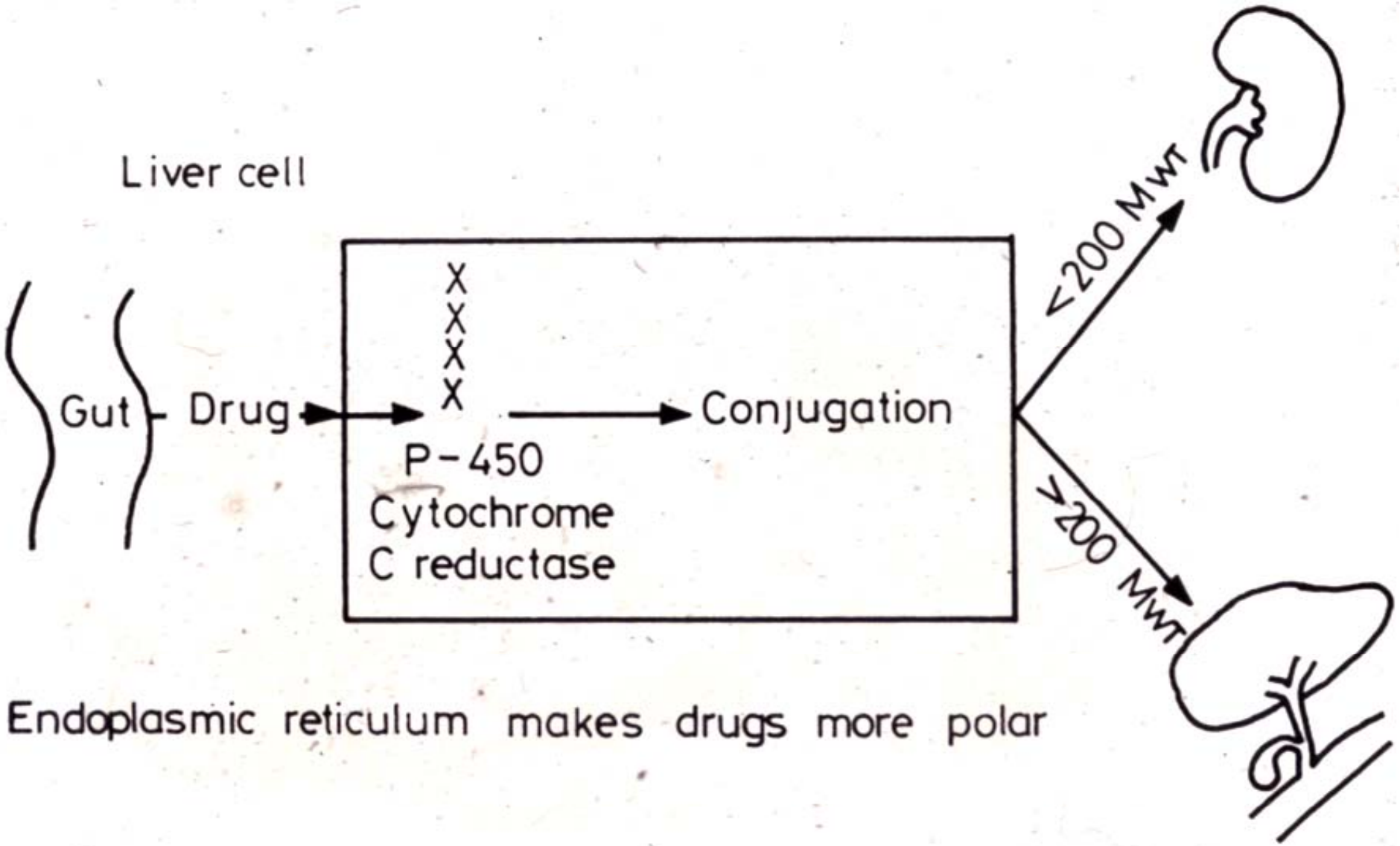
malondialdehyde

- Activate stellate cells
- Cross-link cytokeratins----> M.B.'s
- activate NF-kB--> ↑TNF-alpha + IL-8

