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Training for Medical education via innovative eTechnology

MediTec

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MediTec Project Number:585980-EPP- 1-2017- 1-DE- CBHE-JP

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These lectures were prepared and performed for the students.

we published them in the MediTec websites to wider our educational aims.

With thanks to our team member Prof. Ismail Matalkeh for his efforts.

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King Abdullah University Hospital

Drug-Induced Liver Injury: a penalty for progress

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School of Medicine & King Abdullah University Hospital

Jordan University of Science & Technology

Drug-induced liver injury: a penalty for progress

Hans Popper, MD
Arch intern Med, 1965

Drug-Induced Liver Injury

- Why is it important to know whether a drug is responsible for liver injury?
- What information can be gained from a liver biopsy?
- How can we put the pathology together with the clinical evaluation to decide whether a drug is implicated in the injury?

WHY DILI IS IMPORTANT

- Can produce all forms of acute, chronic, vascular and neoplastic hepatic diseases caused by other aetiologies
- Represent great imitators
- Impose diagnostic challenges
- Require a high degree of clinical suspicion by physicians & patients
- Pathologists should be aware and alert
- Increasing herbal medicine uptake !!


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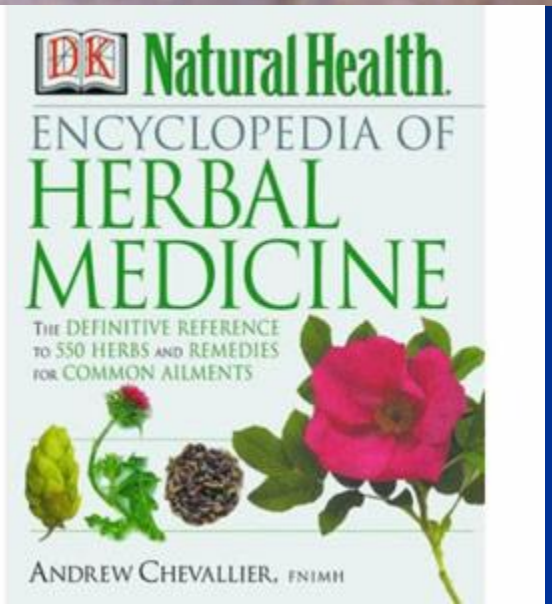

DK Natural Health
ENCYCLOPEDIA OF
HERBAL
MEDICINE
THE DEFINITIVE REFERENCE TO 550 HERBS AND REMEDIES FOR COMMON AILMENTS
ANDREW CHEVALLIER, FNIMH

Hepatotoxicity is the most common single reason for drug withdrawal from the market for safety reasons

- Drug with “black box” warnings
  - Pemoline
  - Dacarbazine
  - Valproate sodium
  - Ketoconazole
  - Zidovudine
  - Zalcitabine
  - Felbamate
  - Trovafloxacin
  - Tolcapone
- Drugs withdrawn
  - Ticrynafen
  - Benoxaprofen
  - Troglitazone
  - Bromfenac sodium

Lasser et al., JAMA 287: 2215; 2006
Temple and Himmel, JAMA 287: 2273; 2006

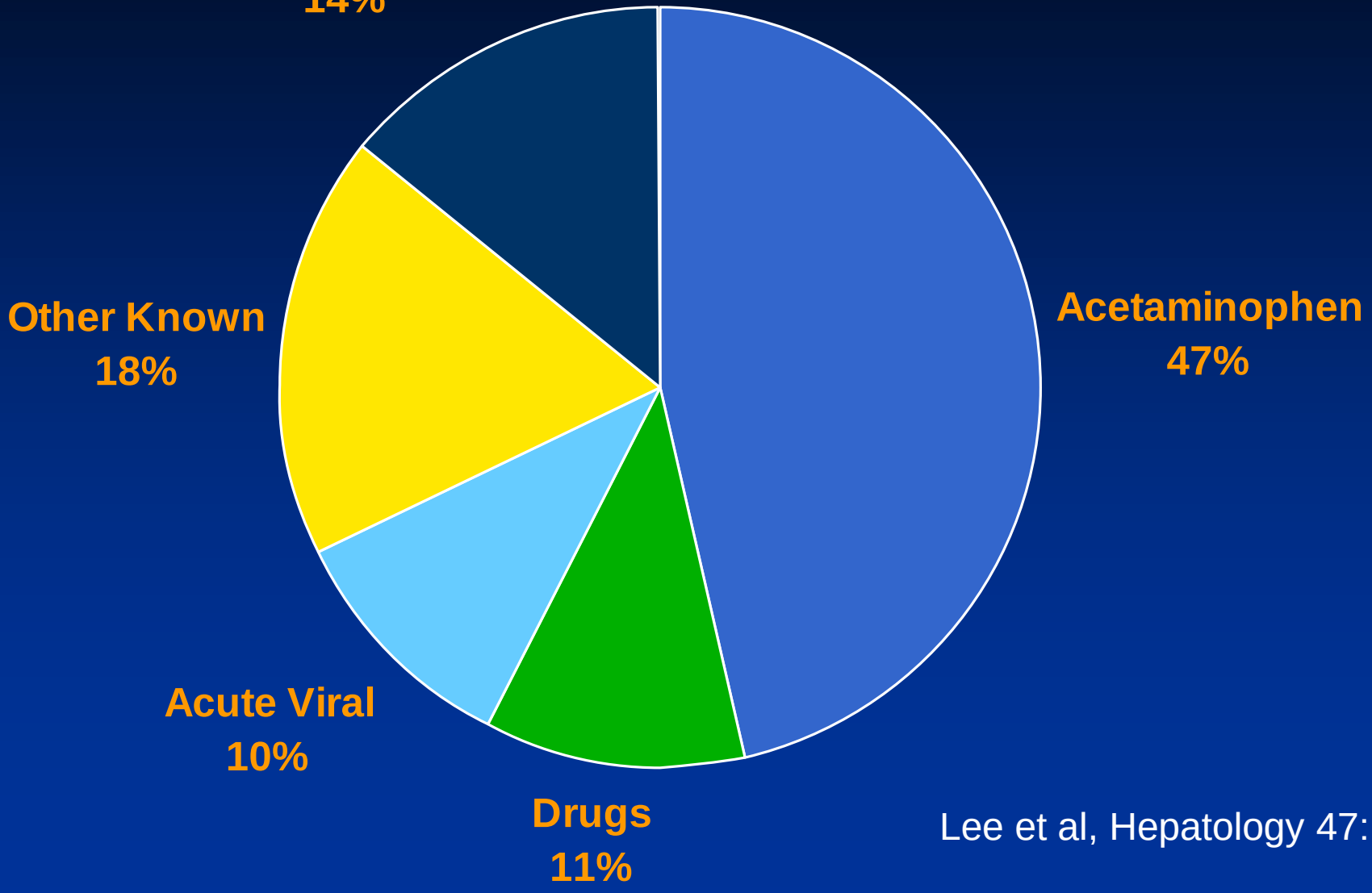
Incidence and Proof of Hepatotoxicity

- DILD is thought to be responsible for around 5% of cases of jaundice.
- 10% of hospital admissions for hepatitis in Europe
- 20-40% of jaundice >50 year old.
- Around 50% of cases presenting with acute liver failure are due to adverse drug reaction

Burden of the disease

- The annual incidence: 1: 10,000 -100,000 (as high as 14 :100,000)
- It accounts for up to 10 % of all adverse drug reactions .
- It is seen in up to 30 % of patients who present with acute hepatitis
- Represents up to 10 % of consultations by Hepatologists, and about 1 percent of all general medical admissions.

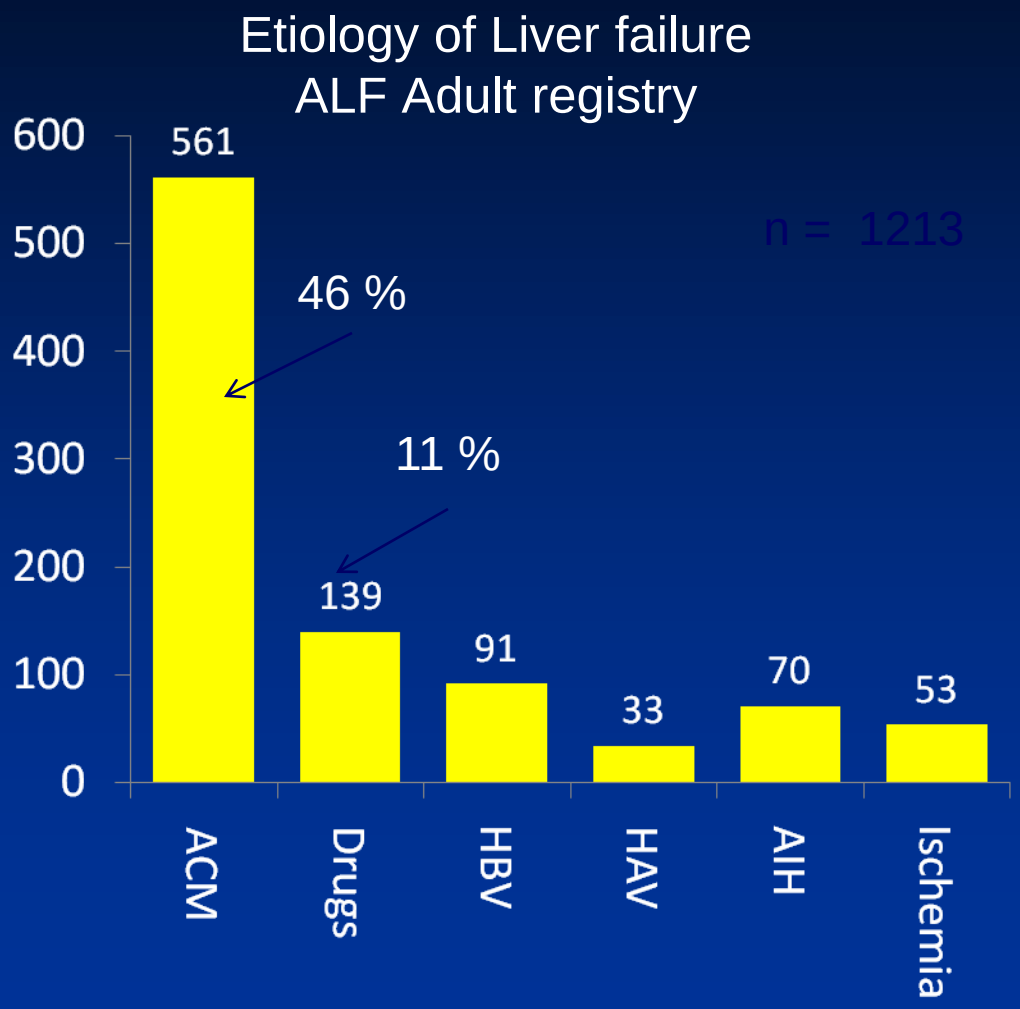
Etiologies of Acute Liver Failure in Adults



Lee et al, Hepatology 47:1401

- Drug-induced liver injury is now the leading cause of acute liver failure (ALF), exceeding all other causes combined.

- Hepatotoxicity has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years



Lee et al, 2007

Incidence of DILI

Author	Year	Setting	Incidence
Koff	1970	Boston	2% of jaundiced pts.
Eastwood	1971	US	20% of jaundice in elderly
Benhamou	1986	France	10% of acute hepatitis
Jmelnitzky	2000	Latin America	5.6% of consults
Russo	2004	UNOS data	15% OLT for toxic/drug ALF
Galan	2005	US ref center	33% of pts with acute hepatitis

Most Commonly Reported Drugs

Series	Year	Drugs Implicated
Chalasani (DILIN-US)	2005	Antimicrobials (46%), CNS agents (15%), NSAIDs (5.5%), methyldopa, IFN beta
Andrade (Spain)	2005	Antimicrobials (32%), CNS agents (17%), NSAIDs (17%), ebrotidine, flutamide, toclopidine
Bjornsson (Sweden)	2005	Antimicrobials (27%), CNS agents and NSAIDs (17% each), disulfiram, enalapril, halothane

References:

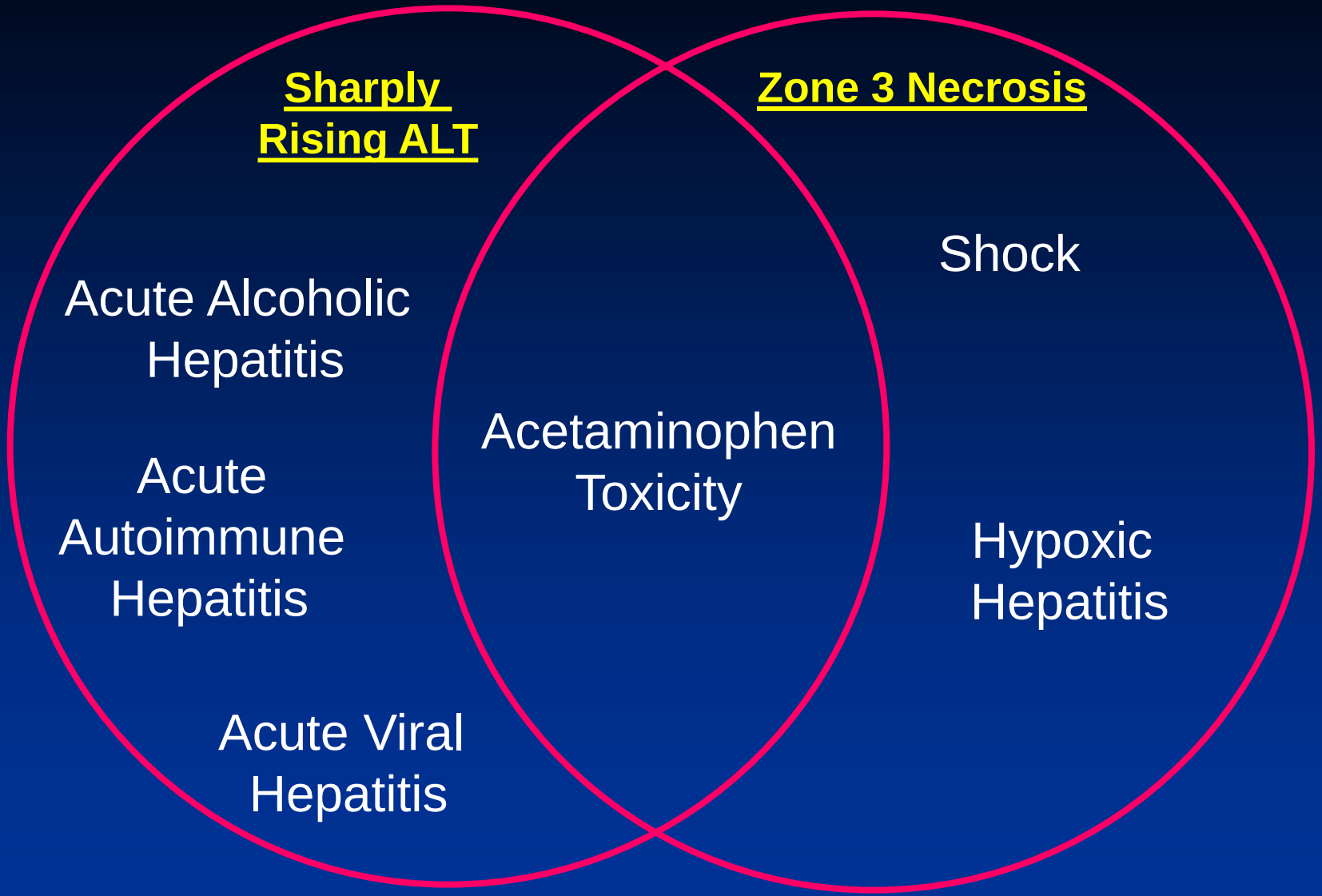
Chalasani et al., Gastroenterology, 2008; 135:1924-34.
Andrade RJ, et al. Gastroenterology, 2005; 129:512–521.
Björnsson E, Davidsdottir L. J Hepatol, 2009; 50:511-517.

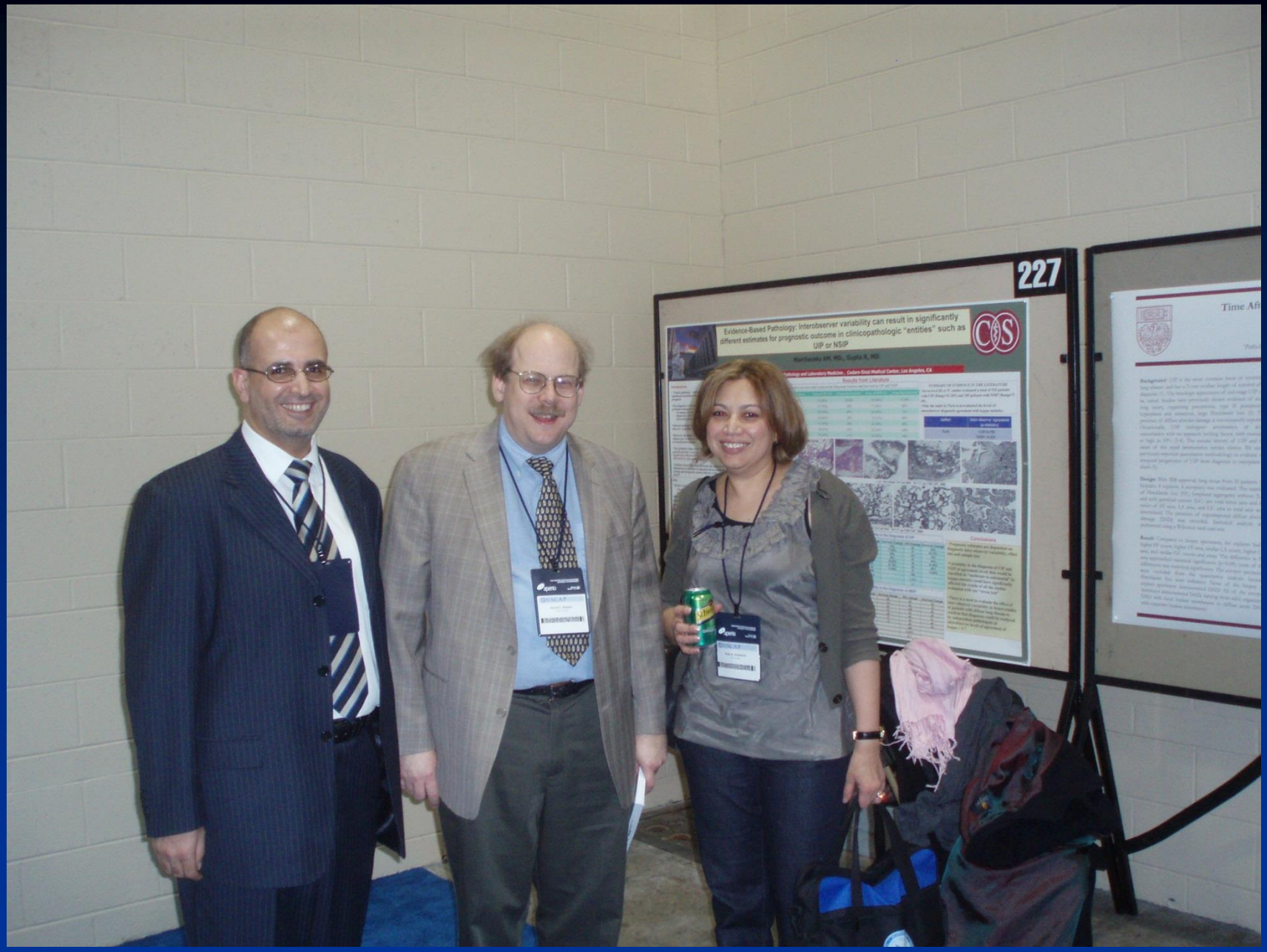
WHY LIVER IS AT RISK?