4-OH-nonenal

- Chemoattractant for PMN's

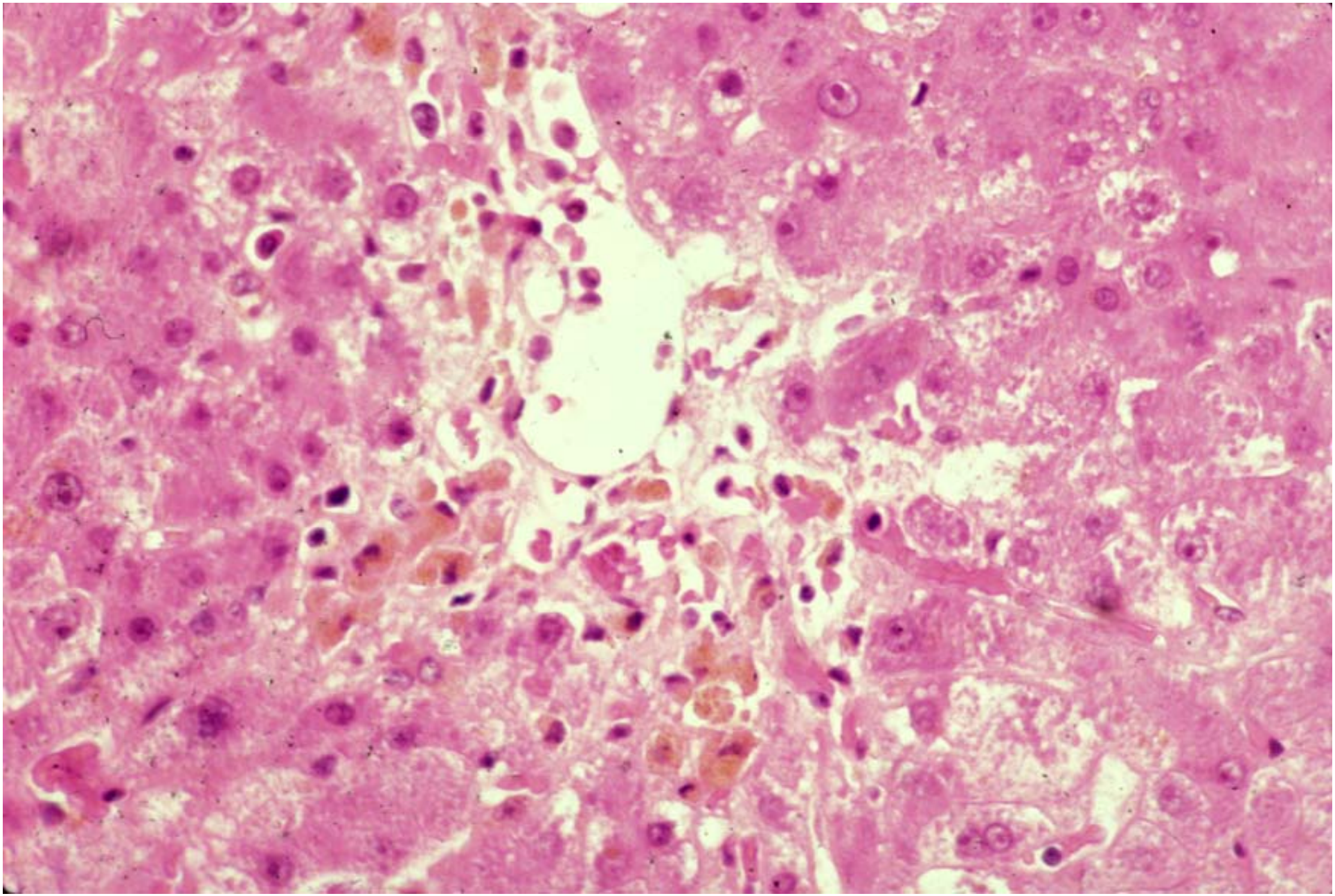
Drug/Chemical Hepatotoxicity

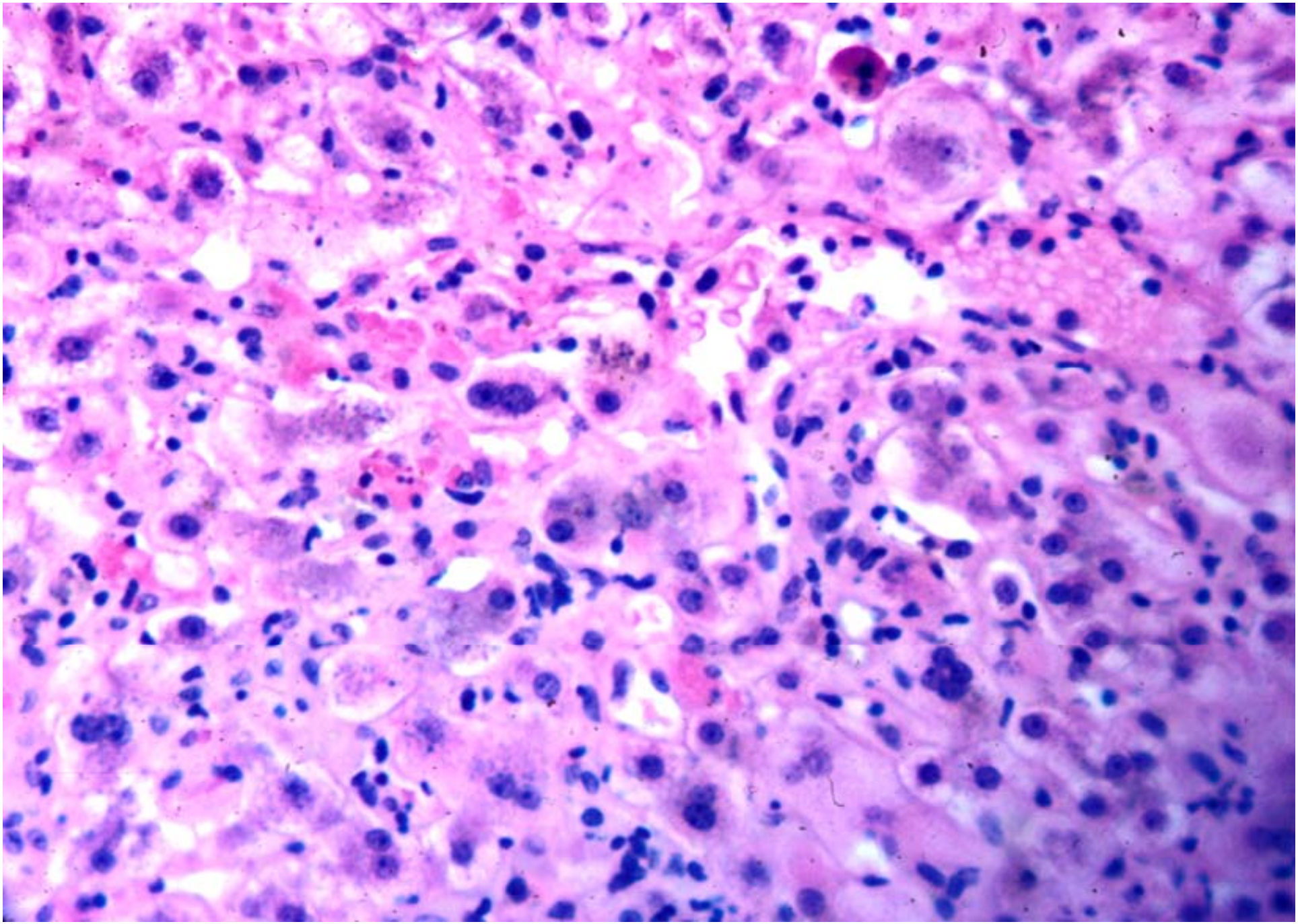


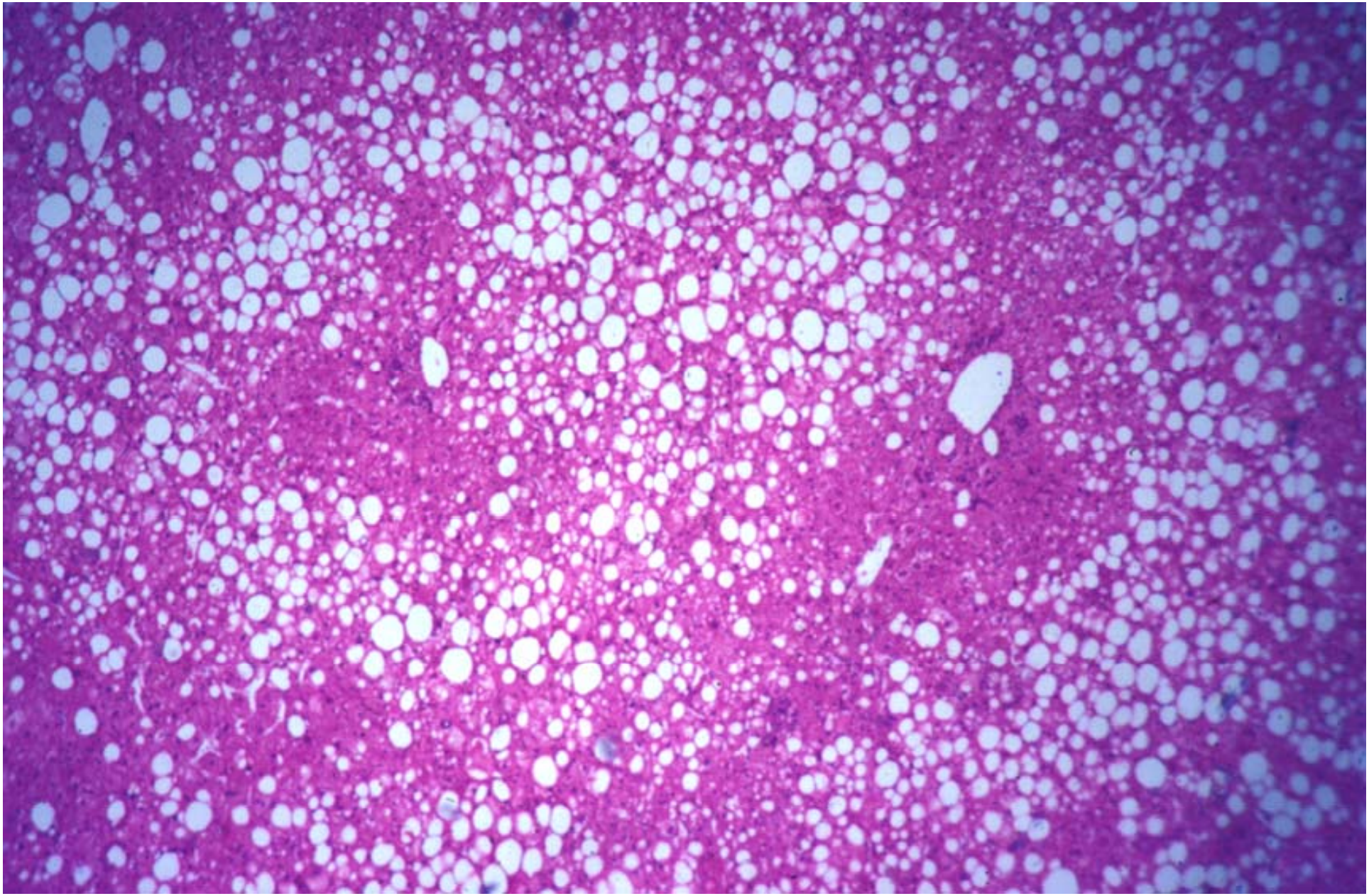
Endoplasmic reticulum makes drugs more polar