- Key role in the biotransformation of virtually all drugs and xenobiotics
- Initial bioactivation is by oxidation or reduction pathways
- There is considerable genetic polymorphism in populations and wide individual variations in biotransformation pathways.

Role of Liver Biopsy in DILI

- Characterize the morphologic changes
  - Morphologic changes may confirm drug injury by matching known/reported patterns
  - Morphologic changes may suggest mechanism of injury
- Assess the degree of injury
- Rule out other causes of hepatic injury
- May help to make diagnosis of DILI in complex cases by careful clinical-pathological correlation
- Sometimes biopsy can exclude DILI, permitting continued use of a necessary drug

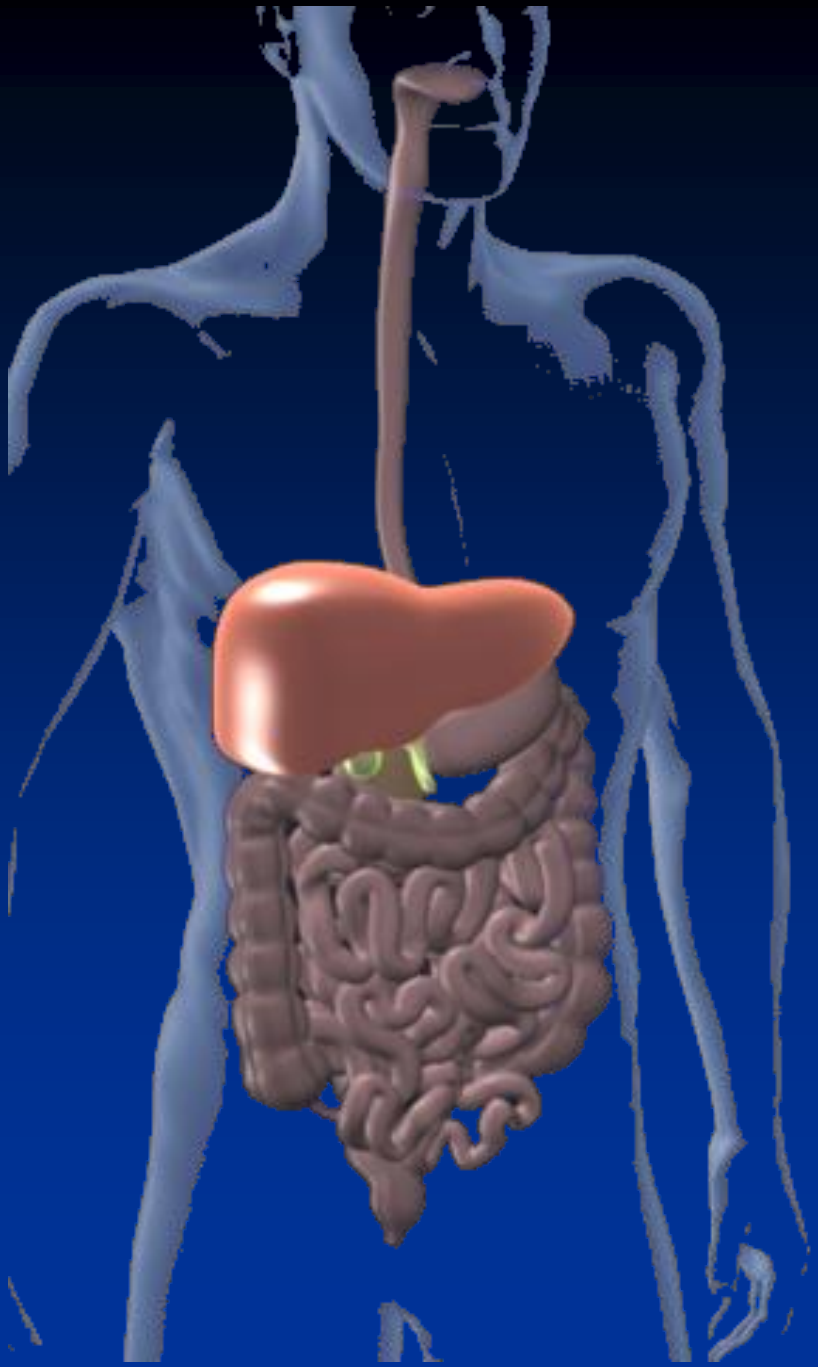

Sharply Rising ALT
Zone 3 Necrosis
Acute Alcoholic Hepatitis
Acute Autoimmune Hepatitis
Acute Viral Hepatitis
Acetaminophen Toxicity
Shock
Hypoxic Hepatitis
Clinical DDx
Pathologic DDx


227
Evidence-Based Pathology: Interobserver variability can result in significantly different estimates for prognostic outcome in clinicopathologic "entities" such as UIP or NSIP
Time Af

Spectrum of Pathologic Changes in DILI

- Hepatic Parenchymal Injury
  - Necrosis/Apoptosis, Ballooning, Fibrosis/Cirrhosis, Cholestasis
- Metabolic Injury without overt Hepatic Injury
  - Bile stasis, Steatosis, Adaptive changes, Inclusions
- Damage to other Cell Types
  - Vascular/Endothelial injury, Bile duct injury
- Neoplastic transformation

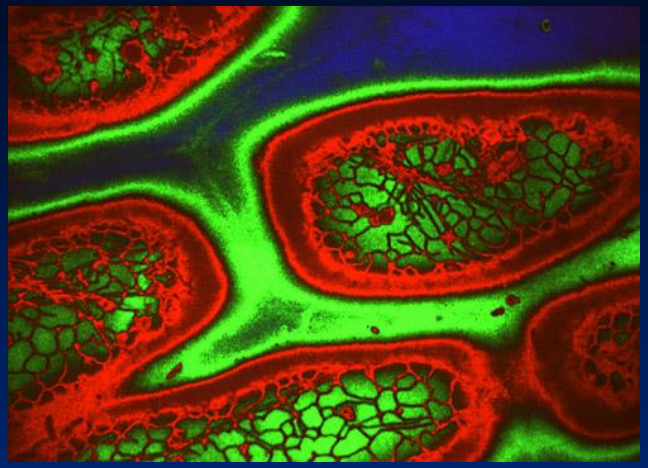
Essentially all patterns of liver injury may be caused by drugs/toxins



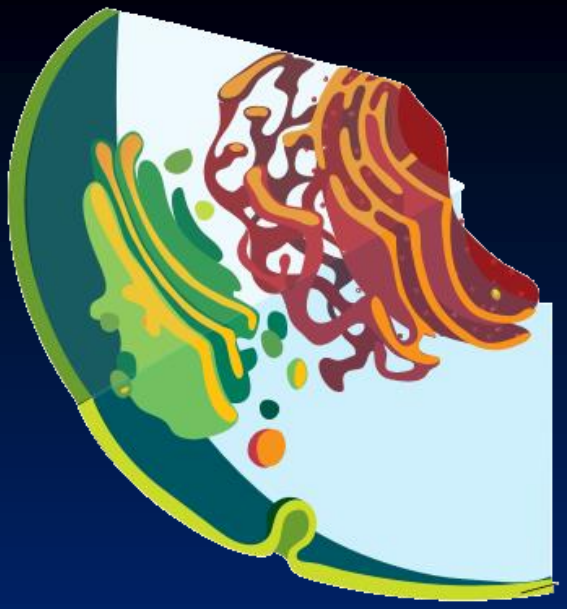
- First pass effect
  - Oral medications absorbed via the GI tract, and enters hepatic circulation through the portal vein to the hepatocytes.

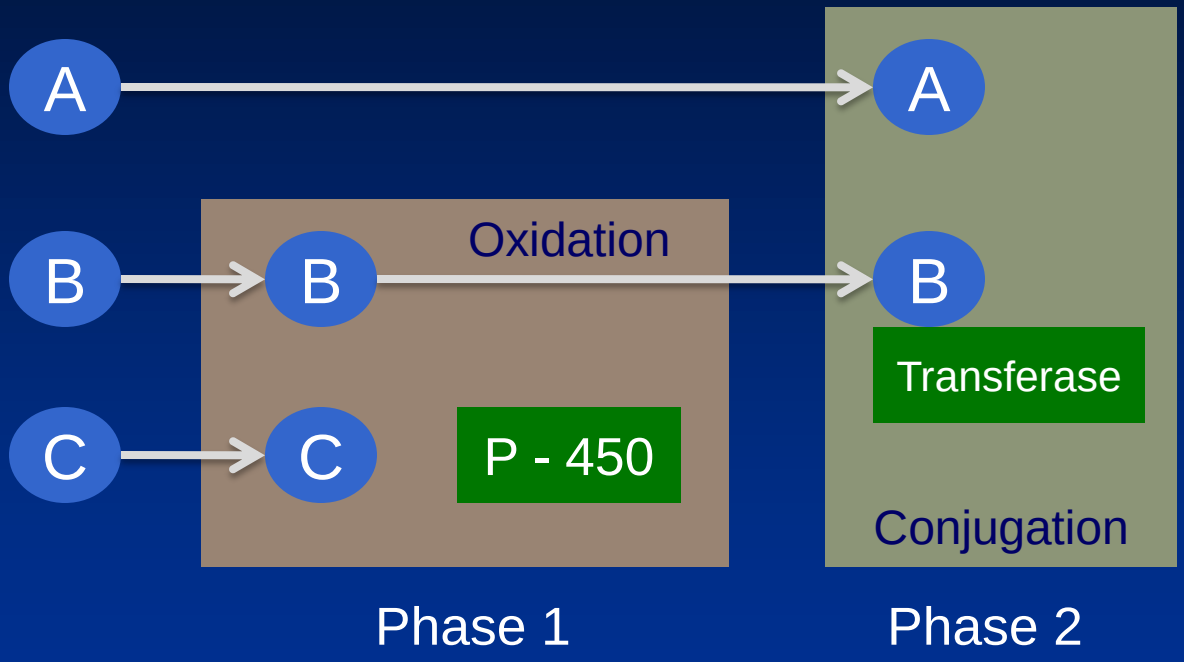
- The human body identifies almost all drugs as foreign substances (Xenobiotics) and subjects them to various chemical processes to make them suitable for elimination.

This involves chemical transformations to reduce fat solubility and change biological activity.



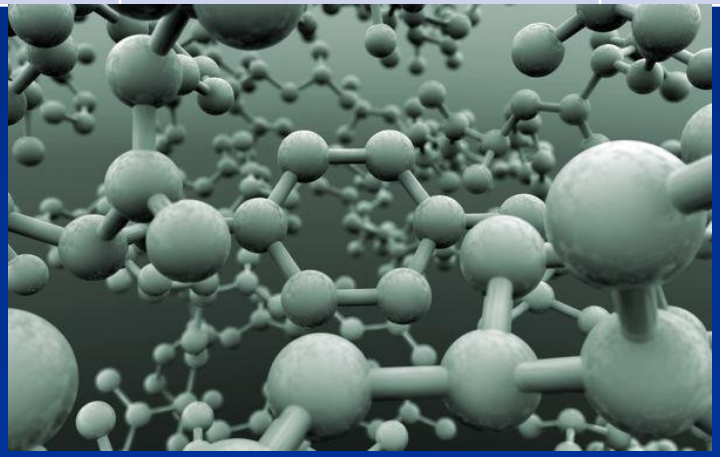
Smooth Endoplasmic Reticulum "metabolic clearing house"




A
A
B
B
B
Oxidation
Transferase
C
C
P - 450
Conjugation
Phase 1
Phase 2

Cytochrome P-450 enzyme induction and inhibition

Potent inducers	Potent inhibitors	Substrates
Rifampin Carbamazepine Phenobarbital Phenytoin	Amiodarone Cimetidine Ciprofloxacin Fluconazole Fluoxetine Erythromycin Isoniazid Dilitazem	Caffiene Clozapine Omepazole Losartan Theophylline



Factors influencing drug induced hepatotoxicity

Age
Ethnicity and race
Gender
Nutritional status
underlying liver disease
Renal function
Pregnancy
Duration and dosage of drug
Enzyme induction
Drug- drug interaction

Intrinsic vs. Idiosyncratic

- Intrinsic Hepatotoxins
  - cause predictable injury, amenable to systematic study, good animal models can be developed
    - ex. Acetaminophen, CCl_4, Household/Occupational Toxins
  - Most drugs in this category are pulled from market
- Idiosyncratic Hepatotoxins
  - cause unpredictable injury in small fraction of patients
    - Hypersensitivity, ex. sulfonamide jaundice
    - Metabolic, ex. isoniazid, valproic acid
  - The majority of DILI falls in this category

Drug Induced and Toxic Liver Disease

Metabolic Idiosyncrasy

- Variable latent period (up to 1 year)
- No features of hypersensitivity
- Delayed recurrence on re-challenge


Intrinsic
Toxicity
Individual
Susceptibility

Drug Induced Liver Disease
Clinical Syndromes

- Subclinical liver test abnormalities
- Acute hepatitis
- Cholestatic hepatitis
- Fulminant liver failure
- “Obstructive” jaundice
- Hypersensitivity + liver disease
- Liver + other organ injury

Classifications of drug-induced liver injury

Clinical Presentation	Subclinical
	Acute
	Chronic
Clinical Laboratory	Hepatocellular
	Cholestatic
	Mixed hepatocellular/cholestatic
Mechanism of Hepatotoxicity	Direct hepatotoxicity
	Idiosyncratic
	Immune-mediated
	Metabolic
Histologic Findings	Cellular necrosis or apoptosis
	Cholestasis
	Steatosis
	Fibrosis
	Phospholipidosis
	Granulomatous
	Sinuoidal obstruction syndrome

Drug Induced Liver Disease
Subclinical Injury

- AST/ALT elevations (hepatocellular)
- Alk Phos/GGT elevations (cholestatic)
- May resolve while drug is continued
- May progress to significant injury
- Monitoring (?)

Clinical Presentation

- Subclinical
  - Asymptomatic elevations in liver enzymes without producing overt clinical disease.
  - ALT is <3 times the upper limit of normal
  - Most subclinical ALT elevations are benign and resolve once the offending agent has been discontinued.

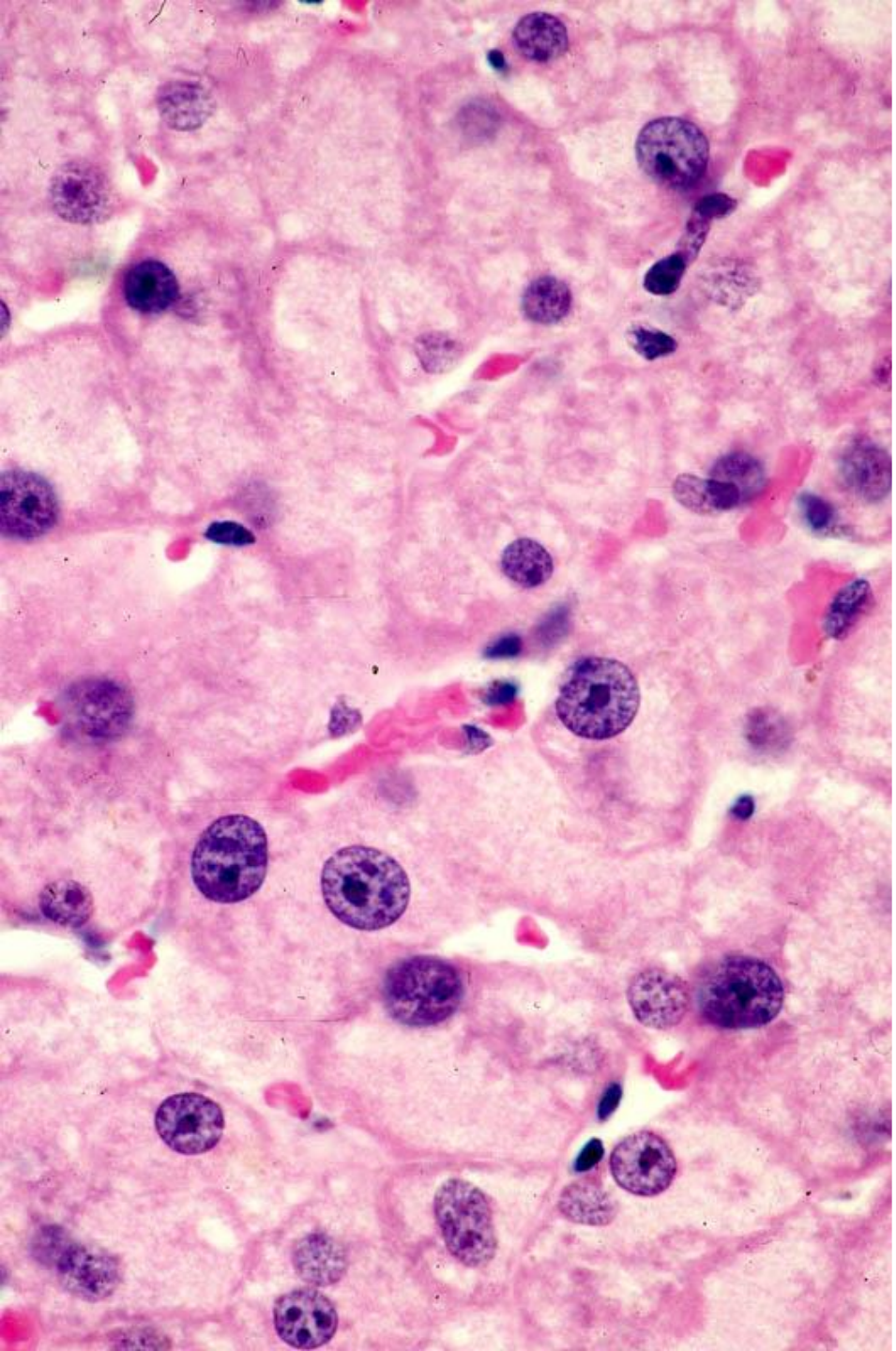
Certain antibiotics
Antidepressants
lipid-lowering drugs
Sulfonamides
Salicylates
Sulfonylureas
Quinidine
Isoniazid
Tacrine

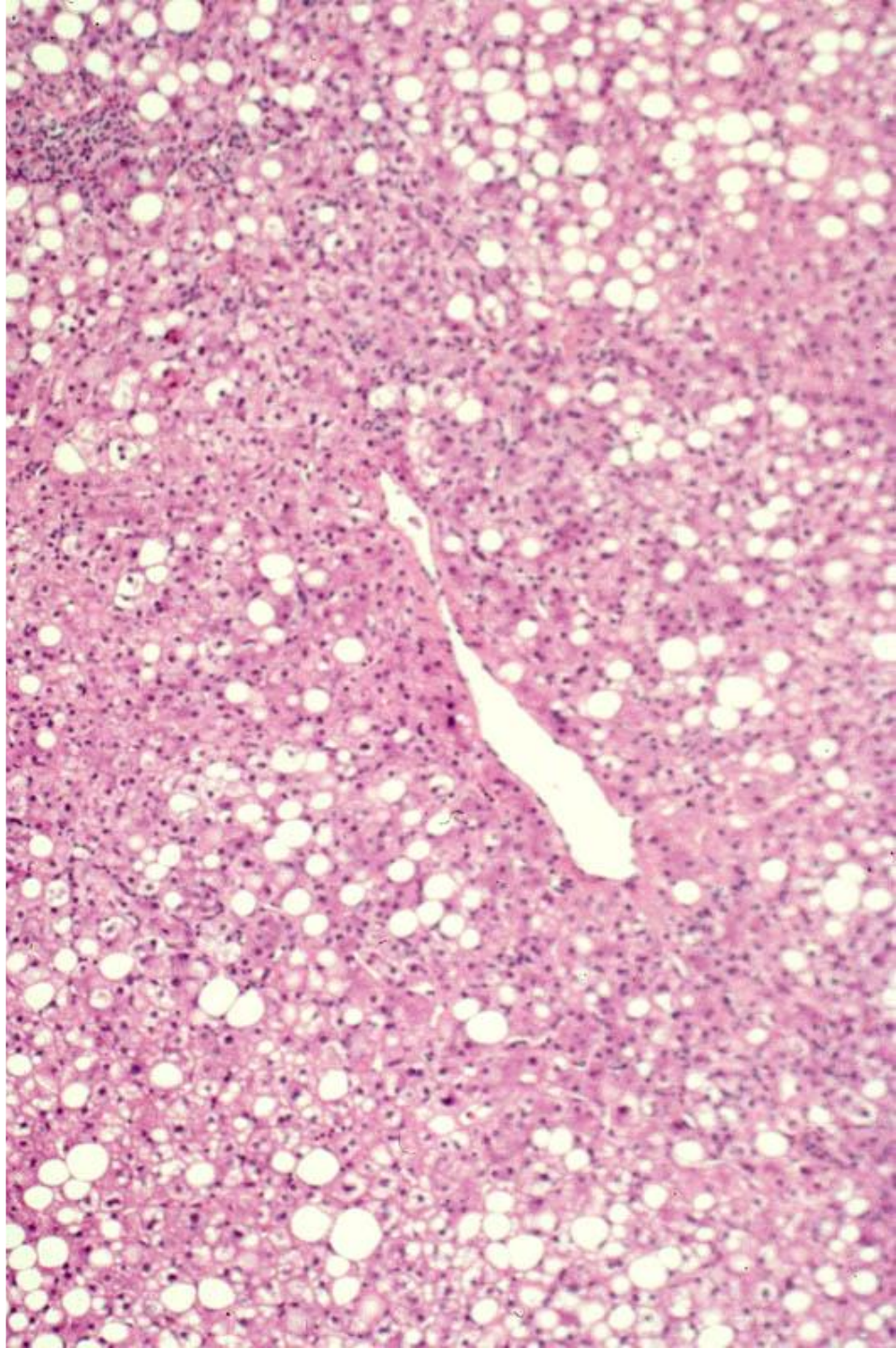
Watkins et al, Hepatology 2006; 43:618

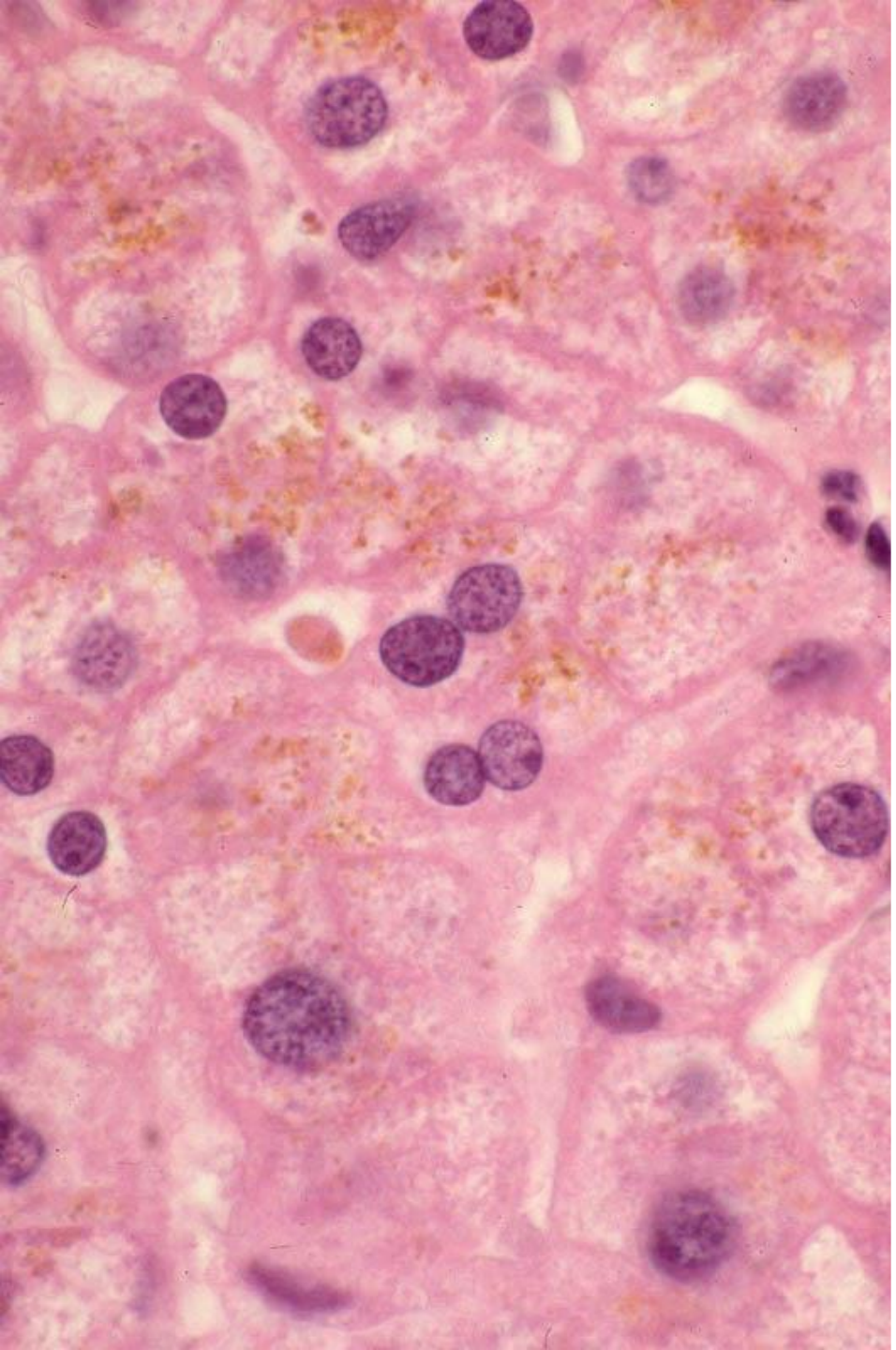
Drug Induced Liver Disease
Subclinical Injury

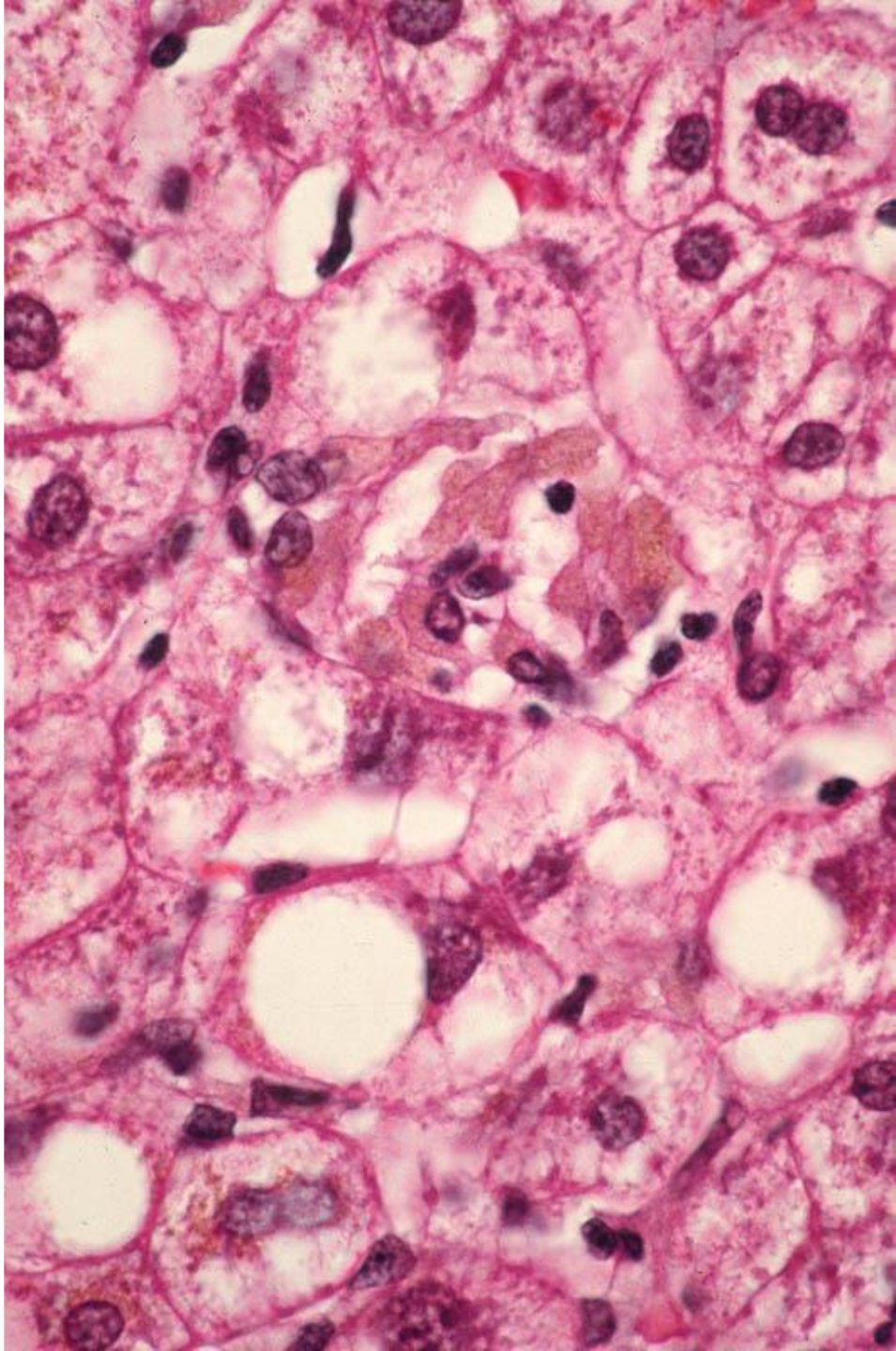
- ± 10% - INH, DPH, valproate, niacin, chlorpromazine
- Biopsy - Nonspecific changes

  Fat, pigment, “ground-glass”, focal necrosis, regeneration









The Type of Injury Can Help Characterize the Toxic Agent

- **Zonal Necrosis - usually intrinsic toxicity**
  - Zone 3 necrosis: p450 system in greater concentration leads to greater conversion of drug into toxic metabolite, zone sees lower oxygen tension.
    - ex: acetaminophen, CCl4
  - Zone 1 necrosis: higher oxygen tension, first zone to see drug, so is affected by direct toxins
    - ex: phosphorus compounds

The Type of Injury May Help With Prognosis

- **Non-zonal necrosis - typically idiosyncratic**
  - spotty “hepatitis-like” necrosis (isoniazid)
  - May lead to massive non-zonal necrosis
  - chronic autoimmune hepatitis (minocycline, methyldopa)

- **Outcome of massive necrosis (assuming survival)**
  - Massive non-zonal necrosis => post-necrotic scar
  - Massive zonal necrosis => non-scarred parenchyma

Other Types of Injury

- **Visible parenchymal injury**
  - **Steatosis:** zonal/non-zonal, results from interference with lipid export, impaired oxidation, increased synthesis, or increased transport of fatty acids from periphery
    - Microvesicular - may be linked to mitochondrial injury, either primary or secondary
  - **Ballooning degeneration:** cell swelling with cytoplasmic clearing, often related to disruption of endoplasmic reticulum

Types of Injury - Non-Necrotic (II)

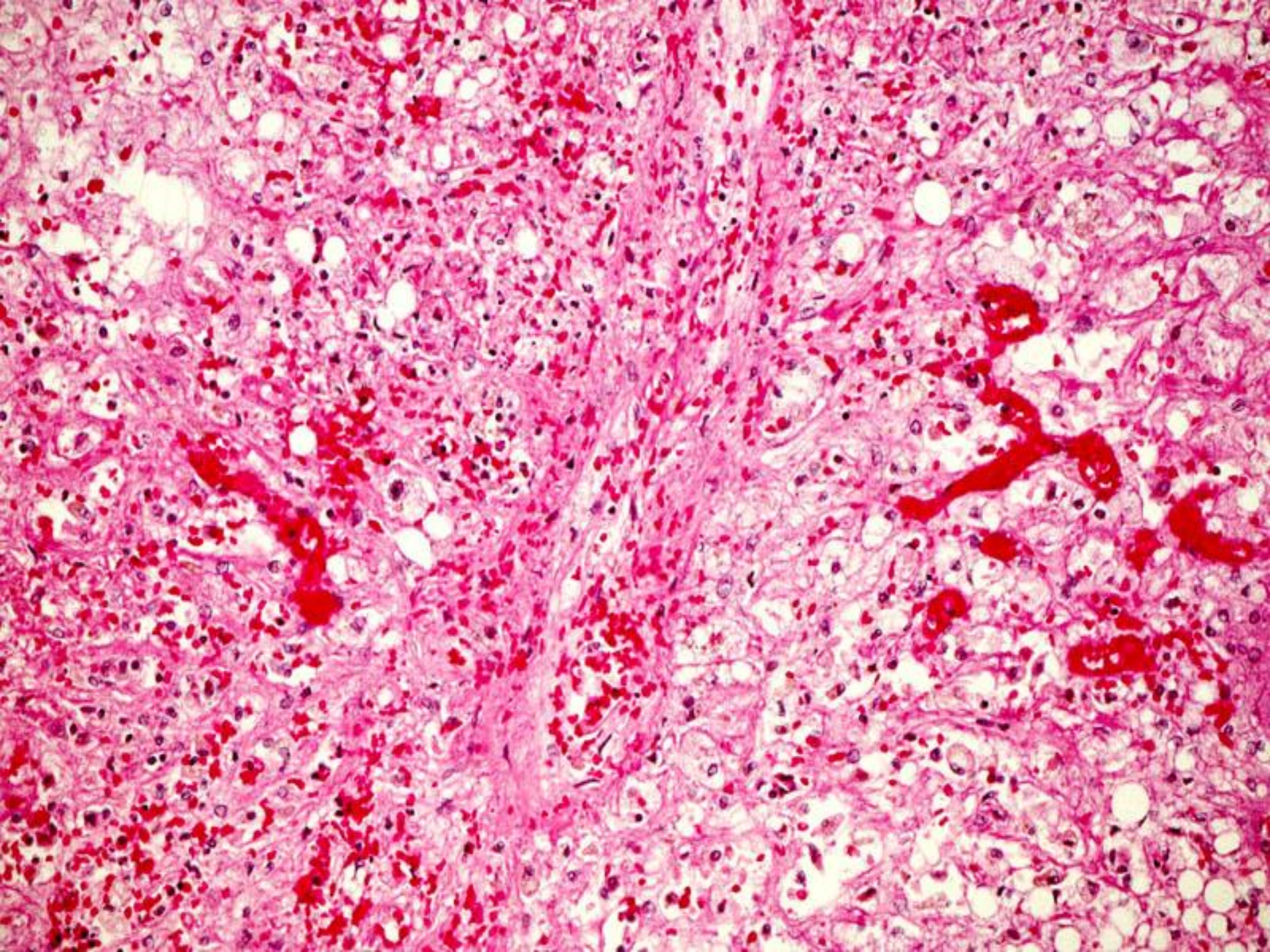
- **Cholestasis**
  - **Pure cholestasis:** bile in canaliculi, hepatocytes (zone 3) results from selective interference with bile formation/flow
    - ex: anabolic steroids, OCPs, erythromycin
  - **Cholestatic hepatitis:** as above, with spotty apoptotic necrosis, often due to hypersensitivity plus mild toxicity
    - ex: captopril, antifungals such as fluconazole, ketoconazole