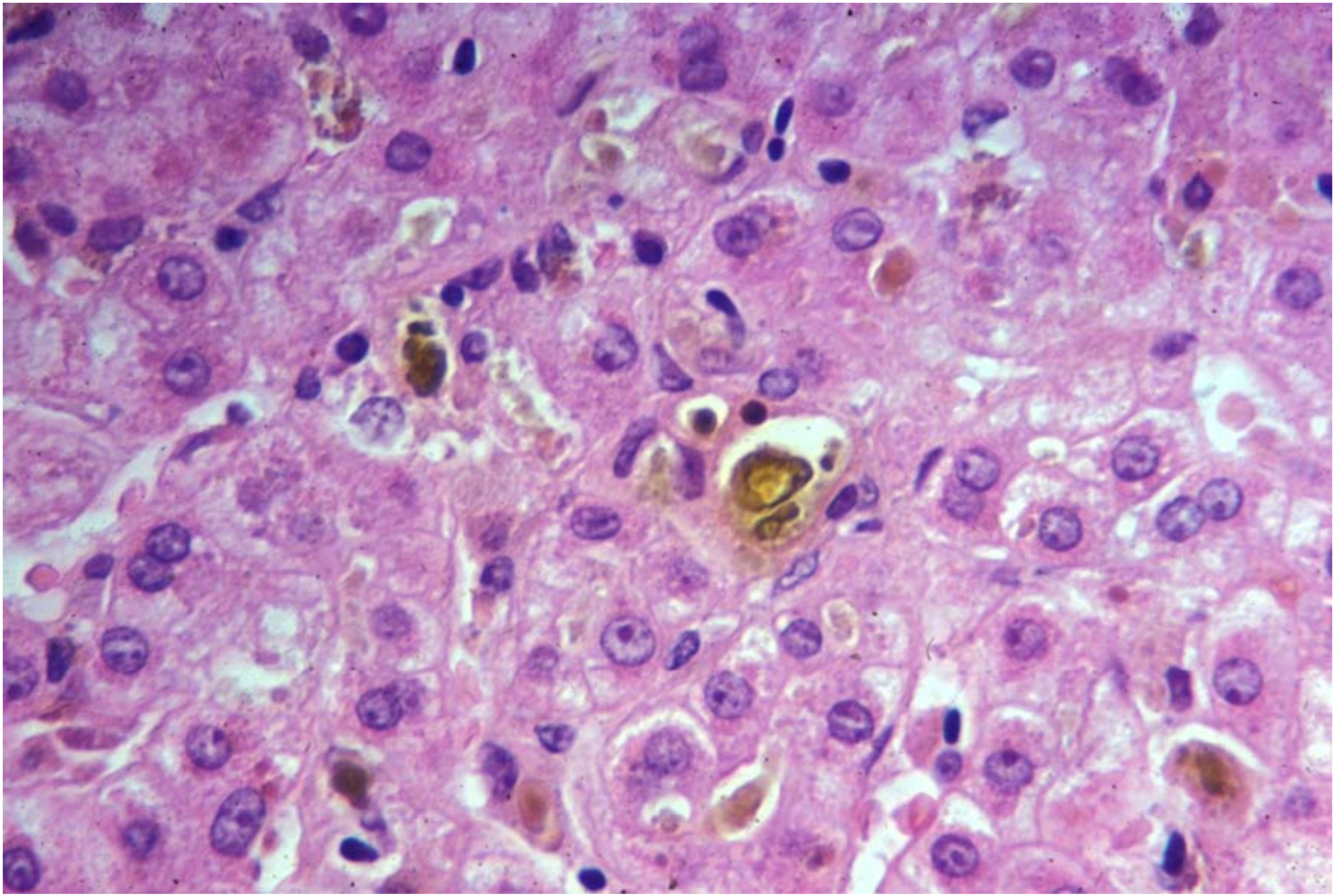
DRUG HEPATOTOXICITY

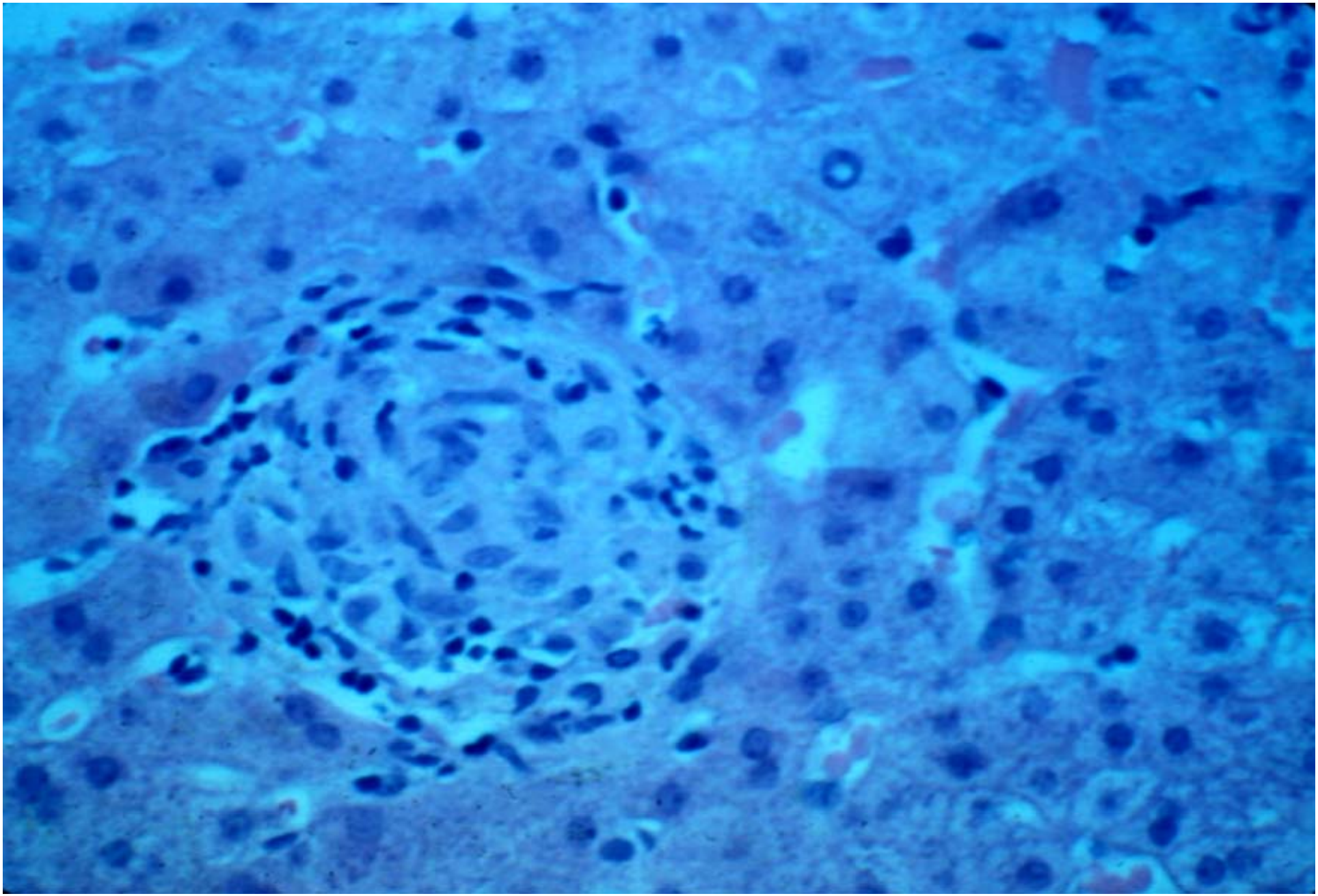
Predictable	Unpredictable
dose related	small dose
many species	selected species
e.g., CCl_4, acetaminophen	e.g., INH, aldomet