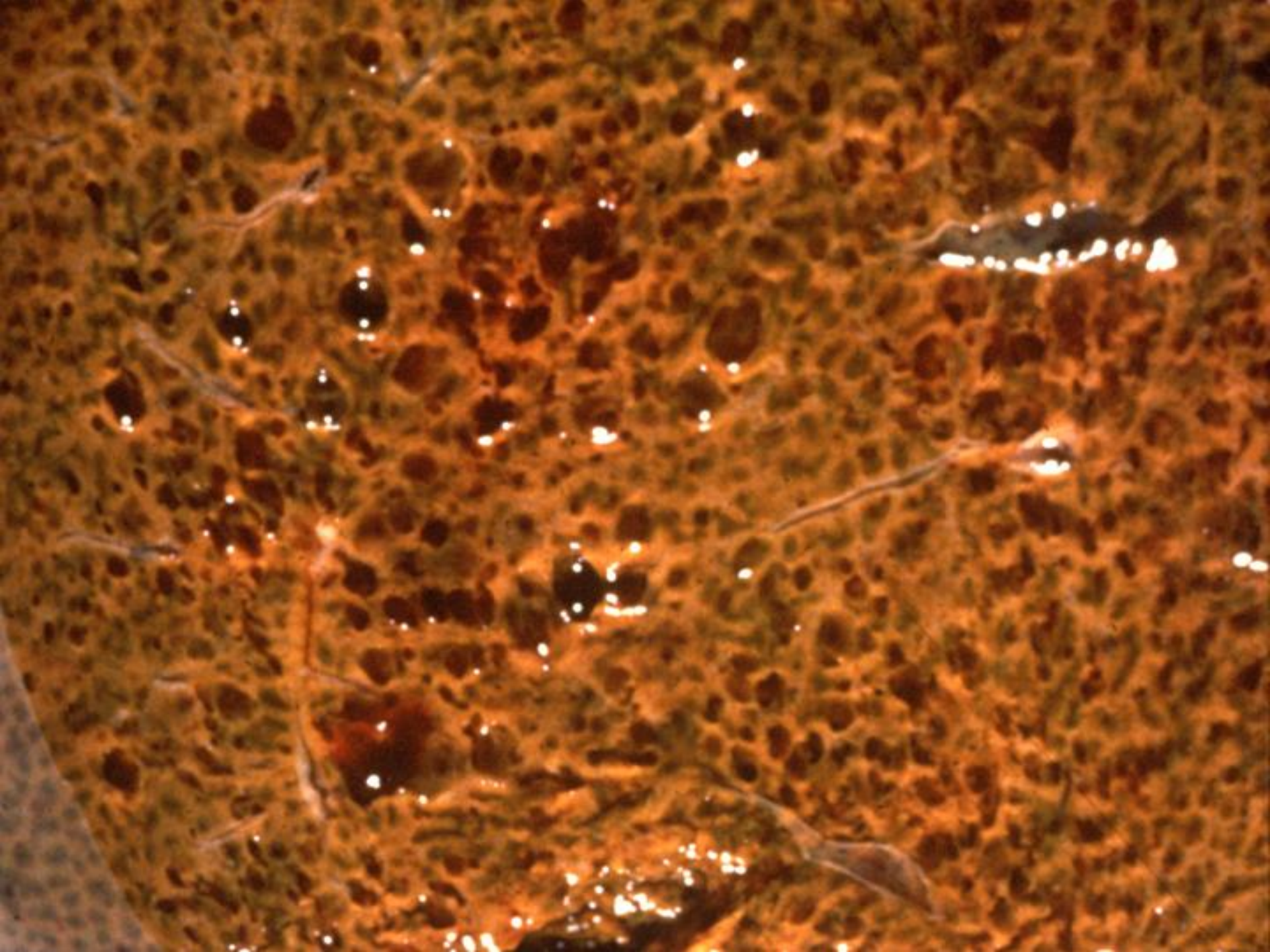
Types of Injury - Other cells

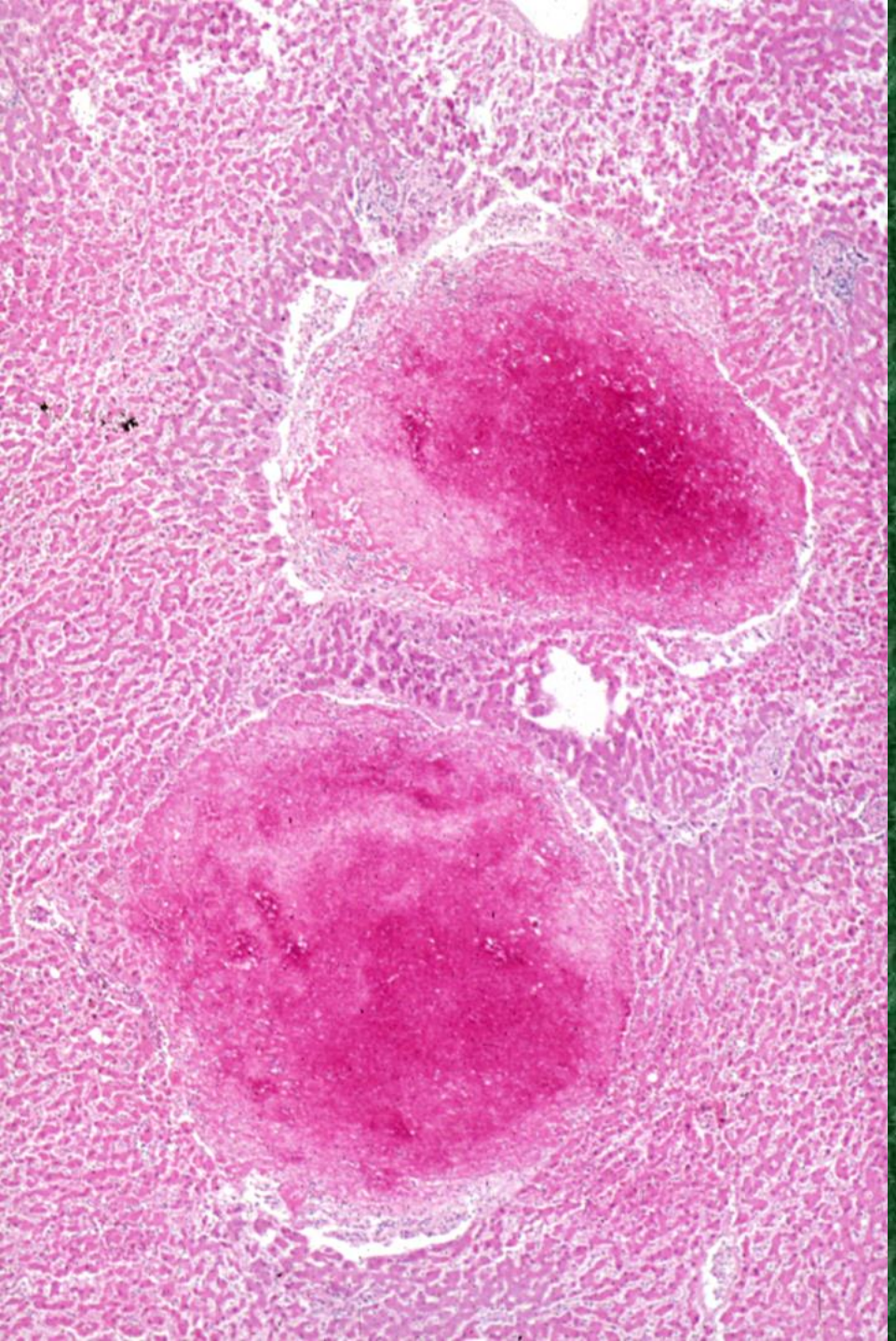
- **Cholangiodestructive/Cholangiosclerotic**
  - Results from direct or indirect destruction of ducts and leads to chronic cholestasis with secondary scarring
    - ex: floxuridine infusion into hepatic artery causing secondary sclerosing cholangitis
- **Vascular injury**
  - VOD patterns: BMT preparative regimens
  - Budd-Chiari: OCP's
  - Peliosis hepatitis: steroids, tamoxiphen

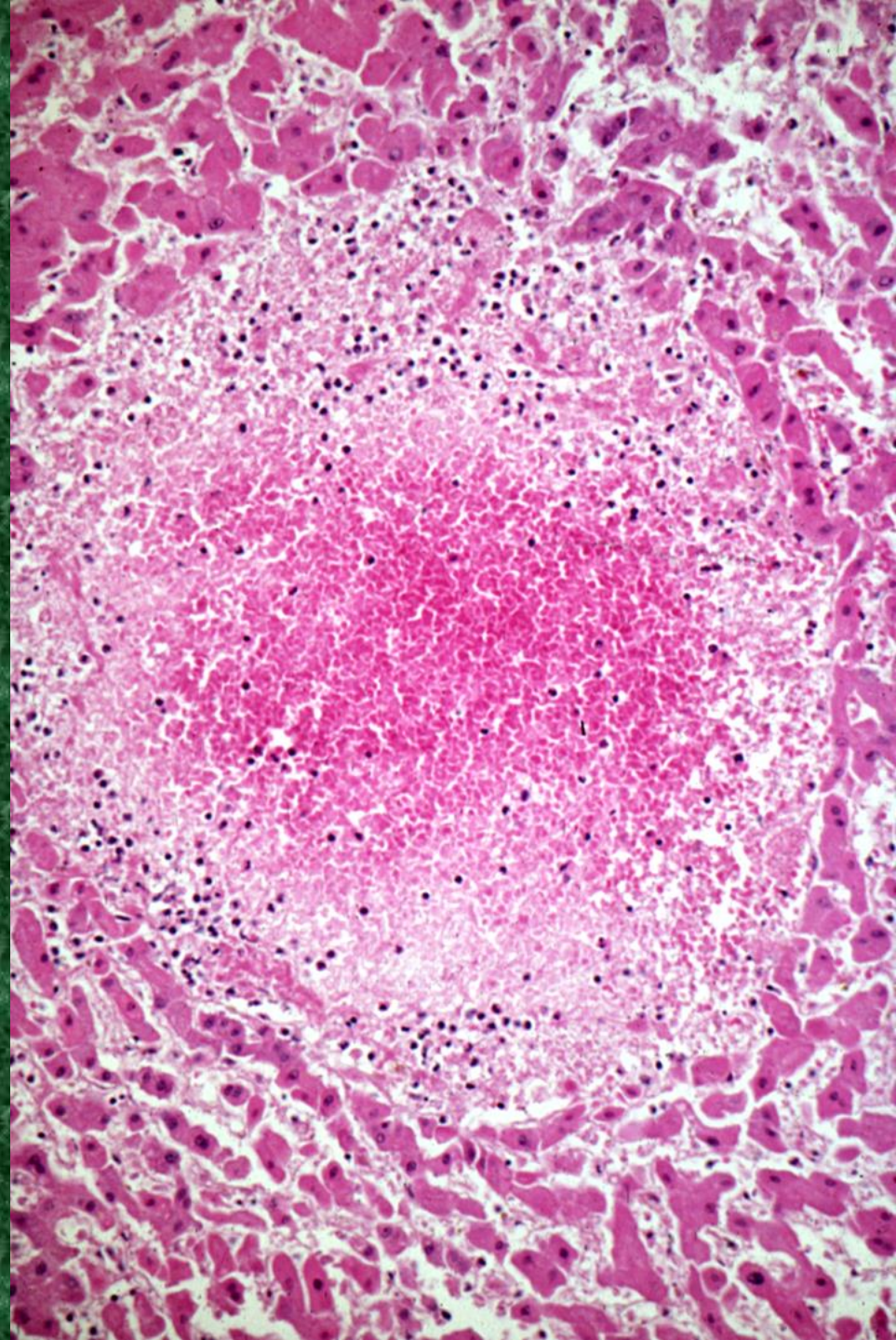
Drug – Induced Vascular Lesions

- Veno-occlusive disease/Sinusoidal obstruction syndrome
- Peliosis
- Sinusoidal dilatation
- Hepatic vein thrombosis
- Hepato-portal sclerosis
- Nodular regenerative hyperplasia
- Vasculitis

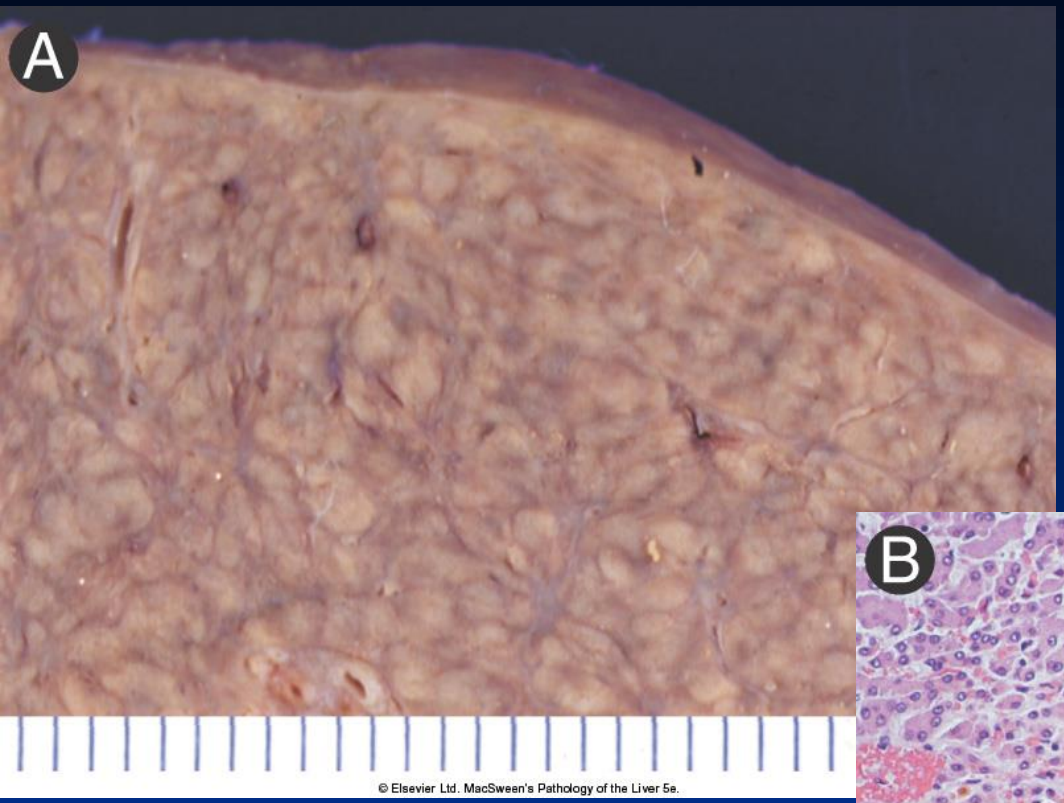








Nodular Regenerative Hyperplasia



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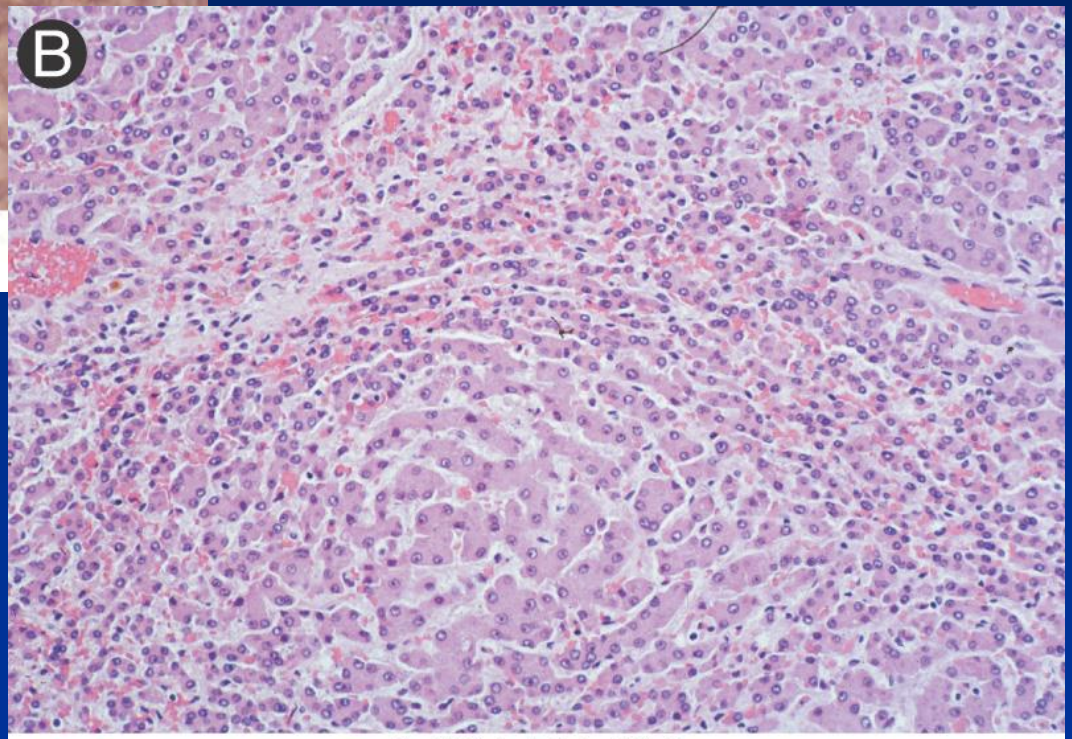

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A Systematic Approach

- Forewarned is Forearmed – From the Concerned Clinician to the Grossing Bench
- Examination of the biopsy – Identify the Pattern(s) of Injury
- Evaluation of the Clinical History
- Causality Analysis – Finding the Guilty Parties

First Steps

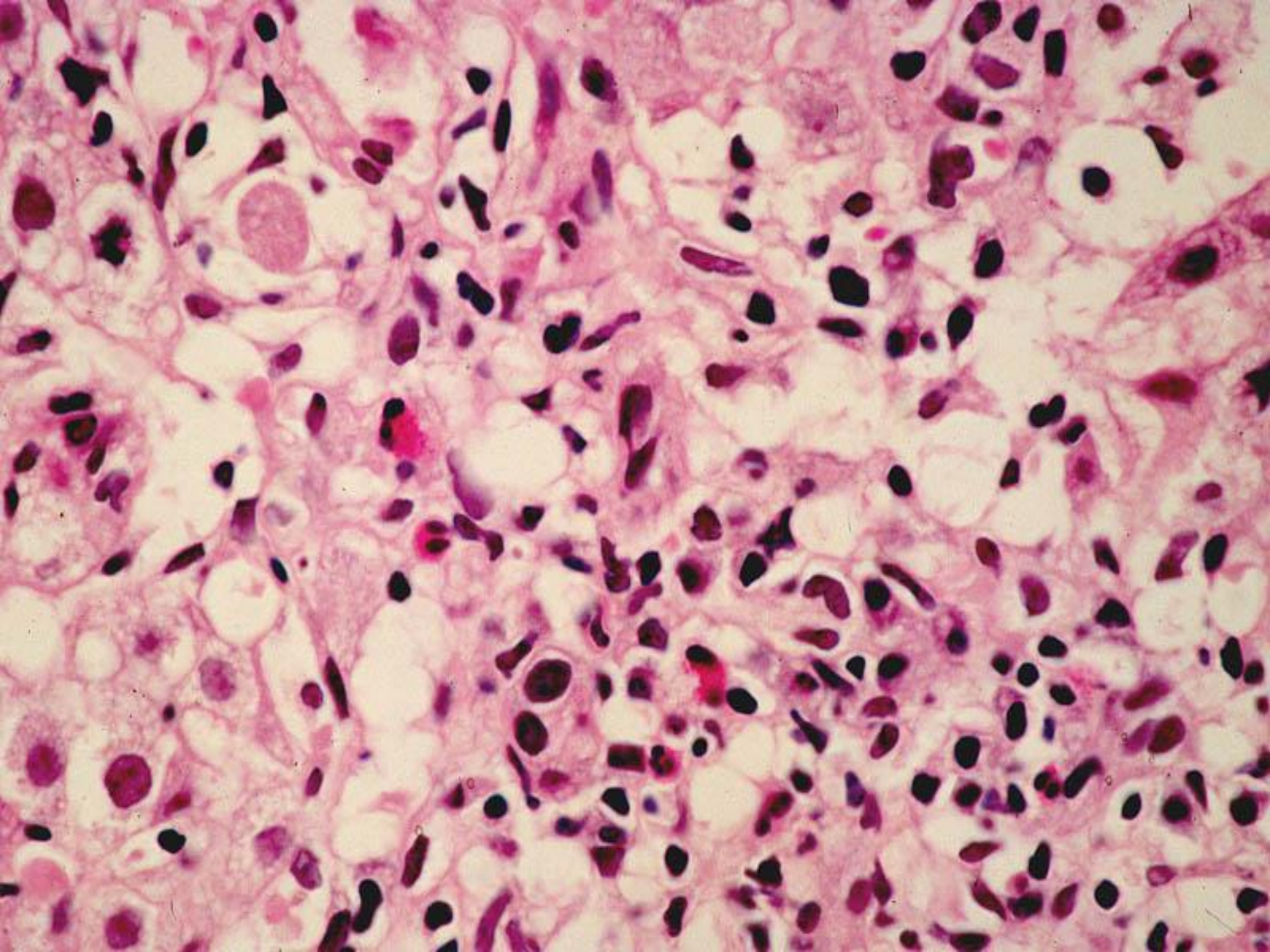
- First warning about a potential DILI case may come with a phone call from a concerned clinician
  - Chance to review history, identify drugs, herbals, other agents
  - Arrange a time to discuss case
- At the grossing bench
  - Make decisions about processing, special stains, sections for fat stains, EM

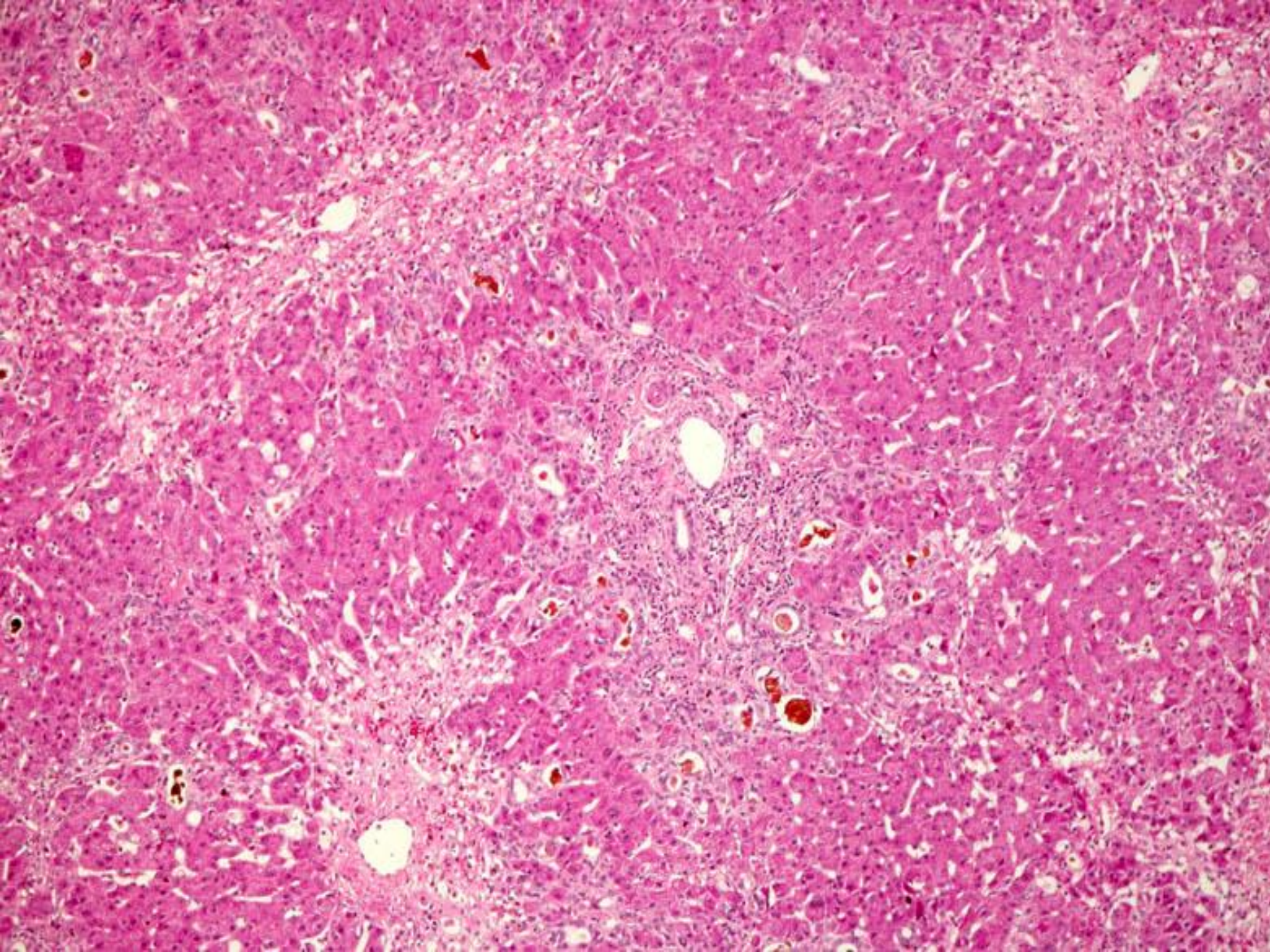
When To Suspect DILI

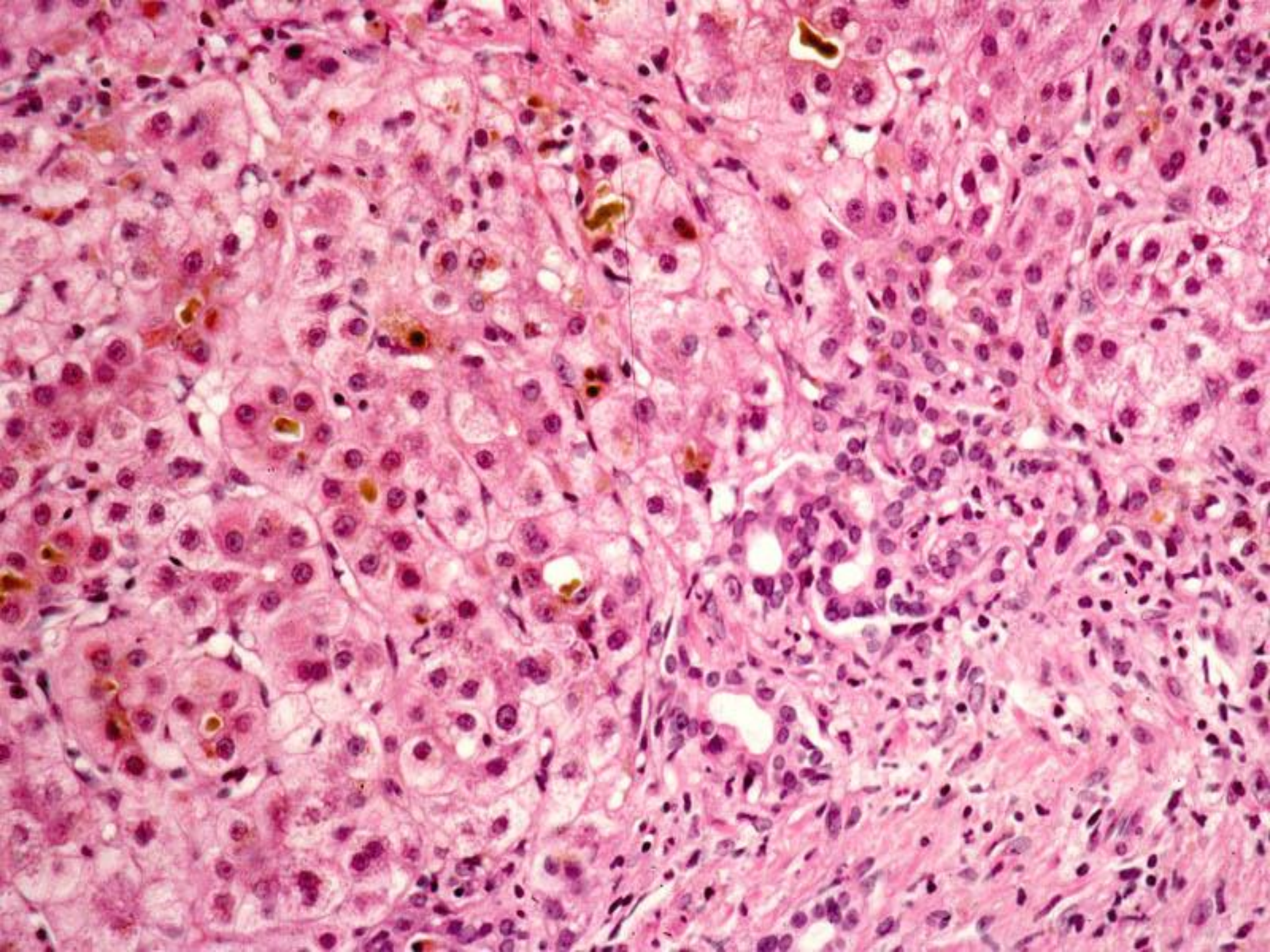
- Always
- Severe acute injury with zonal, submassive, or massive hepatitis
- Severe acute hepatitis
- Cholestatic hepatitis (combined injury pattern)
- Granulomatous hepatitis
- Prominent eosinophilic infiltrate
- Weird mixed patterns (Atypical Patterns)

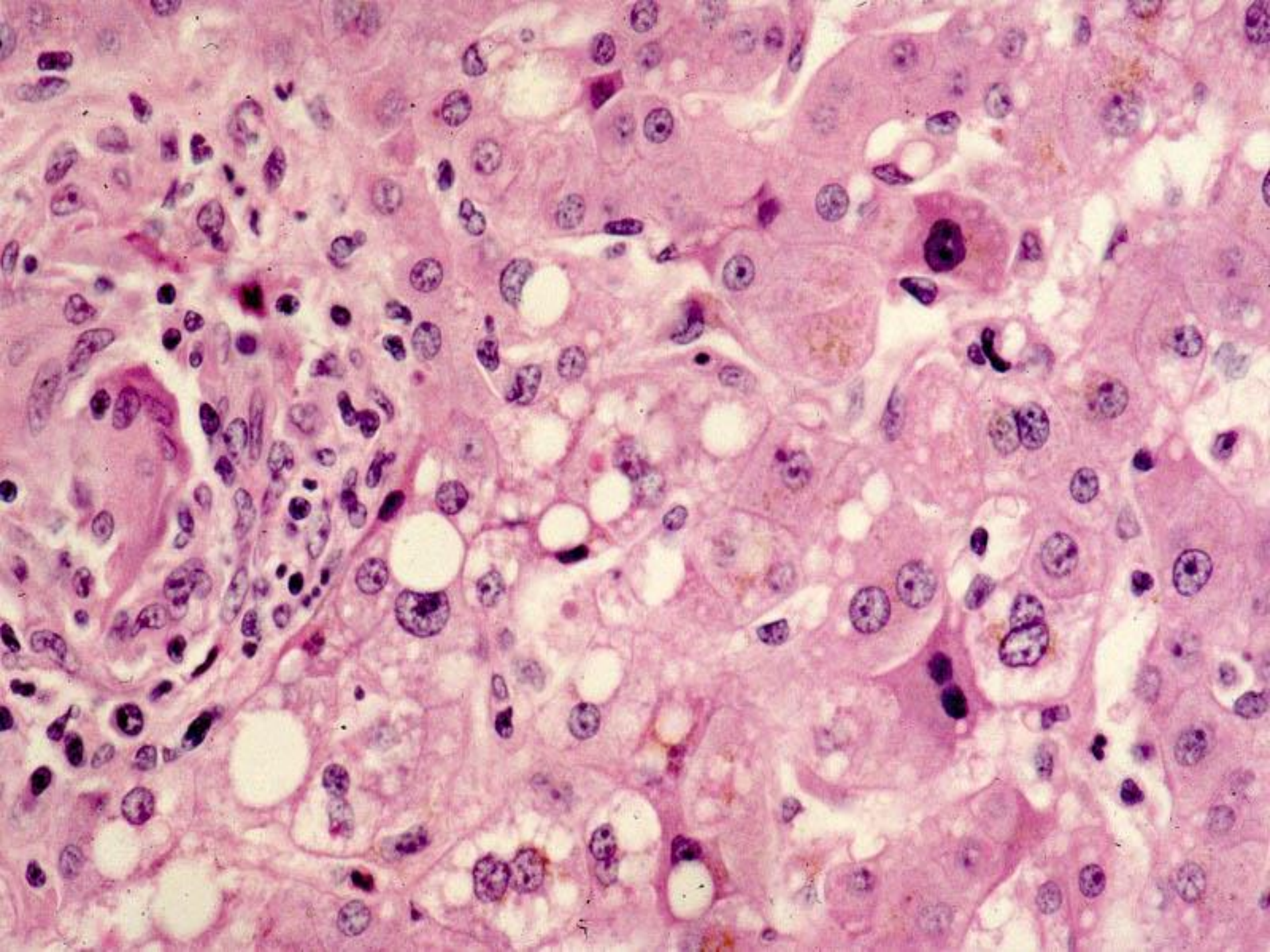
Drug-Induced Hepatitis
Pathological Clues

- Many eosinophils
- Cholestasis out of proportion with Hepatocellular injury
- Granulomas
- Demarcated zones of perivenular necrosis
- Bile duct damage
- Multinucleated giant hepatocytes
- Poorly developed portal reaction
- Many neutrophils
- Steatosis









Identify the Pattern of Injury

While drugs/toxins have been implicated in causing every known pattern of hepatic injury…

Individual drugs have been related to a limited set of patterns

and

Patterns have a limited differential of non-toxic causes

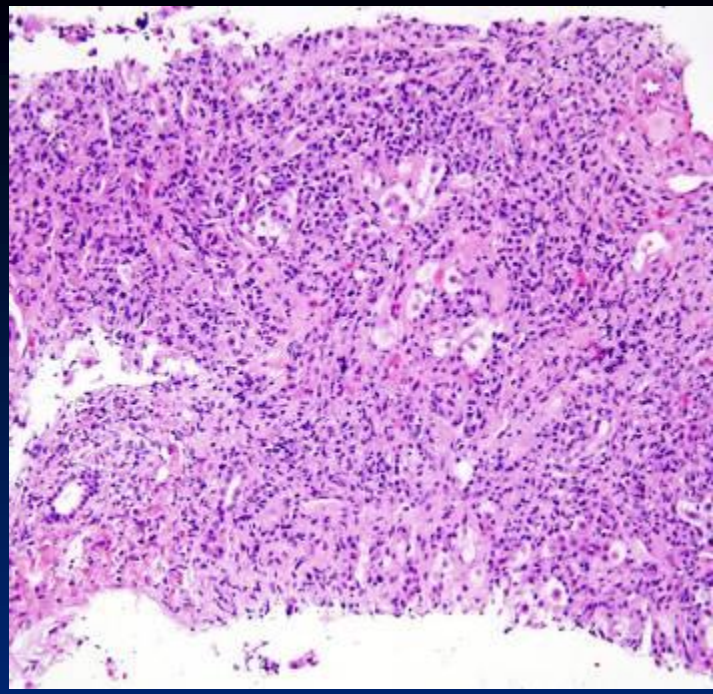
DILI Pathology Patterns

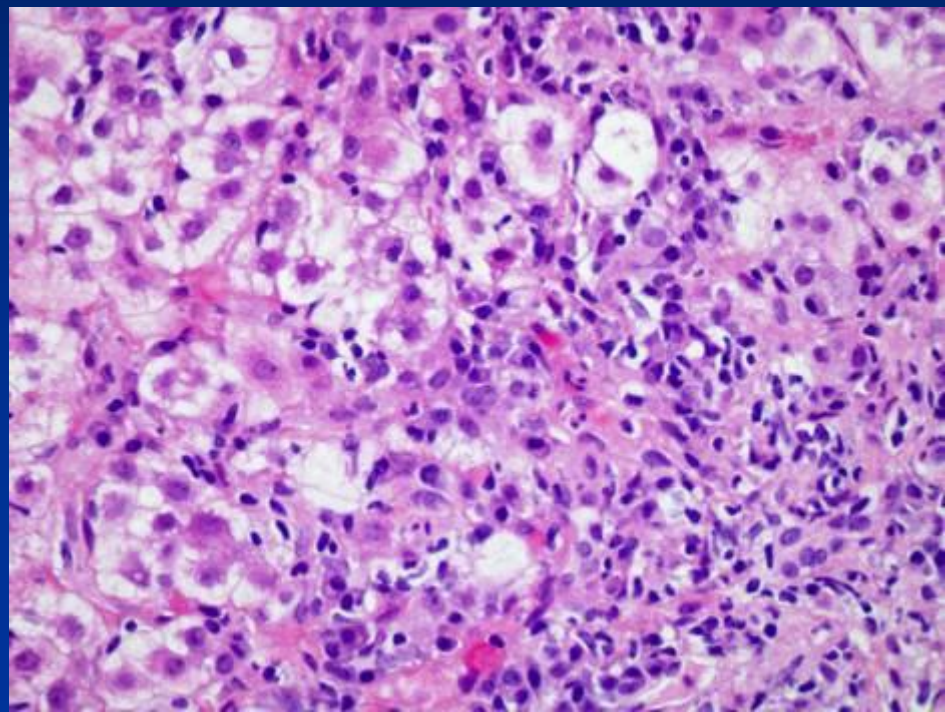
- Necroinflammatory
  - Zonal (coag) necrosis
  - Acute hepatitis
  - Chronic hepatitis (including mono-like patterns)
  - Granulomatous
- Cholestatic
  - Acute cholestasis
  - Chronic cholestasis
- Cholestatic Hepatitis (Mixed hepatocellular and cholestatic injury)
- Fatty liver disease
  - Microvesicular steatosis
  - Macrovesicular steatosis
  - Steatohepatitis
- Vascular injury
  - VOD/SOS
  - Peliosis
  - Portal venopathy/HPS
  - Nodular regenerative hyperplasia
- Fibrosis/cirrhosis
- Neoplasms

Acute Hepatitic Injury

(DILIN case- Probable Atomoxitine DILI)

- Lobular predominant lymphocytic-plasmacytic infiltration +/- hepatocellular degeneration, lobular disarray, no cholestasis
- DDx: Acute Viral or Autoimmune Hepatitis, Early chronic hepatitis or PBC, Non-specific reactive changes
- Ex: Isoniazid, sulfamides, rifampin