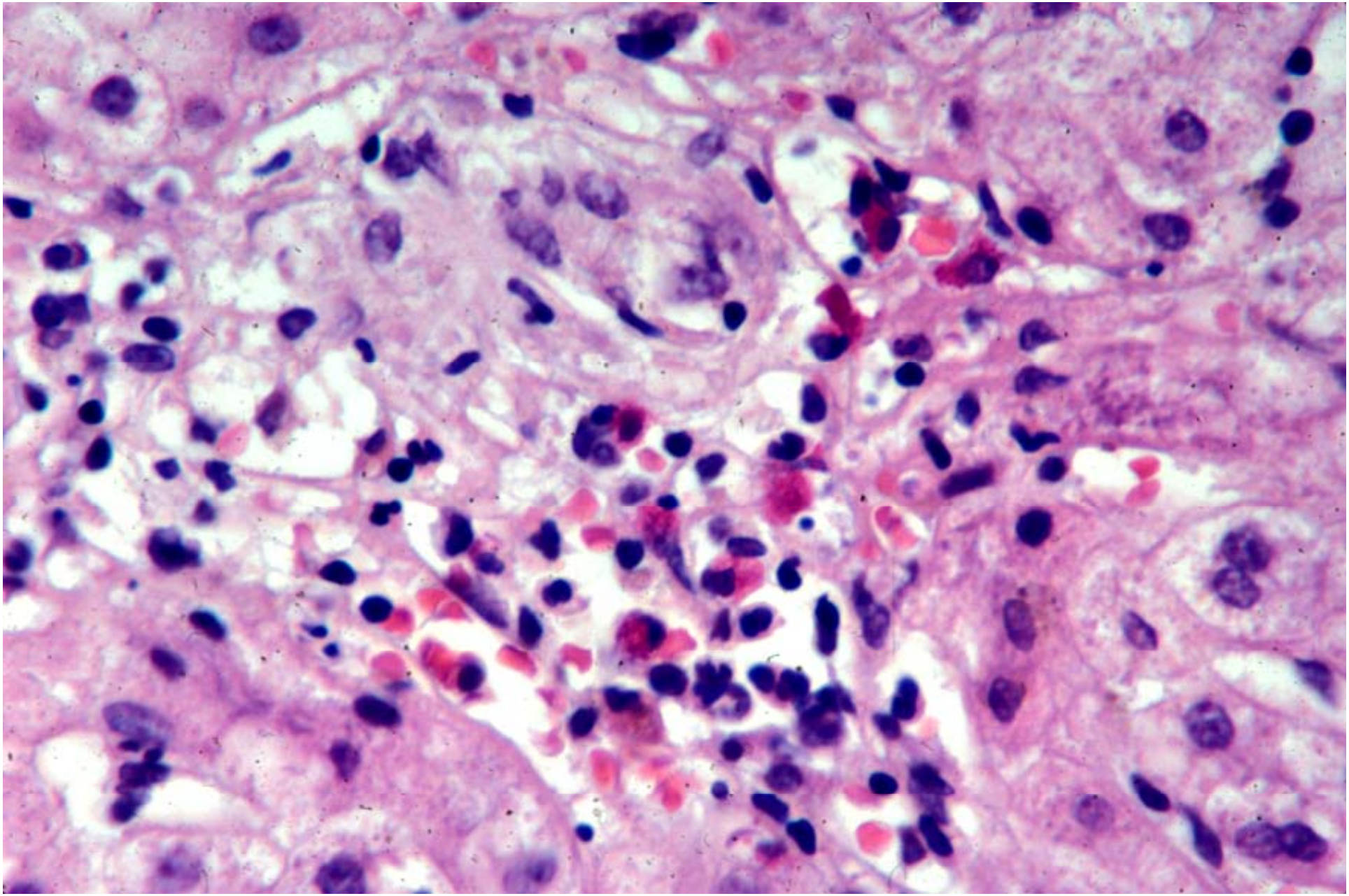




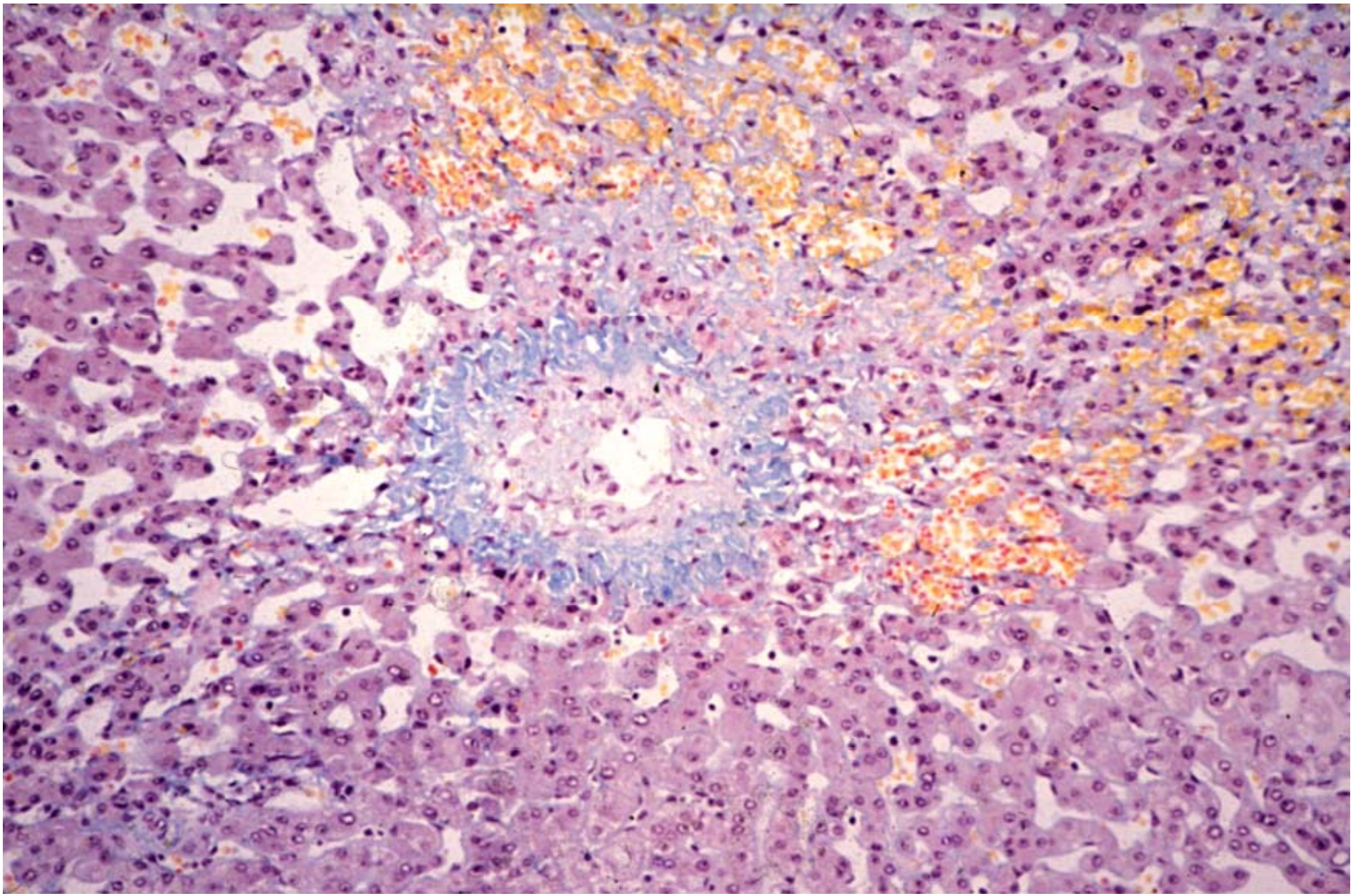








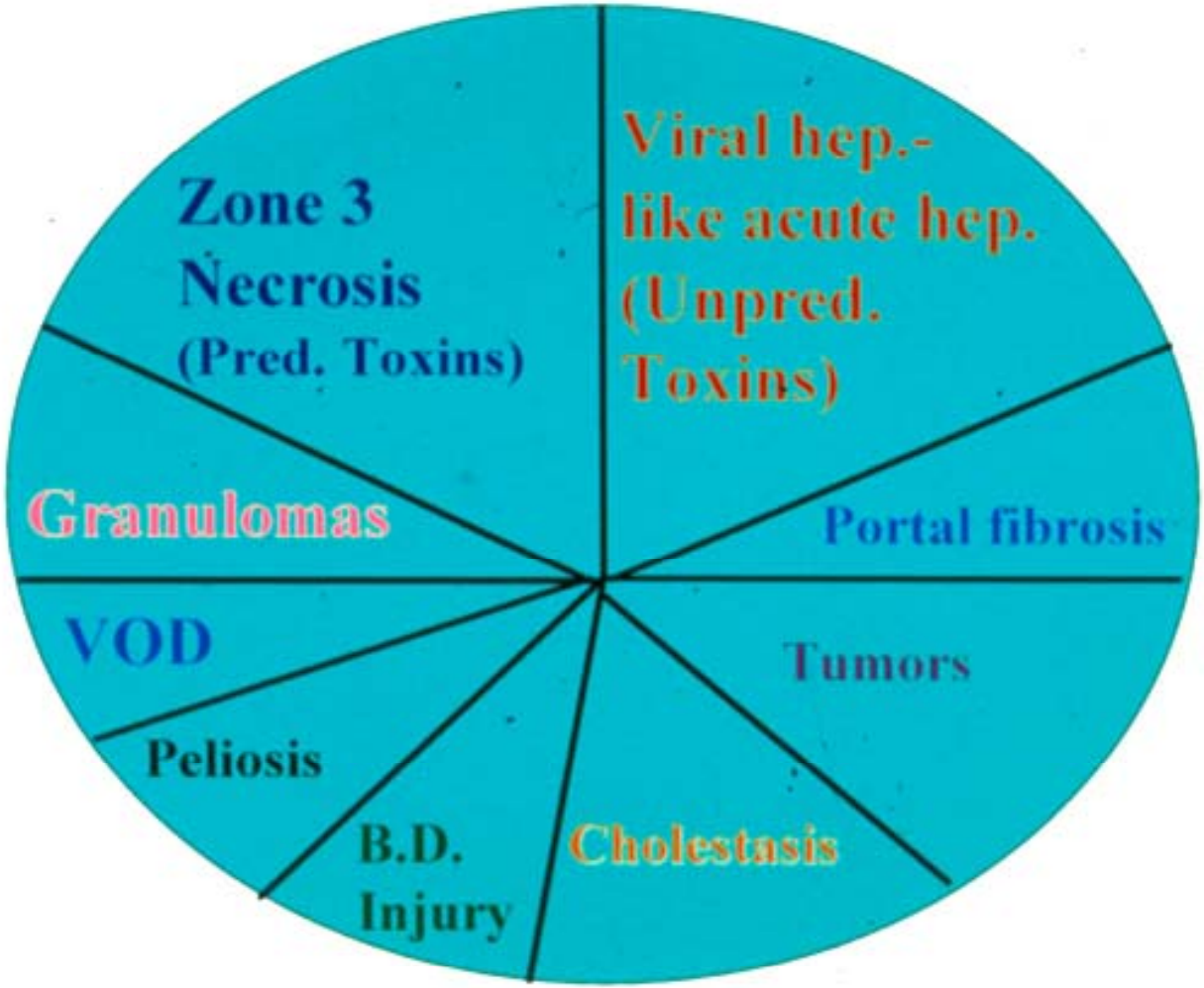
Veno-occlusive disease (VOD): pyrrolizidine alkaloids (“bush tea”)