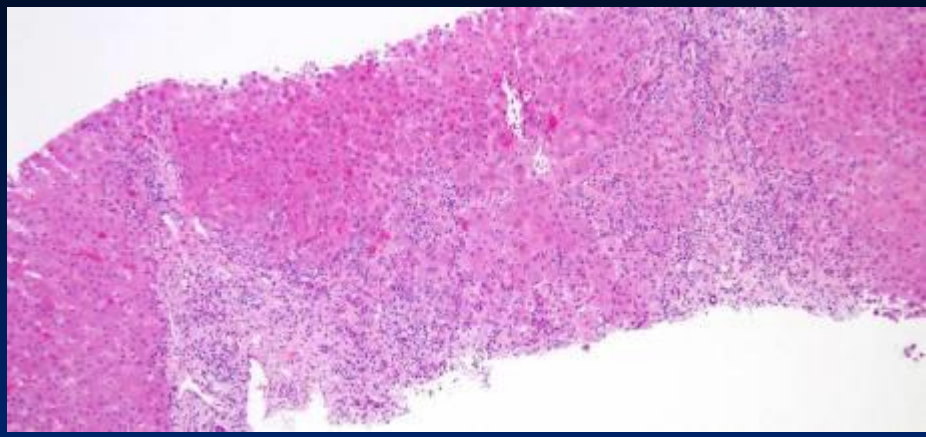


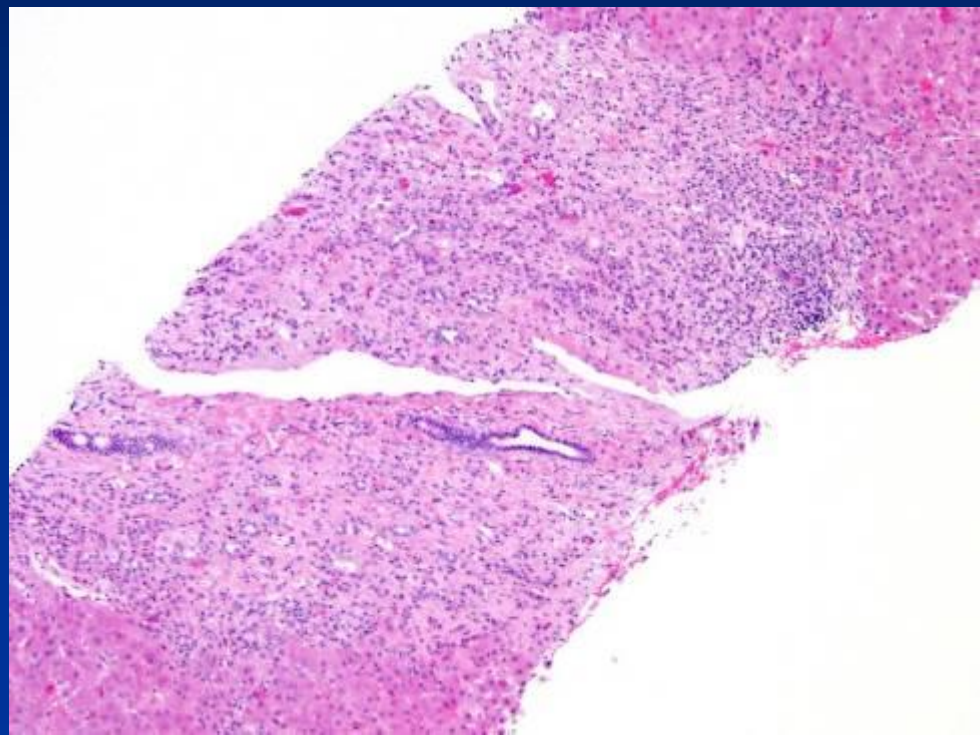


Chronic Hepatitic Injury

(DILIN case – Likely Nitrofurantoin injury)

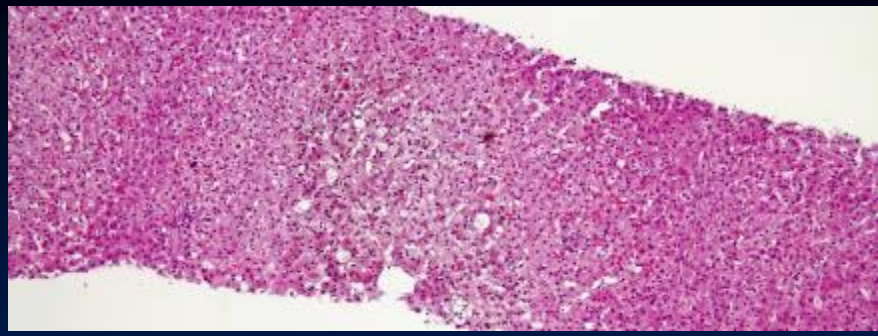
- Portal predominant, interface hepatitis, portal-based fibrosis, no cholestasis
- DDx: Chronic viral or autoimmune hepatitis, early PBC/PSC
- Isoniazid, minocycline, methyldopa



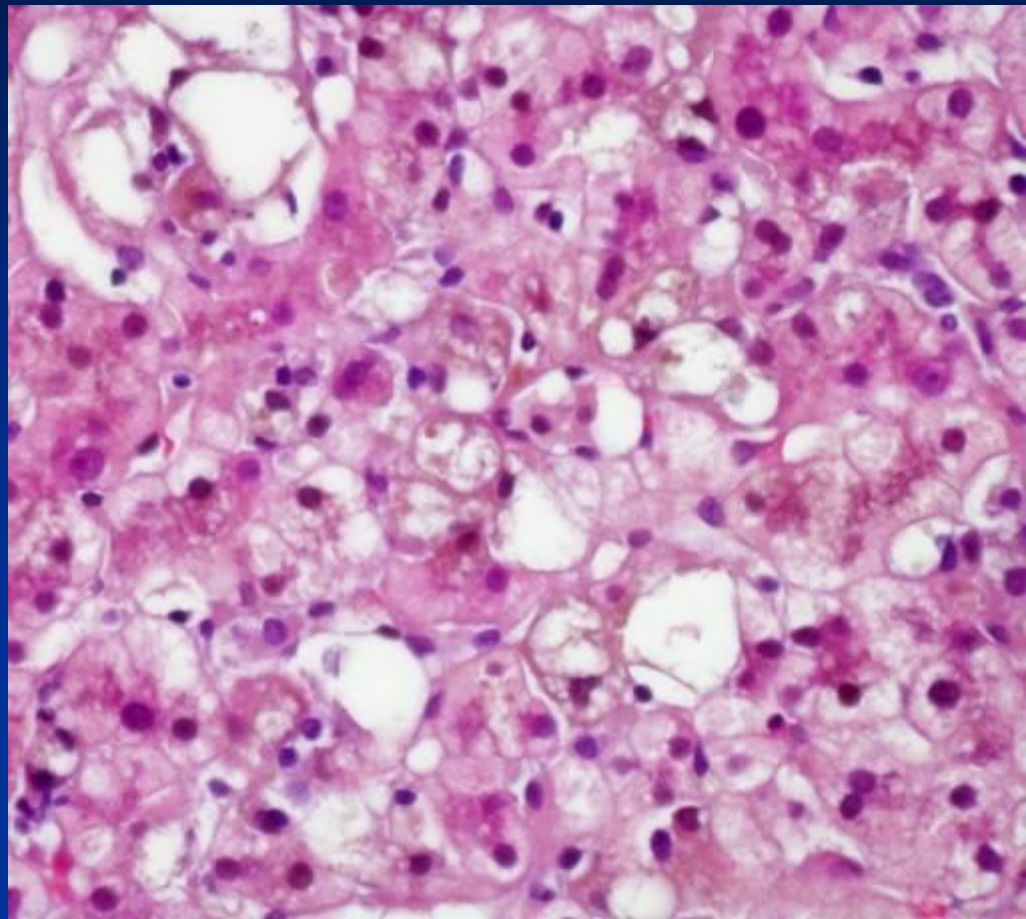


Acute Cholestatic

DILIN Case – Probable Azithromycin injury



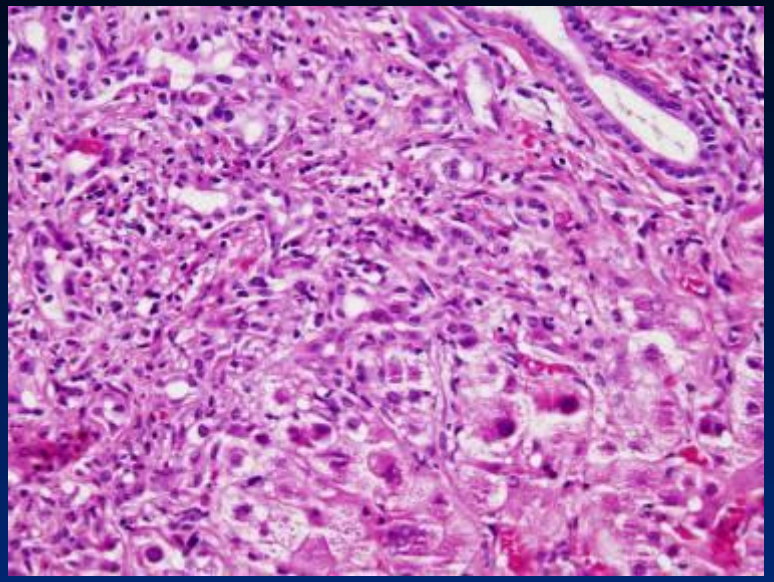
- Pure hepatocellular or canalicular cholestasis, mild injury and inflammation, mild portal changes
- DDx: Sepsis, post-surgical, acute LDO, cholestasis of pregnancy, benign recur cholestasis
- Androgens/Estrogens, Chlorpromazine, Erythromycin

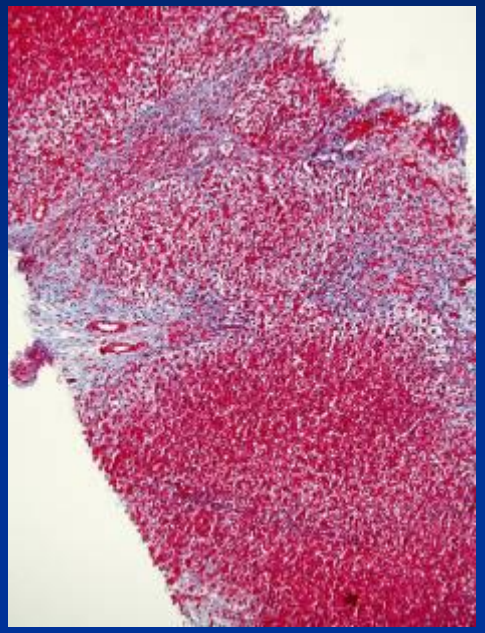


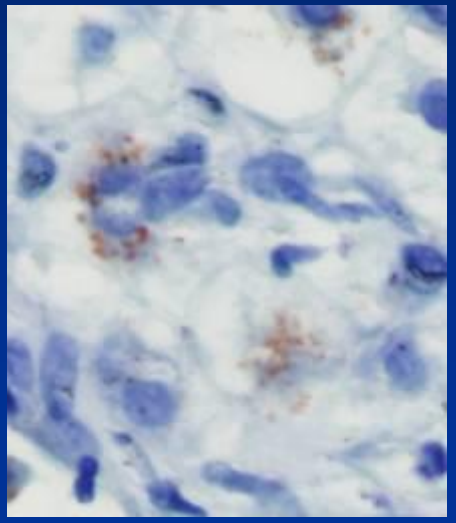
Chronic Cholestatic

DILIN case – Likely Cefuroxime injury

- Duct injury/paucity with cholate stasis, copper accum, fibrosis, may have chronic hep changes
- DDx: PBC, PSC, Chronic LDO, chronic hepatitis with duct injury, GVHD
- Ex: Chlorpromazine, imipramine, thiabendazole



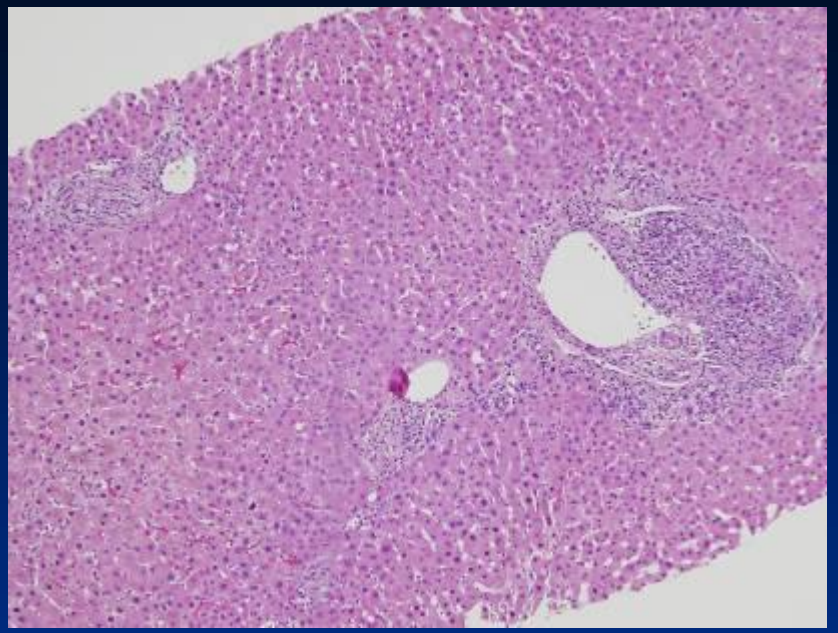


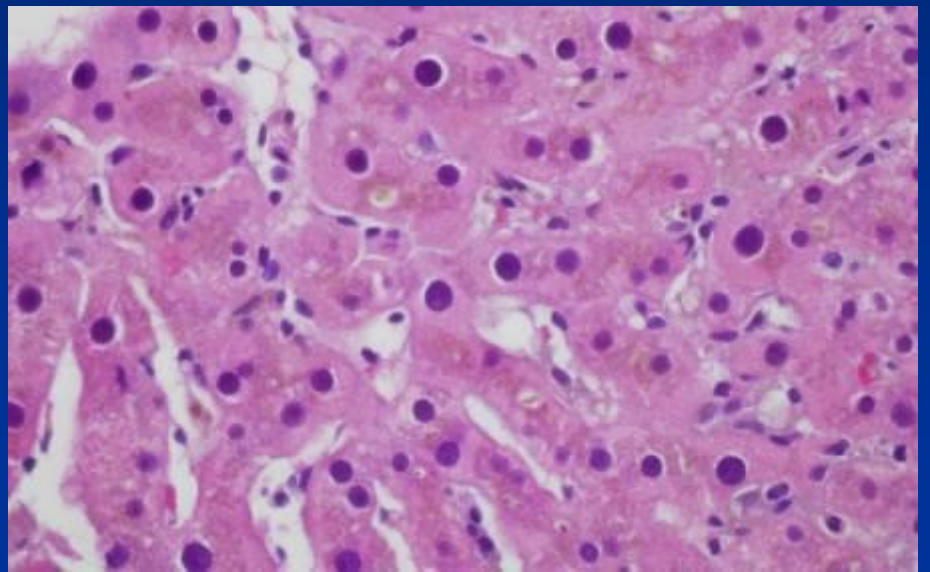


Cholestatic Hepatitis (Mixed Injury)

(DILIN Case – Likely Sevoflurane injury)

- Combination of hepatitis (usually acute) with canalicular/ hepatocellular cholestasis, duct injury
- Acute cholestatic viral hepatitis, GVHD
- Isoniazid, phenylbutazone, chlorpropamide, diphenylhydantoin

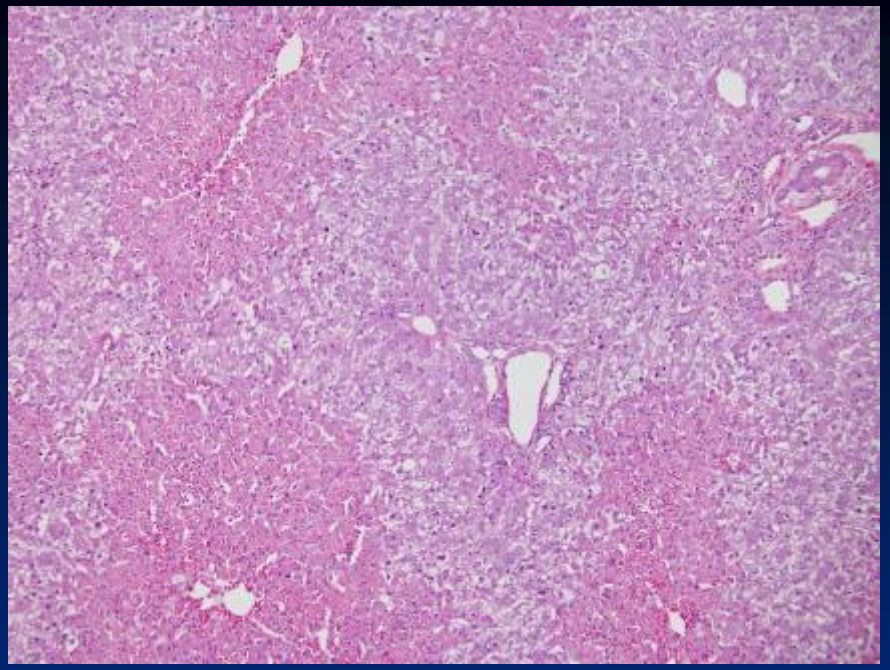


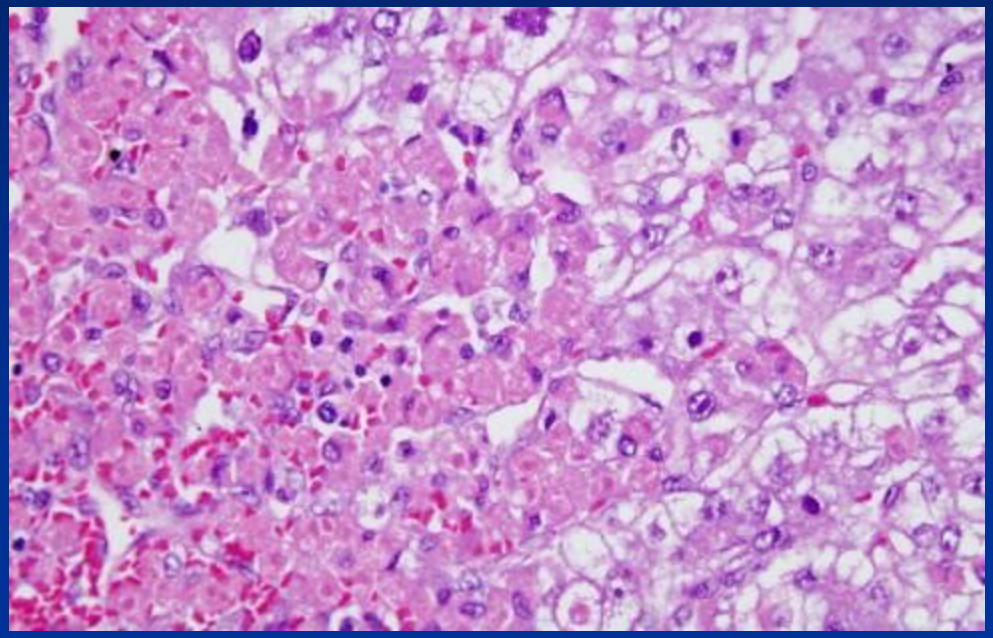


Zonal Necrosis

(Acetaminophen Injury)

- Coagulative/confluent necrosis and/or hepatocyte drop-out in a zonal or pan-acinar pattern with little inflammation
- DDx: Hypoxic-ischemic injury, shock
- Acetaminophen

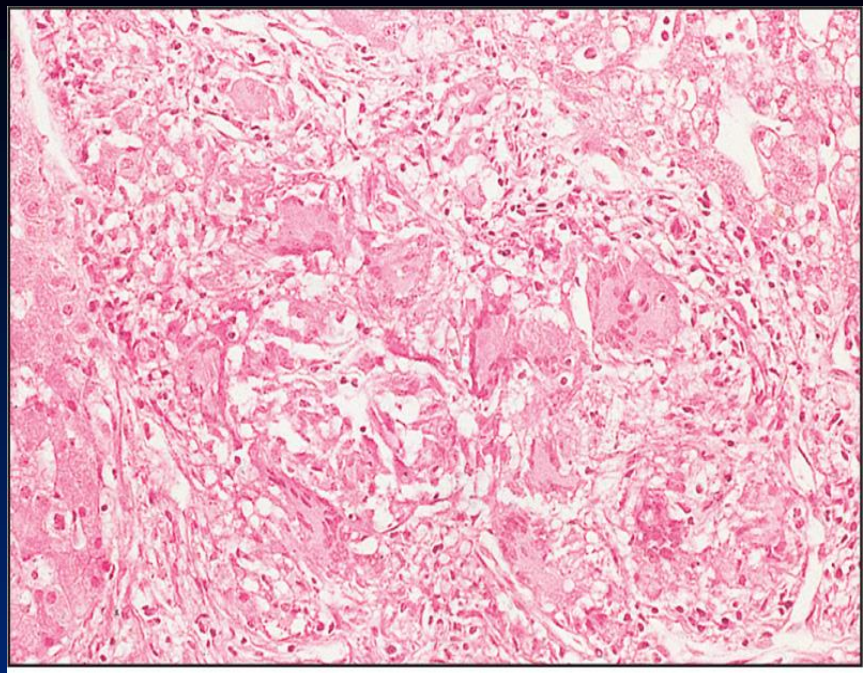




Granulomatous Injury

(Phenylbutazone injury)

- Large non-caseating granuloma
  Cholestasis & acidophilic bodies
- DDX : PBC
  Sarcoidosis
  Tuberculosis
  Infections
  Neoplasm
  Foreign Material
  Immunological Dis.



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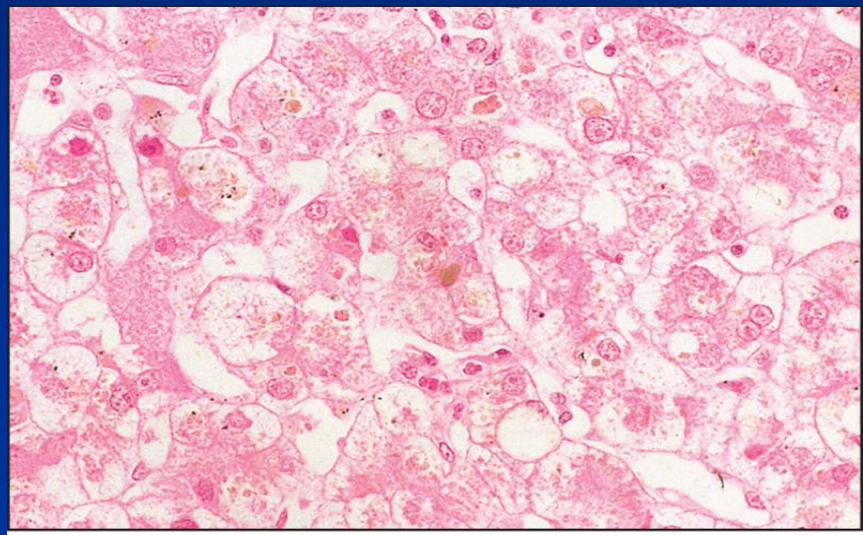

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Granulomatous Injury

Incriminated Drugs

Table 14.12 Drugs that can lead to hepatic granulomas

- Acetylsalicylic acid
- Actiretin
- Allopurinol
- Amoxicillin-Clavulinate
- Aprindine
- Azapropazone
- Barium salts
- BCG
- Beryllium
- Carbamazepine
- Carbutamide
- Cephalexin
- Cephalosporin
- Chinidin
- Chlorpromazine
- Chlorpropamide
- Clavulanic acid
- Clometacin
- Contraceptive steroids
- Copper sulphate
- Dapsone
- Detajmium tartrate
- Diazepam
- Didanosine
- Diltiazem
- Dimethicone
- Diphenylhydantoin
- Disopyramide
- Feprazone
- Glibenclamide
- Glyburide
- Gold
- Green-lipped mussel (Seatone)
- Halogenated Hydrocarbons
- Halothane
- Hydralazine
- Imipramine
- Interferon
- Isoniazid
- Mestranol
- Metahydrin
- Methimazole
- Methotrexate
- Methyldopa
- Metolaxone
- Metolazone
- Mineral oil
- Nitrofurantoin
- Nomifensine
- Norethindrone
- Norethynodrel
- Norgestrel
- Oral contraceptives
- Oxacillin
- Oxyphenbutazone
- Oxyphenisatin
- Papaverine
- Paracetamol
- Penicillin
- Phenazone
- Phenothiazines
- Phenprocoumon
- Phenylbutazone
- Phenytoin
- Polyvinyl pyrrolidone
- Prajmalium
- Probenecid
- Procainamide
- Procarbazine
- Pronestyl
- Quinidine
- Quinine
- Ranitidine
- Salicylazosulfapyridine
- Silica
- Succinylsulphathiazole
- Sulphadiazine
- Sulphadimethoxine
- Sulphadoxine-pyrimethamine
- Sulphanilamide
- Sulphasalazine
- Sulphathiazole
- Sulphonamides
- Sulphonylurea
- Tacrine
- Thorotrast
- Tocainide
- Tolbutamide
- Trichlormethiazide
- Trimethoprim-Sulphamethoxazole
- Verapamil

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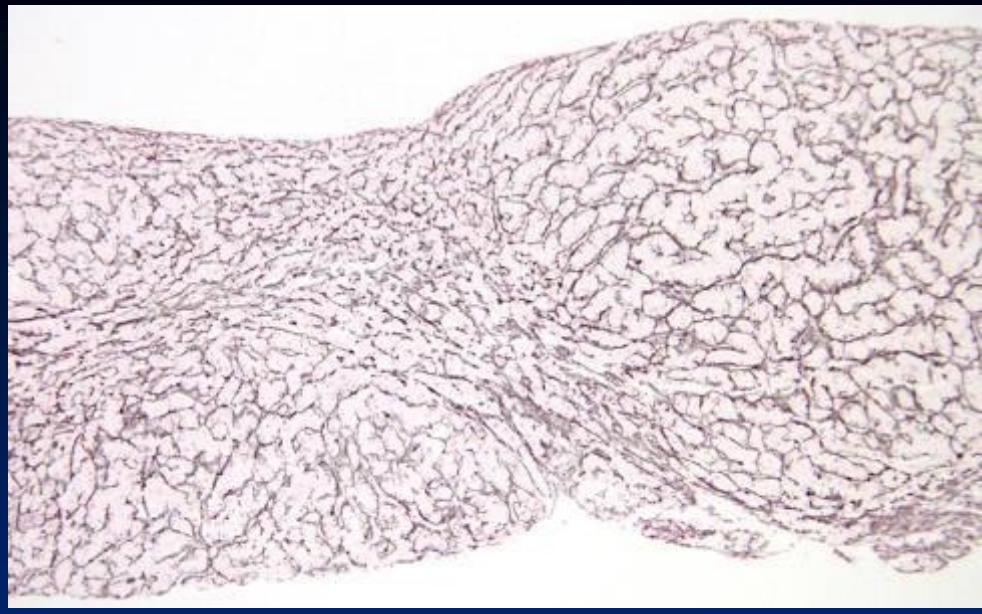
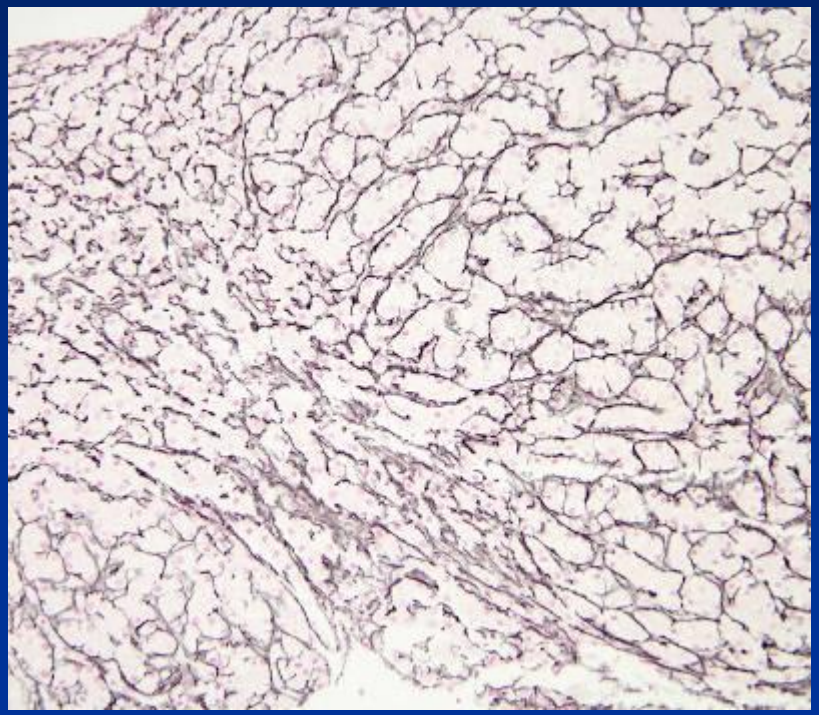
Vascular- NRH

(6-Mercaptopurine injury)

- Nodular regeneration without significant fibrosis or inflammation
- Hepato-portal sclerosis, collagen-vascular diseases
- Chemotherapeutic agents, Purine analogue immunosupressants





Clinical Evaluation of DILI

- Focused on characterizing injury biochemically and eliminating other causes of liver disease
- Thorough drug history, including herbals, environmental exposures, dose and duration
- Viral serology and molecular tests
  - HAV, HBV, HCV, EBV, Herpes, Adenovirus
- Autoimmune serologies
  - ANA, AMA, ASMA, Anti-LKM, etc.
- Iron studies, thyroid studies, ceruloplasmin

Biochemical Characterization

- Most of the DILI literature is organized by the biochemical presentation of injury
- ALT and AP are taken from the first point that they were noted to be abnormal (ALT > 5x ULN, AP > 2x ULN)
- Ratio of ALT to AP normalized by the ULN

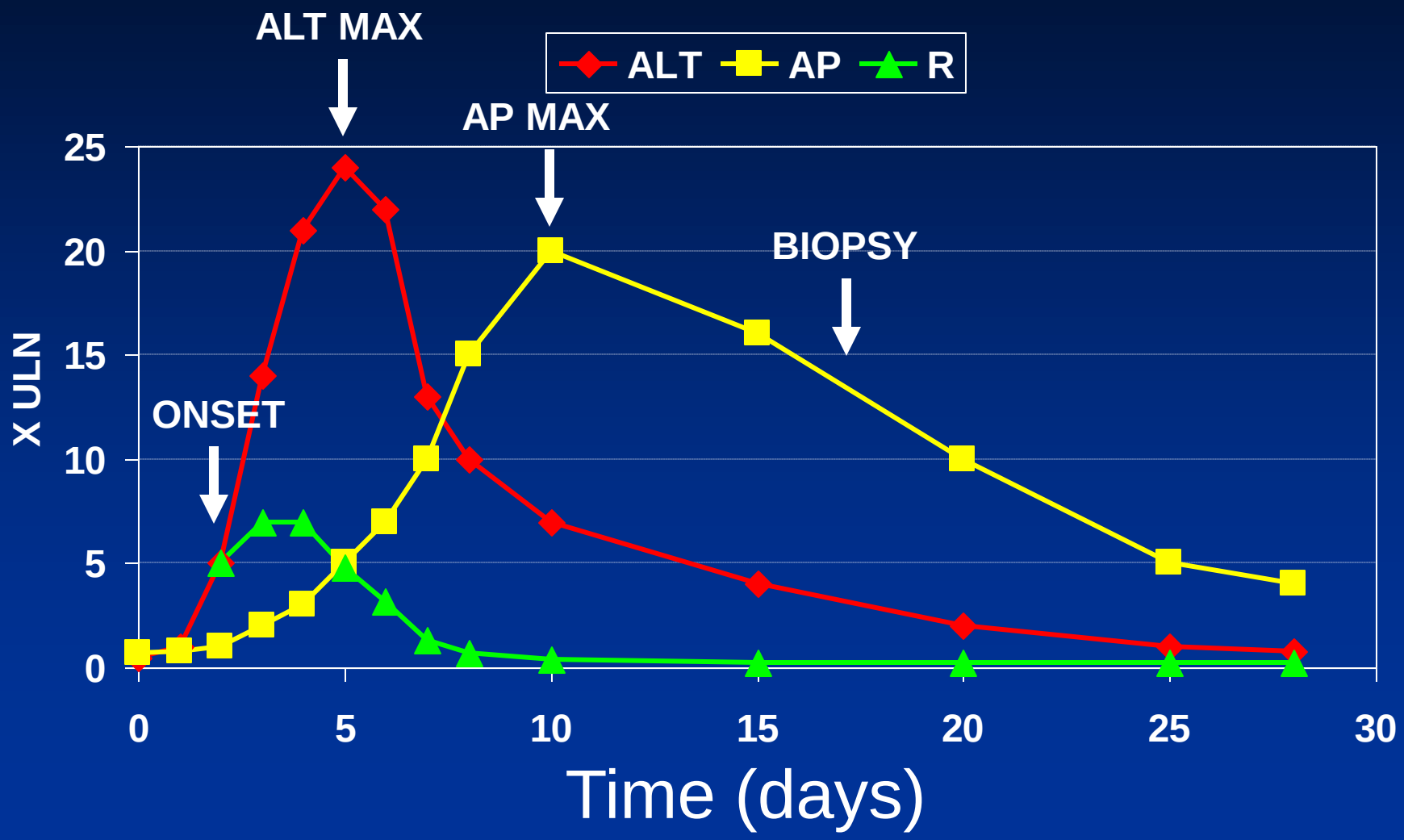
R= (ALT/ULN)/ (AP/ULN)

R >= 5: Hepatocellular Injury

2 <= R < 5: Mixed Hepatocellular/Cholestatic Injury

R < 2: Cholestatic Injury

Biochemical Injury Class May Vary As Injury Evolves



Practical Evaluation of Drug Toxicity for the Pathologist

Irey's Methodology

Temporal eligibility

Exclusion of other drugs, toxins, diseases

Known potential for injury

Precedent for injury pattern

De-challenge/Re-challenge

Toxicologic analysis

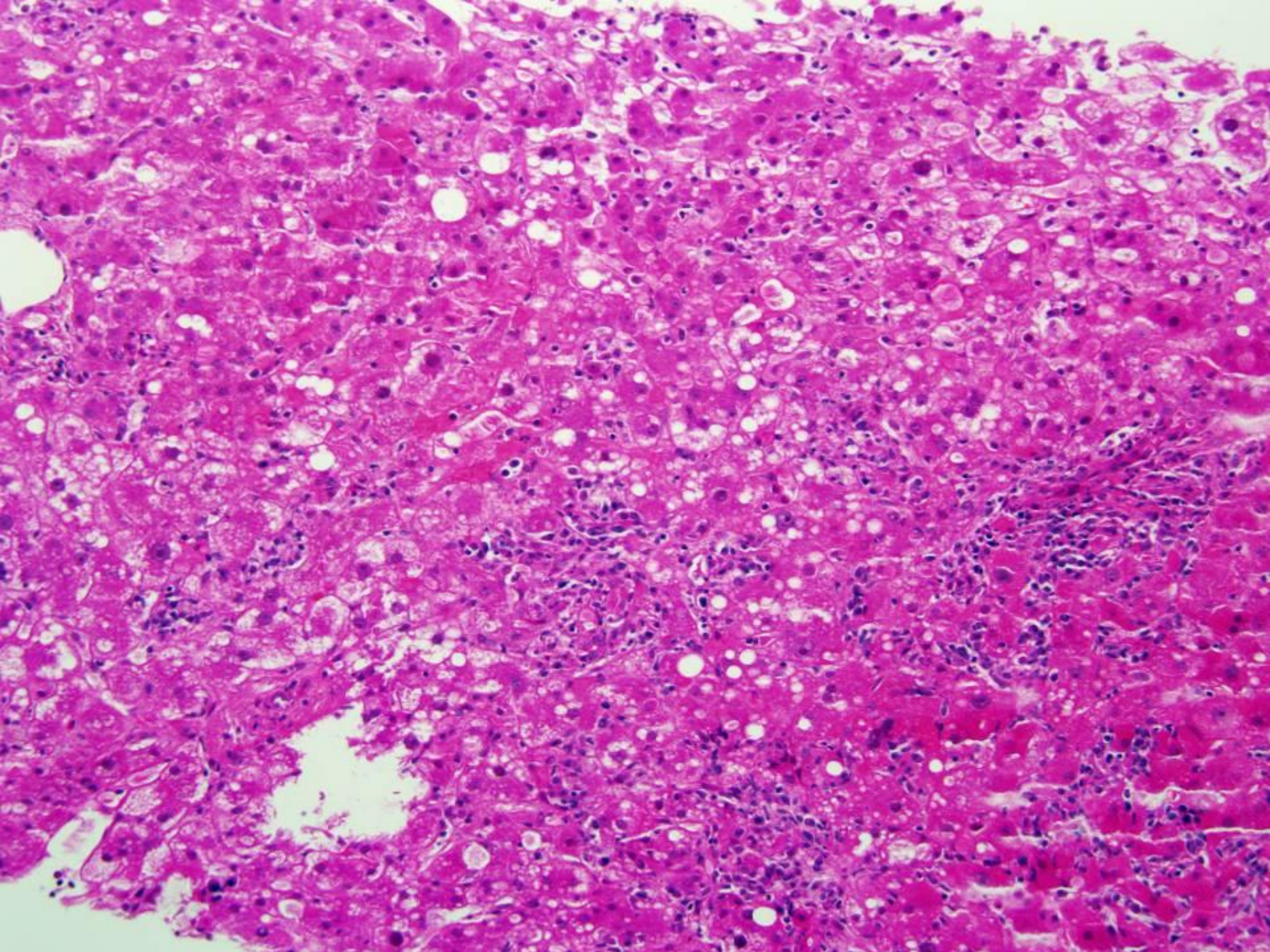
Categorization of Drug Toxicity (DILIN)