Oral Contraceptives

- cholestasis
- liver-cell adenoma
- peliosis hepatis

Pathology of Drug Hepatitis



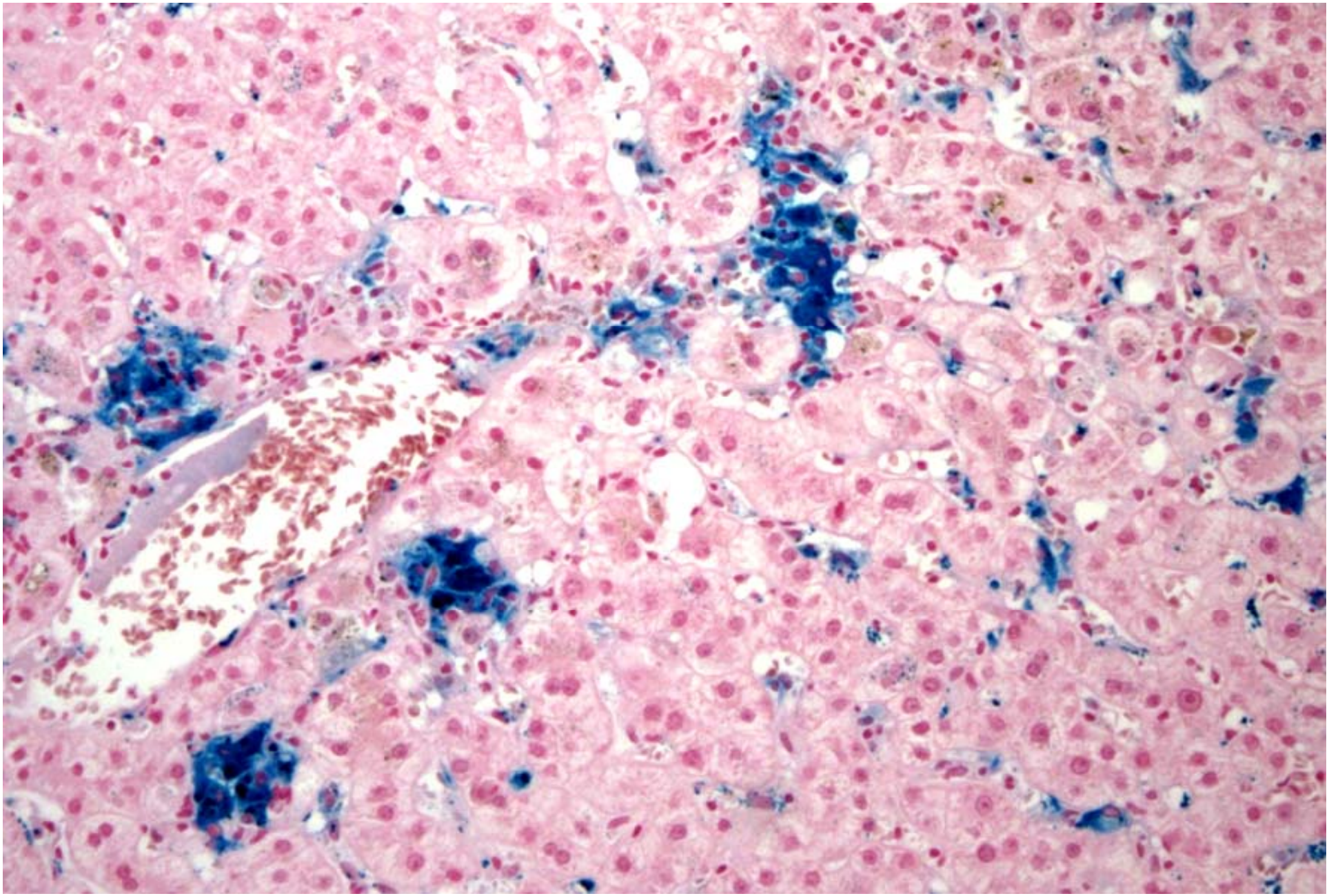
Metal storage diseases: Fe and Cu

Iron Overload Disorders

- **Primary Iron Overload**
  -hereditary hemochromatosis

- **Secondary Iron Overload**
  -transfusion/hemolysis/
  -hemodialysis

Kupffer cell hemosiderosis: hemolysis—transfus.--hemodialysis



Hereditary Hemochromatosis (HHC)

1889: von Recklinghausen: "hemochromatosis" ("bronzed diabetes")

Fe overload with tissue damage in liver, heart, joints, panc. islets, other organs

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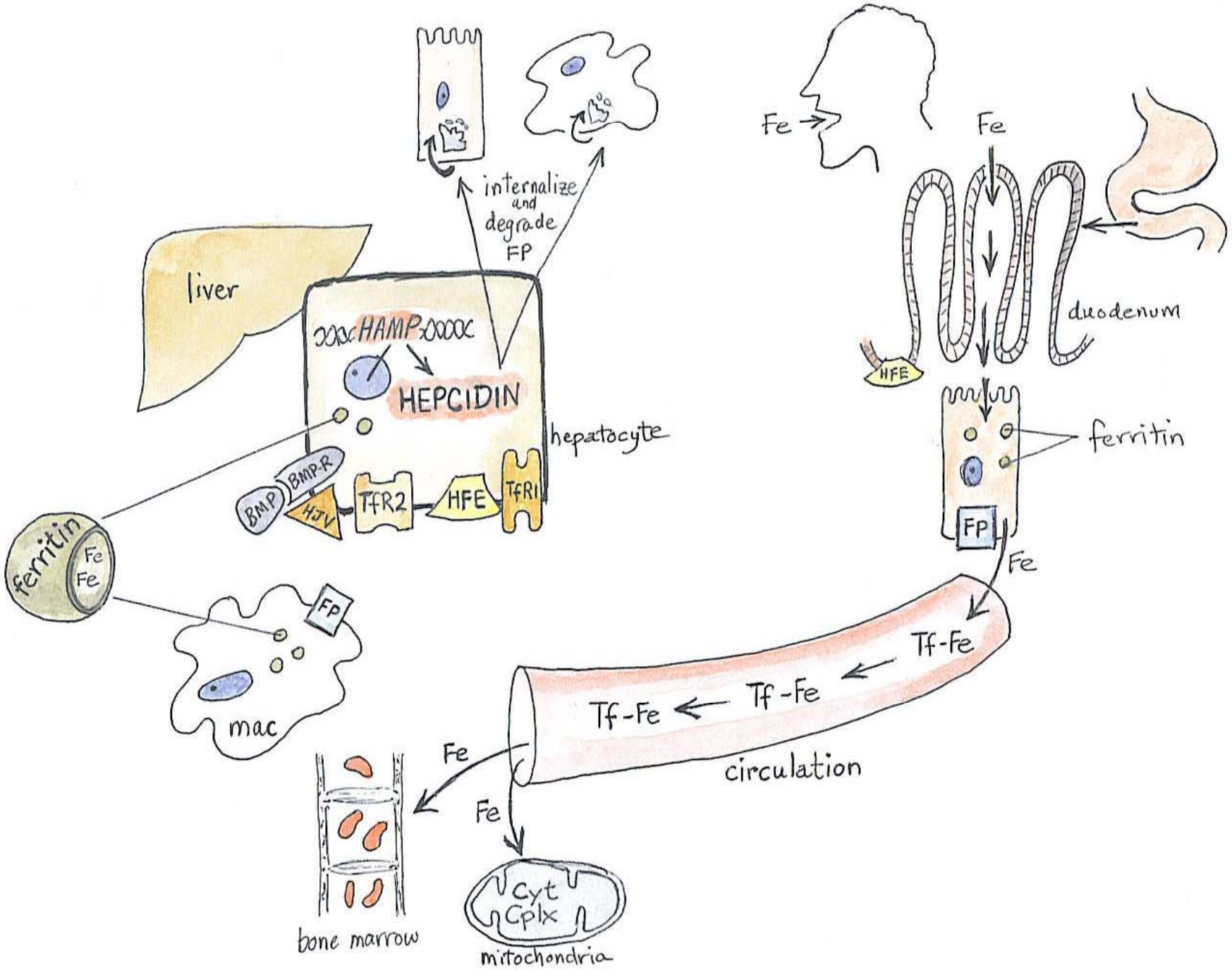
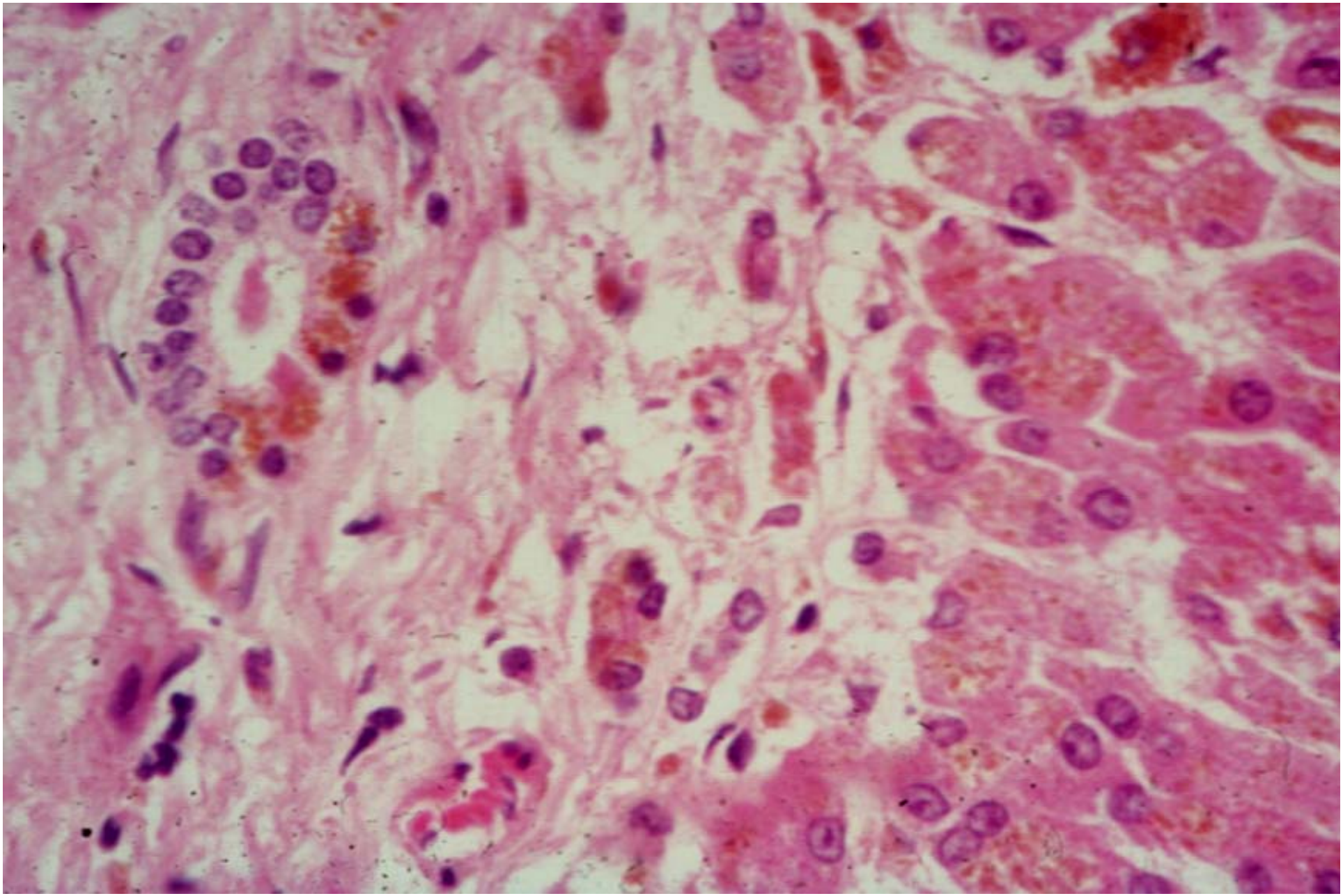
-85-100% due to HFE mutation (C282Y/C282Y)

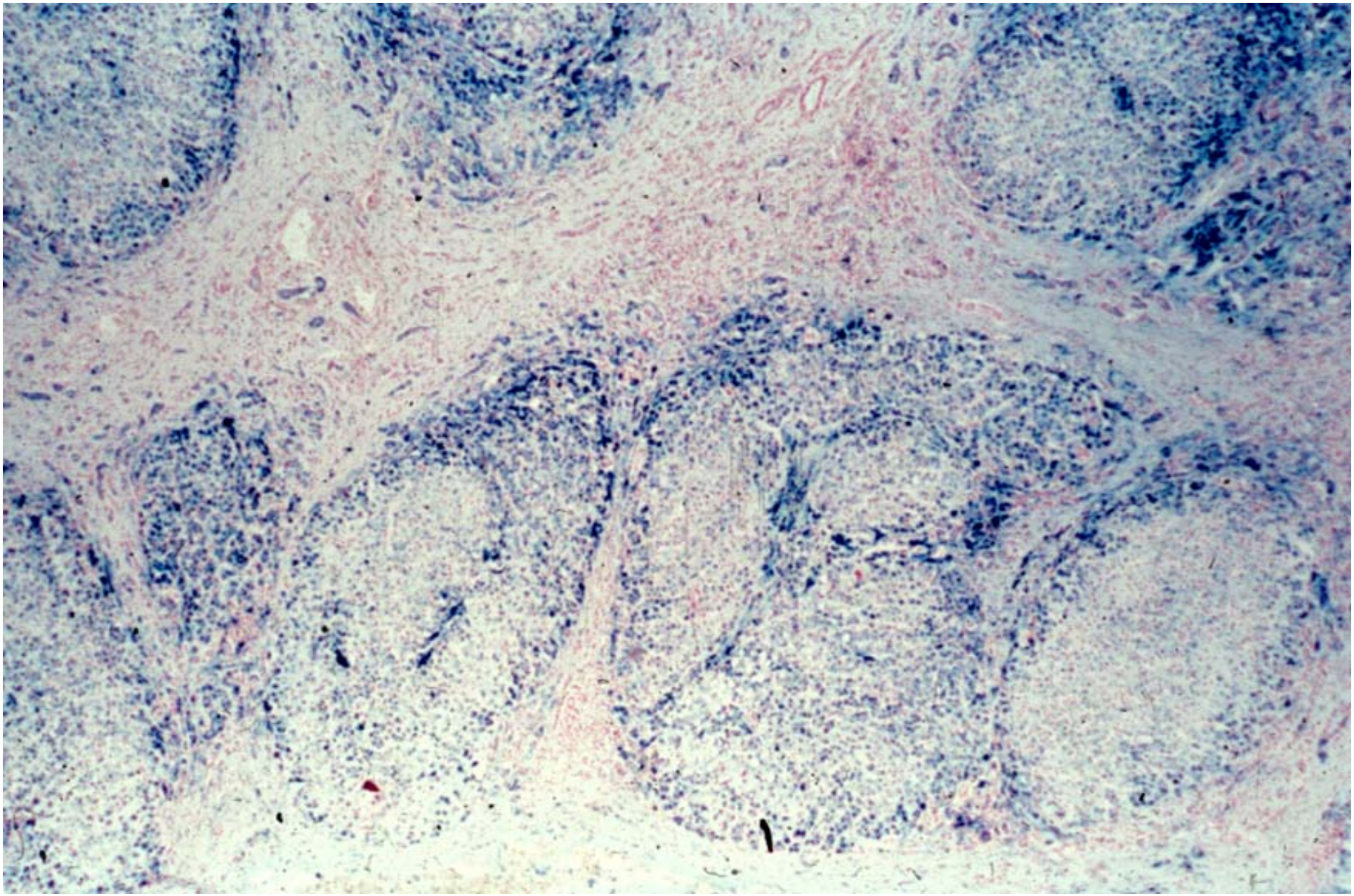
-<5% due to other non-HFE mutations

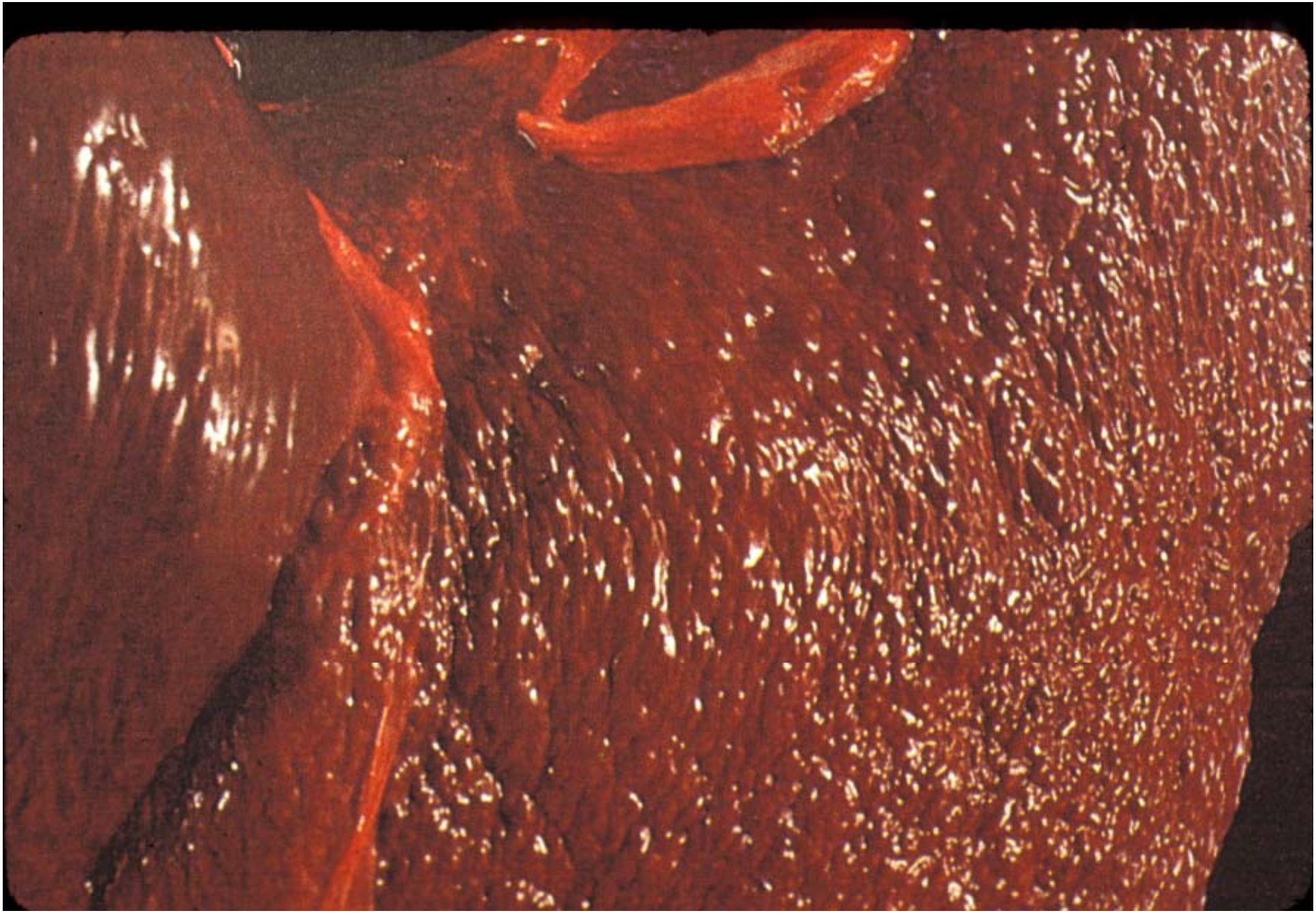

internalize and degrade FP
liver
xxxHAMPxxxxx
HEPCIDIN
hepatocyte
BMP
BMP-R
HJV
TfR2
HFE
TfR1
ferritin
Fe
Fe
FP
mac
Fe
Fe
duodenum
HFE
ferritin
FP
Fe
Tf-Fe
Tf-Fe
Tf-Fe
circulation
Fe
Fe
bone marrow
Cyt
Cplx
mitochondria

Hereditary Hemochromatosis

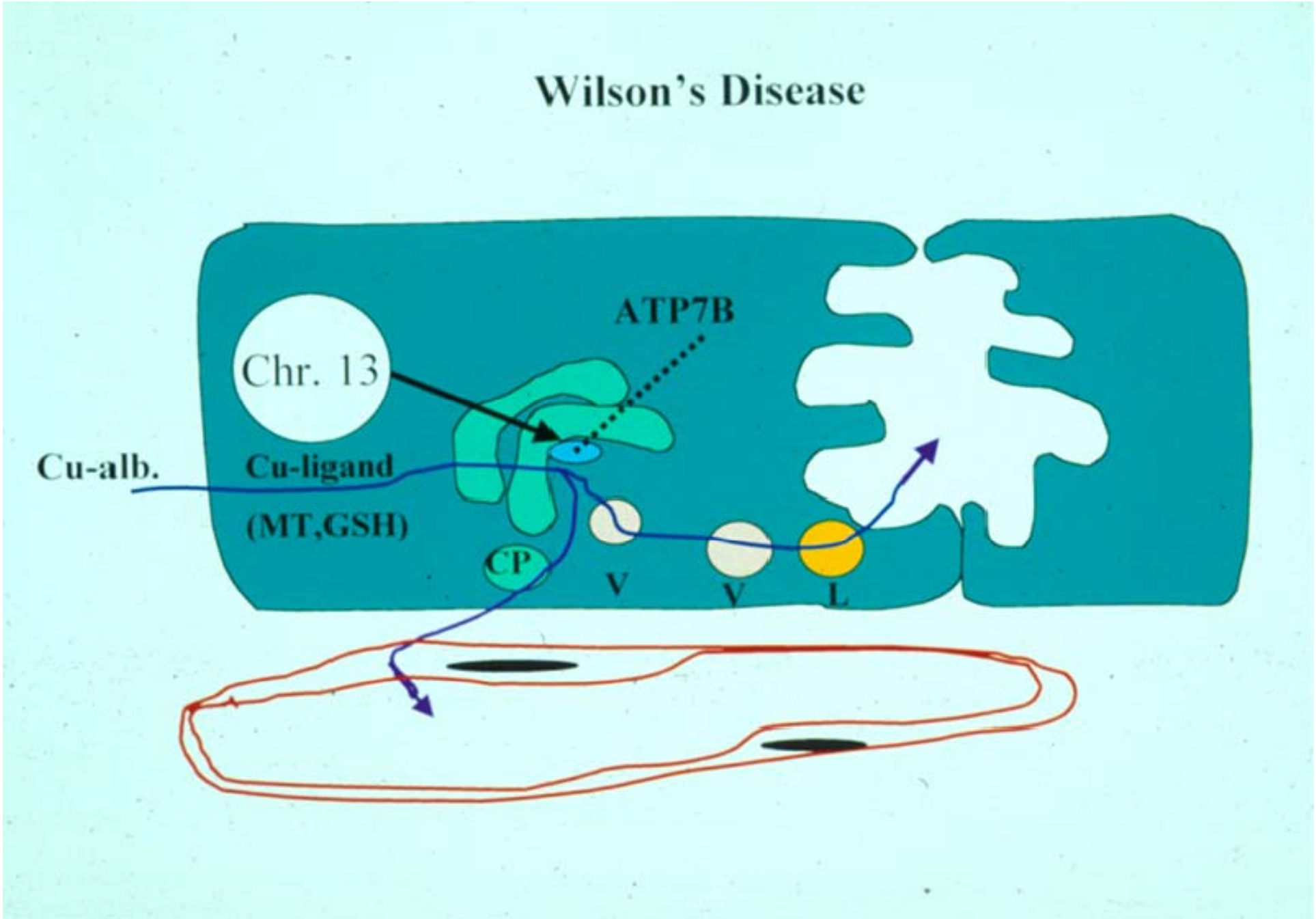
- **Type 1: HFE (C282Y)**
- **Type 2: Juvenile hemochromatosis**
  - **-hemojuvelin: 2A**
  - **-HAMP: 2B**
- **Type 3: TfR2**
- **Type 4: Ferroportin**

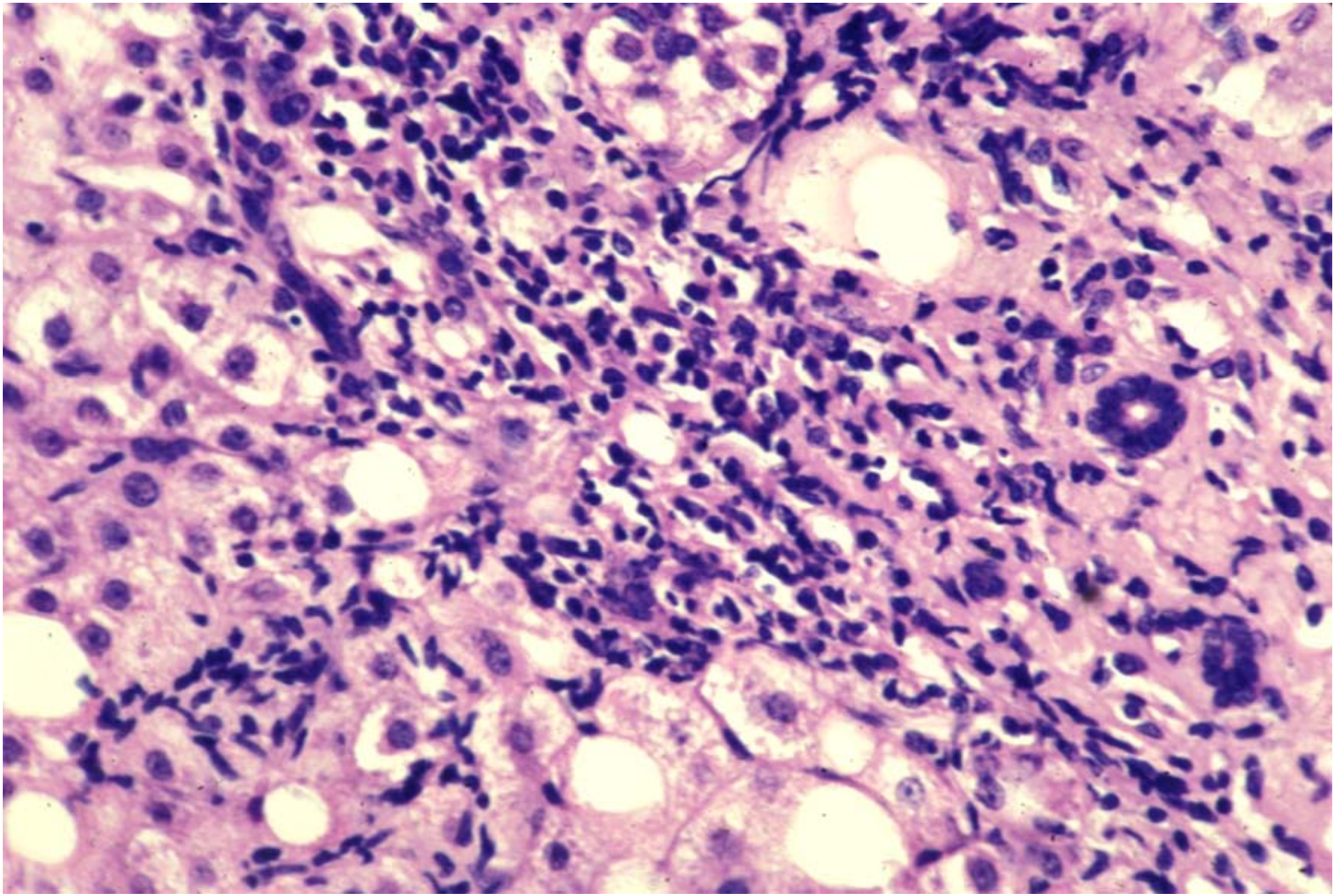


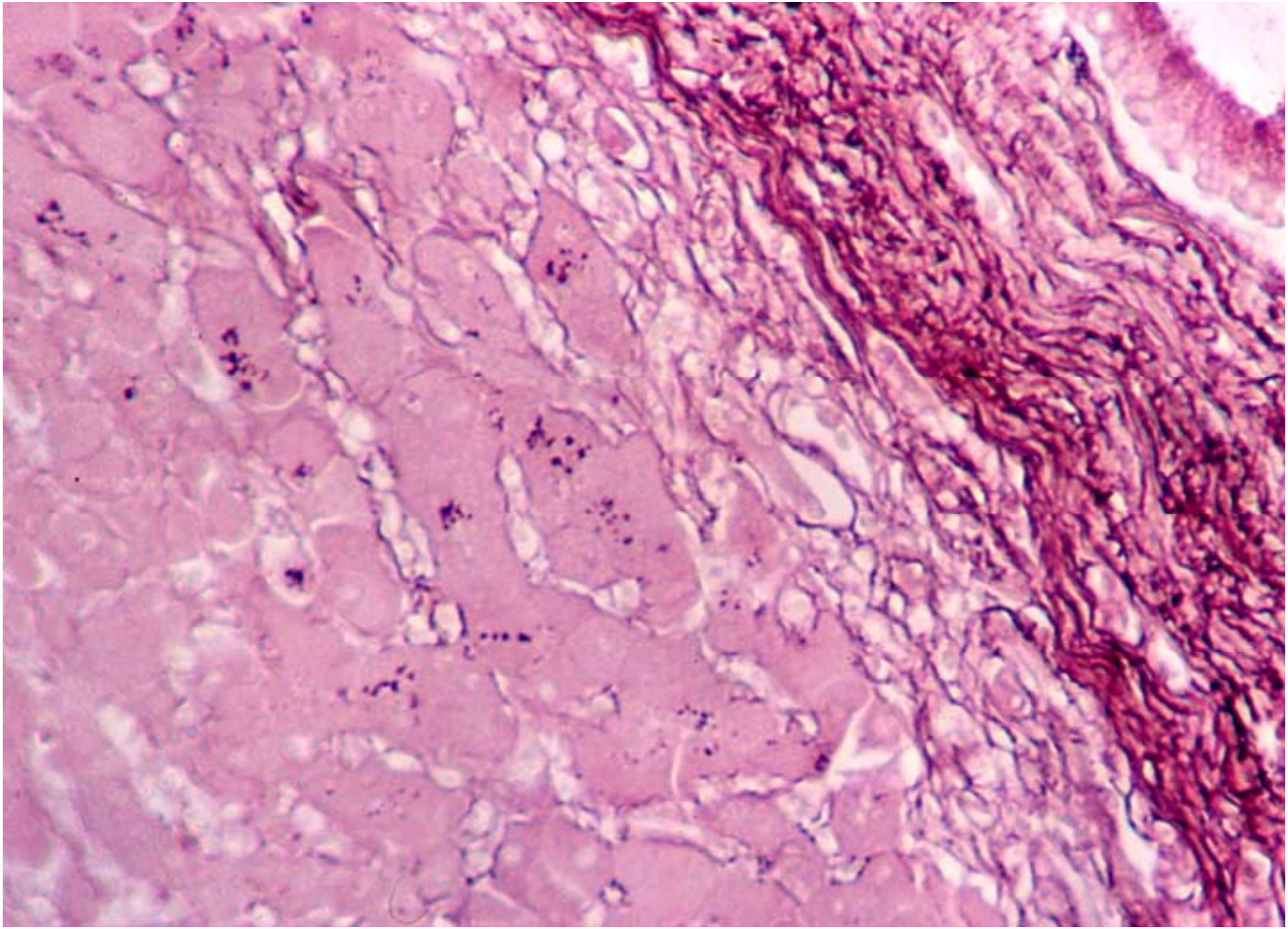


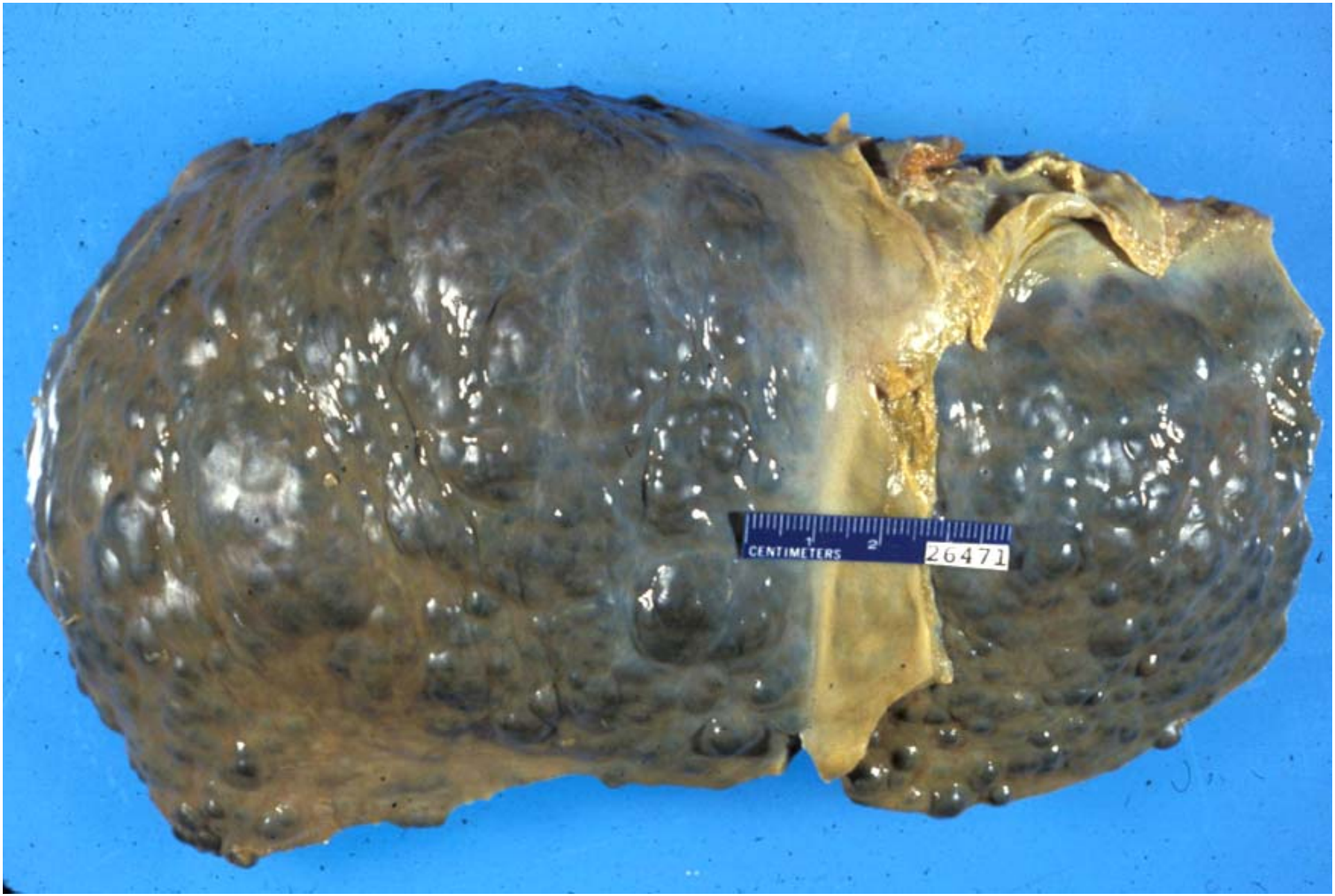


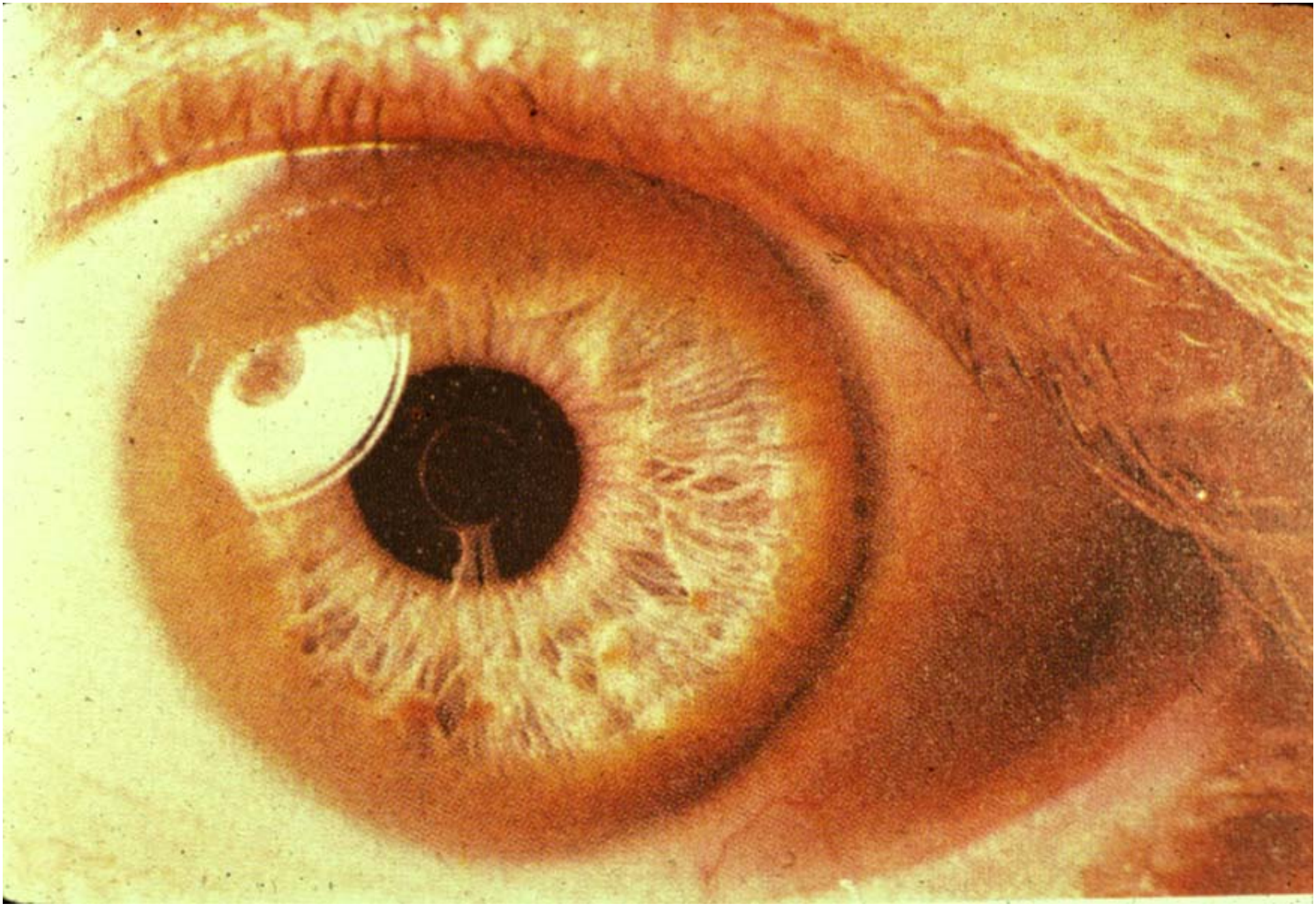
Wilson's Disease








CENTIMETERS
26471



Alpha-1-Antitrypsin Deficiency (AAT Def.)

- Mutation in AAT: enzyme retained in the liver, with resultant disease
  - –normal allele=M
  - –normal phenotype=PiMM
  - –mutated allele=Z (or S, malton, etc.)
  - –homozygous AAT Def. = PiZZ (<10% normal serum level)
  - –heterozygous AAT Def.= PiMZ (60% normal serum level)

Alpha-1-Antitrypsin Deficiency