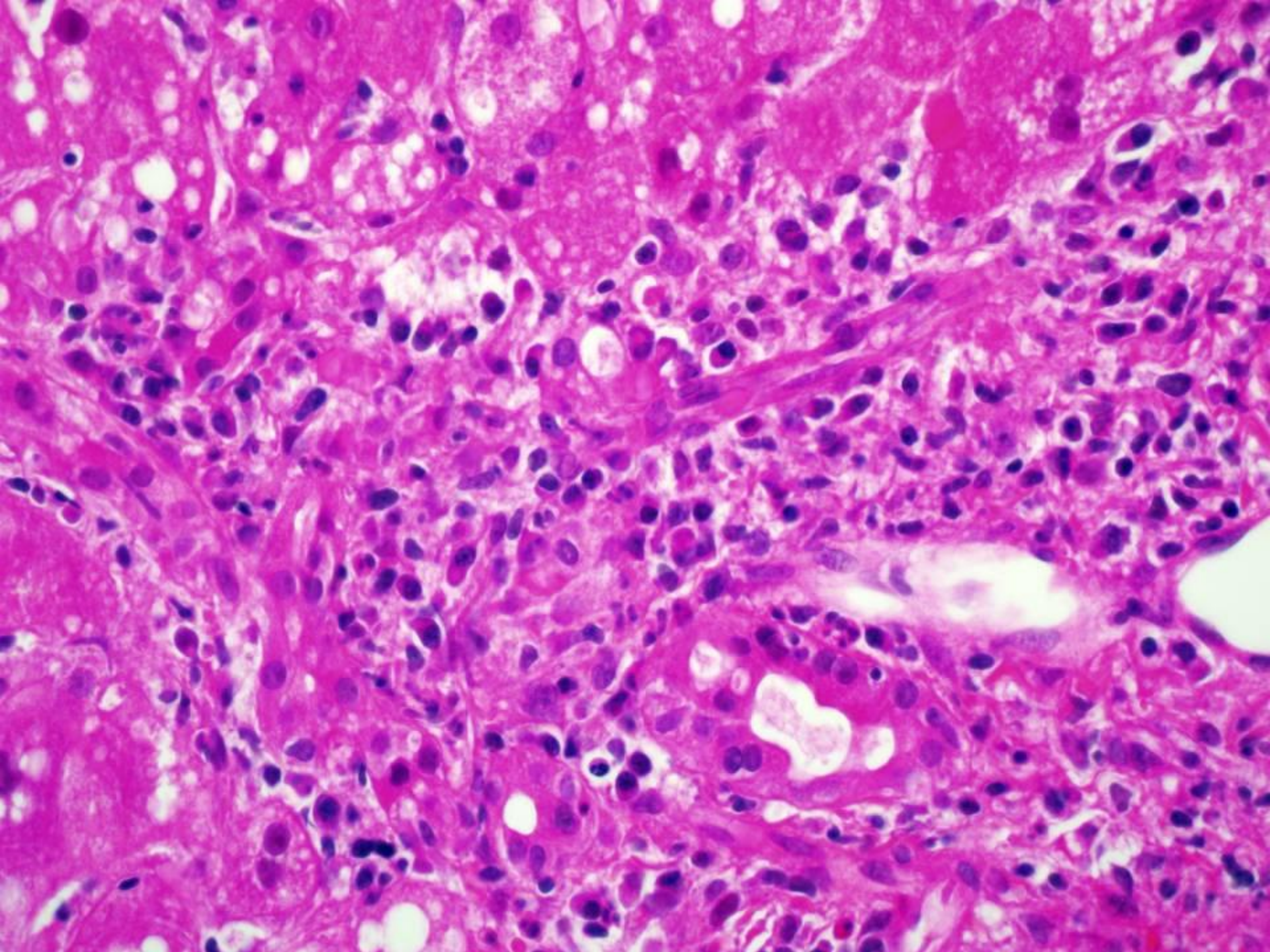
- **Definite** - >95% chance – all competing causes excluded, typical injury pattern for agent, positive rechallenge (if attempted)
- **Very Likely** - 75-95% chance – most other possibilities excluded, but typical injury pattern unknown
- **Probable** - 50-75% chance – competing causes unlikely but cannot be fully excluded
- **Possible** - 25-50% chance – other etiologies possible and cannot be excluded
- **Not DILI** - <25% chance - other etiology identified, pattern doesn't match agent

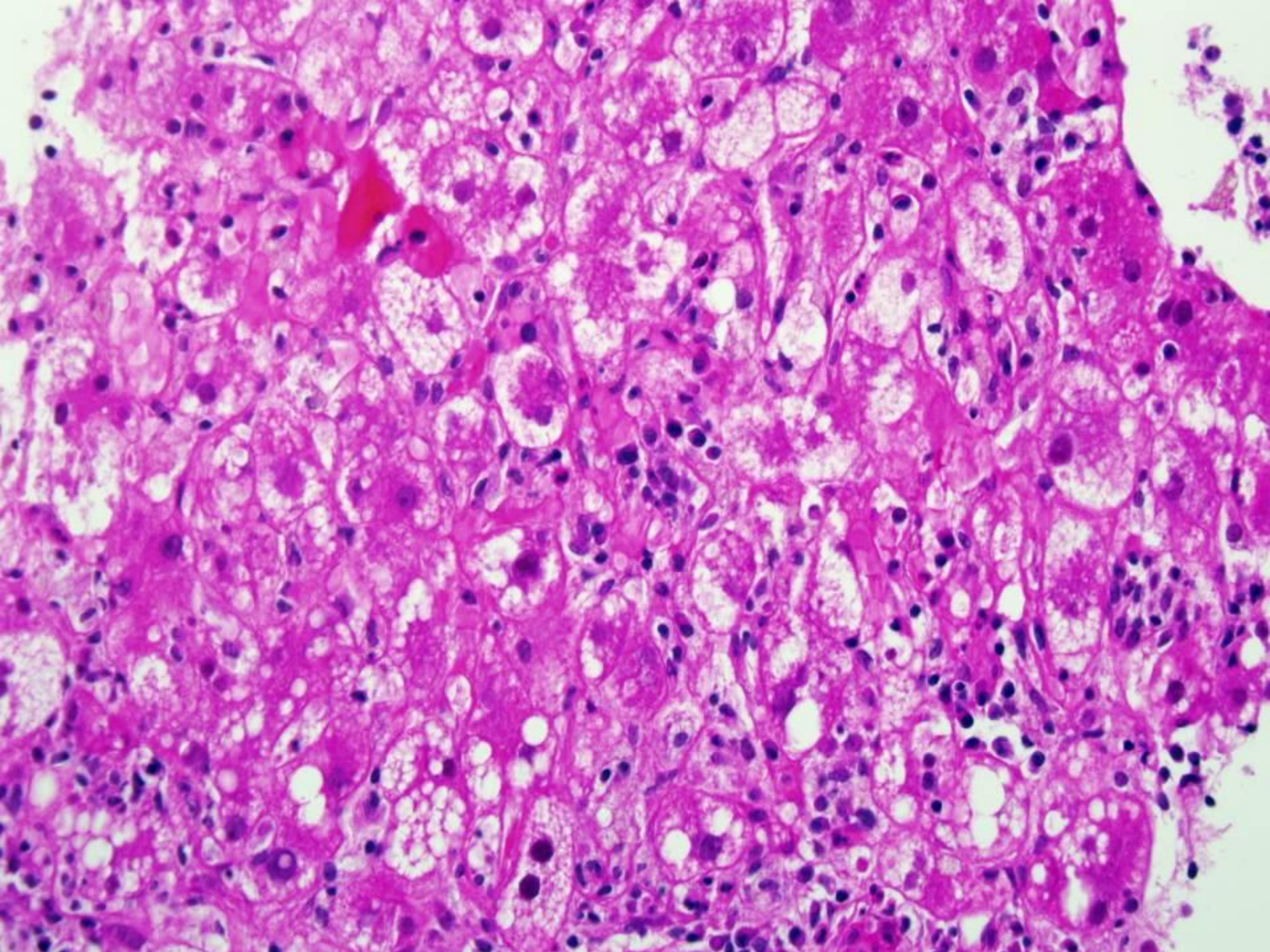
Some Practical Applications

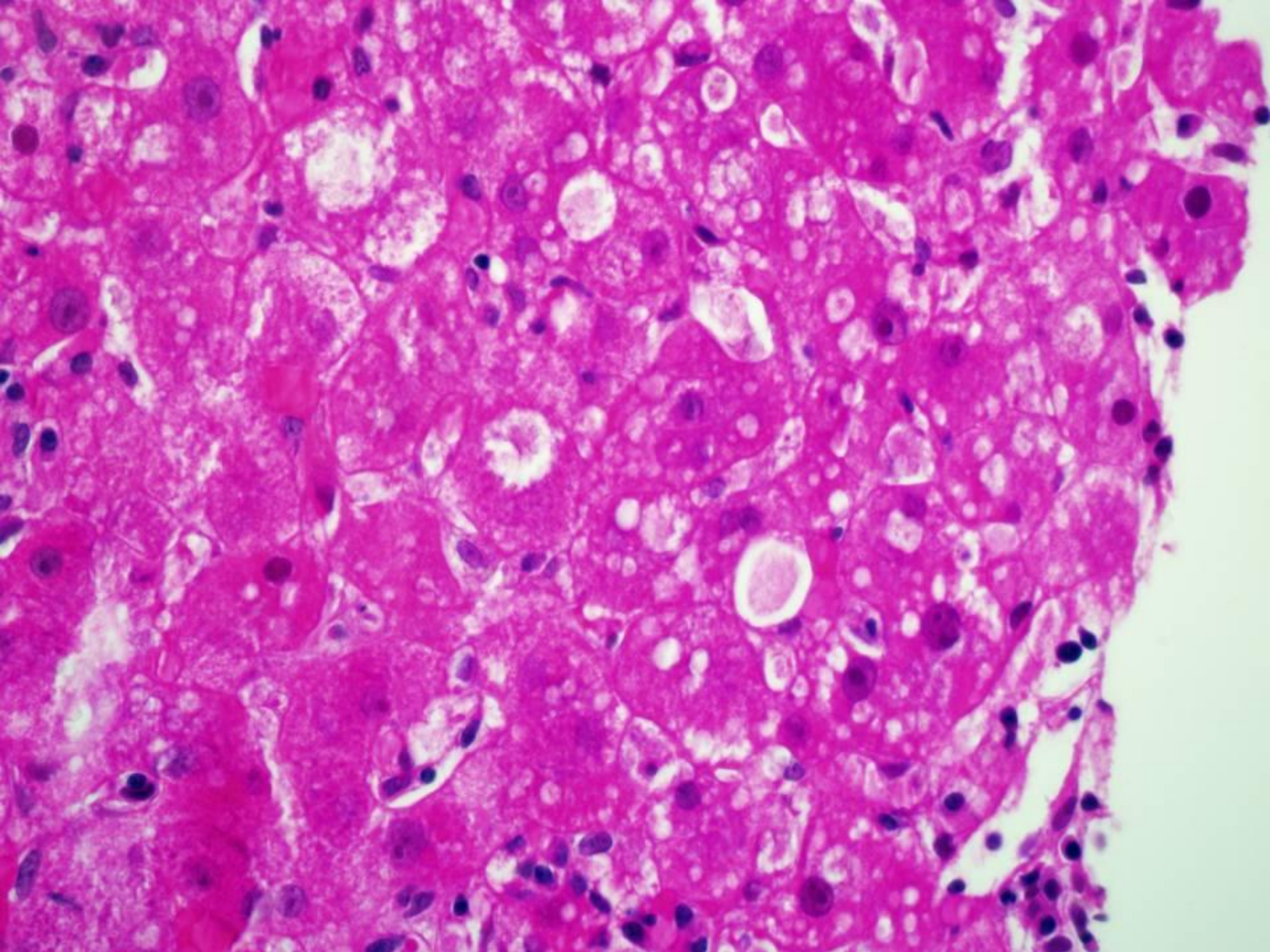
DILI Example # 1

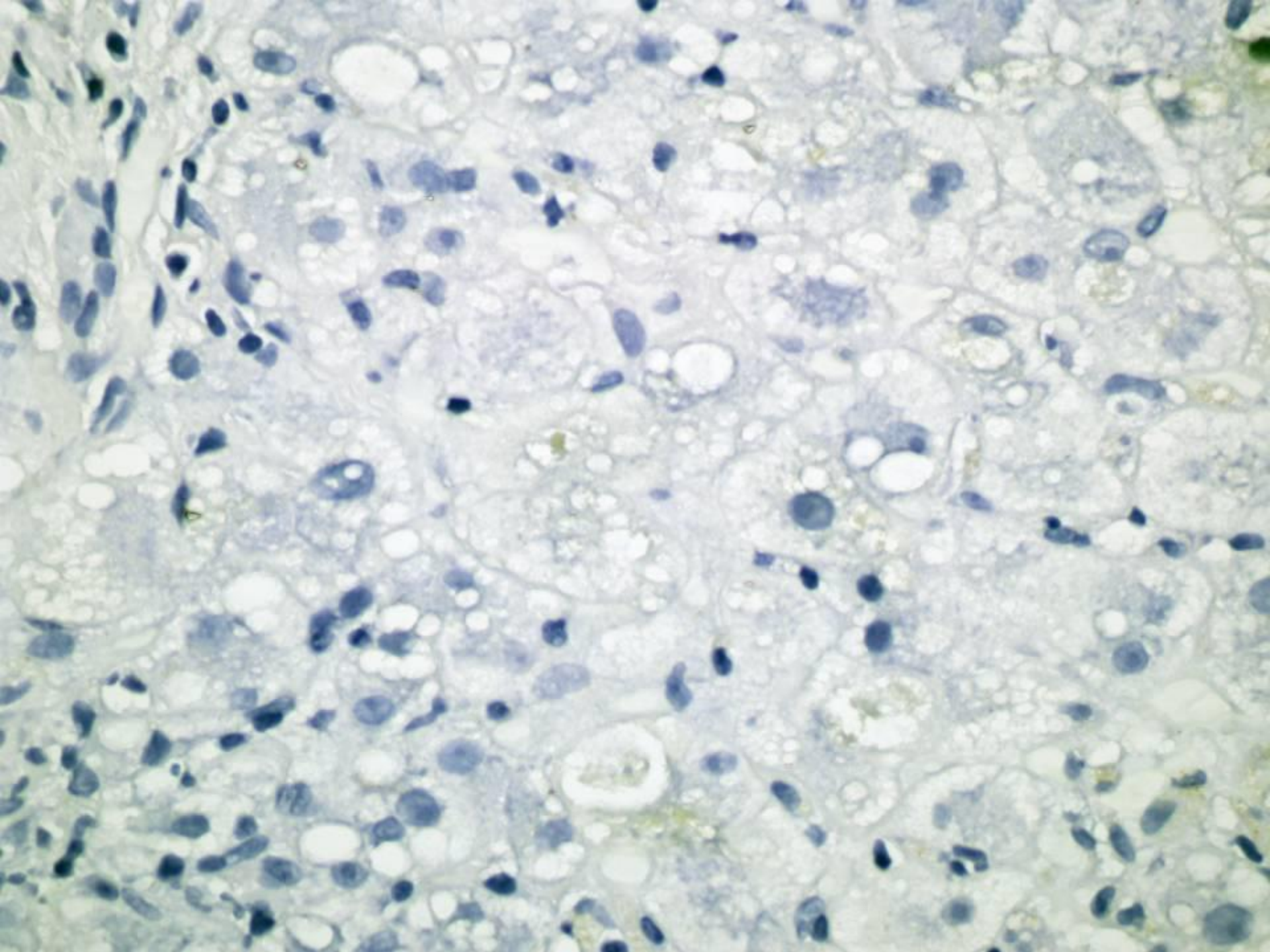
- 82 yr old man with DM and GERD
- Presents with 3 wk hx of epigastric pain and nausea
- Jaundiced on physical exam
- ALT 1737, AST 1919, AP 260, tBili 5.3
- Neg for Hep A, B, C and ANA, ASMA weakly positive
- Abd CT neg for gallstones, biliary dilation
- Medications
  - Simvastatin (4 months)
  - Metformin (years)
  - Bupropion (years)
  - Escitalopram (4 days)
- All medications were stopped

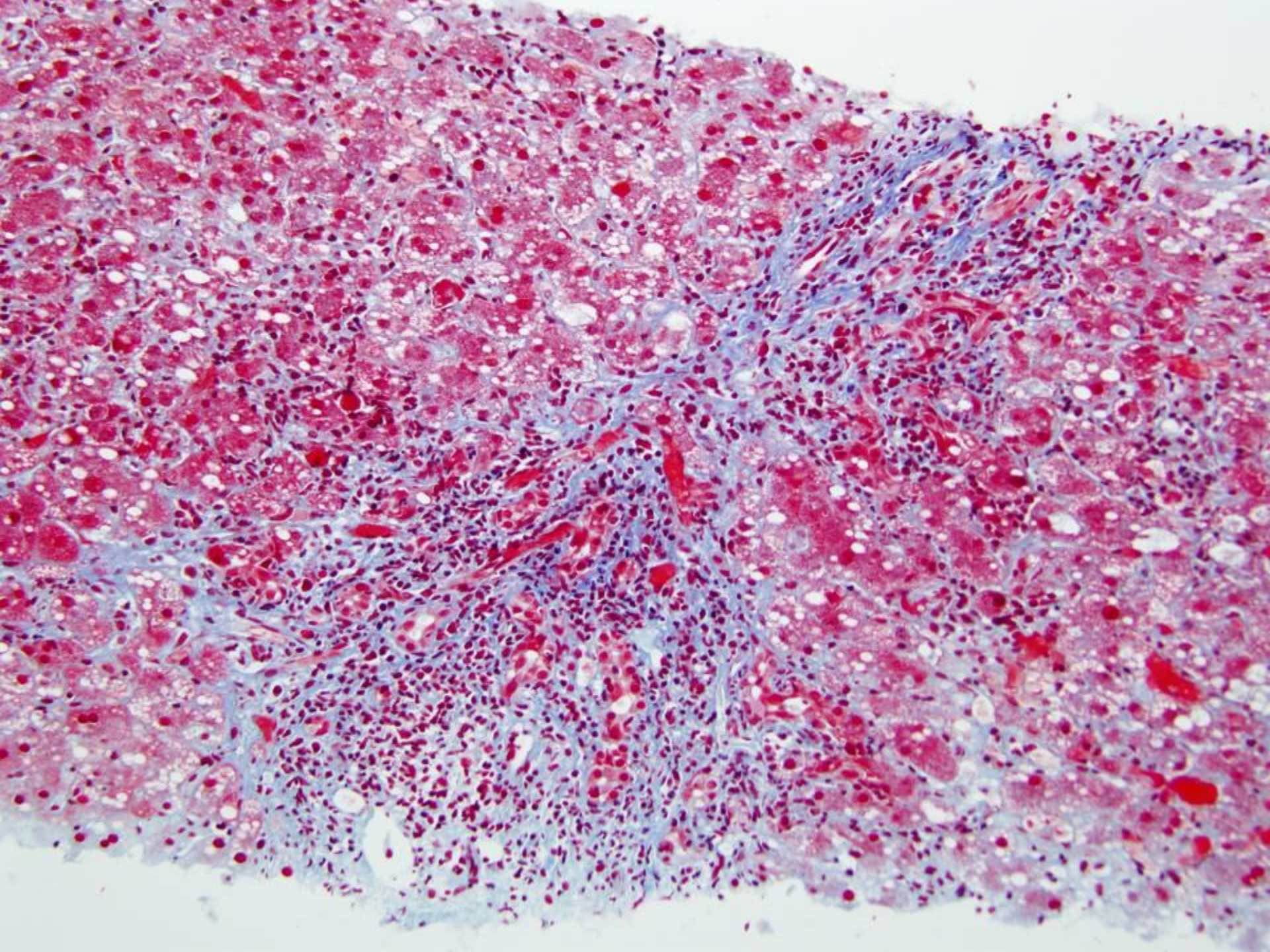












Pathology Evaluation

- Overall pattern – Cholestatic hepatitis, combining features of acute hepatitis with prominent hepatocellular and canalicular cholestasis
- Probable underlying fatty liver disease related to the patient's diabetes
- Degree of injury – moderate necroinflammation, marked cholestasis, early portal fibrotic expansion

Statin-Associated Liver Injury

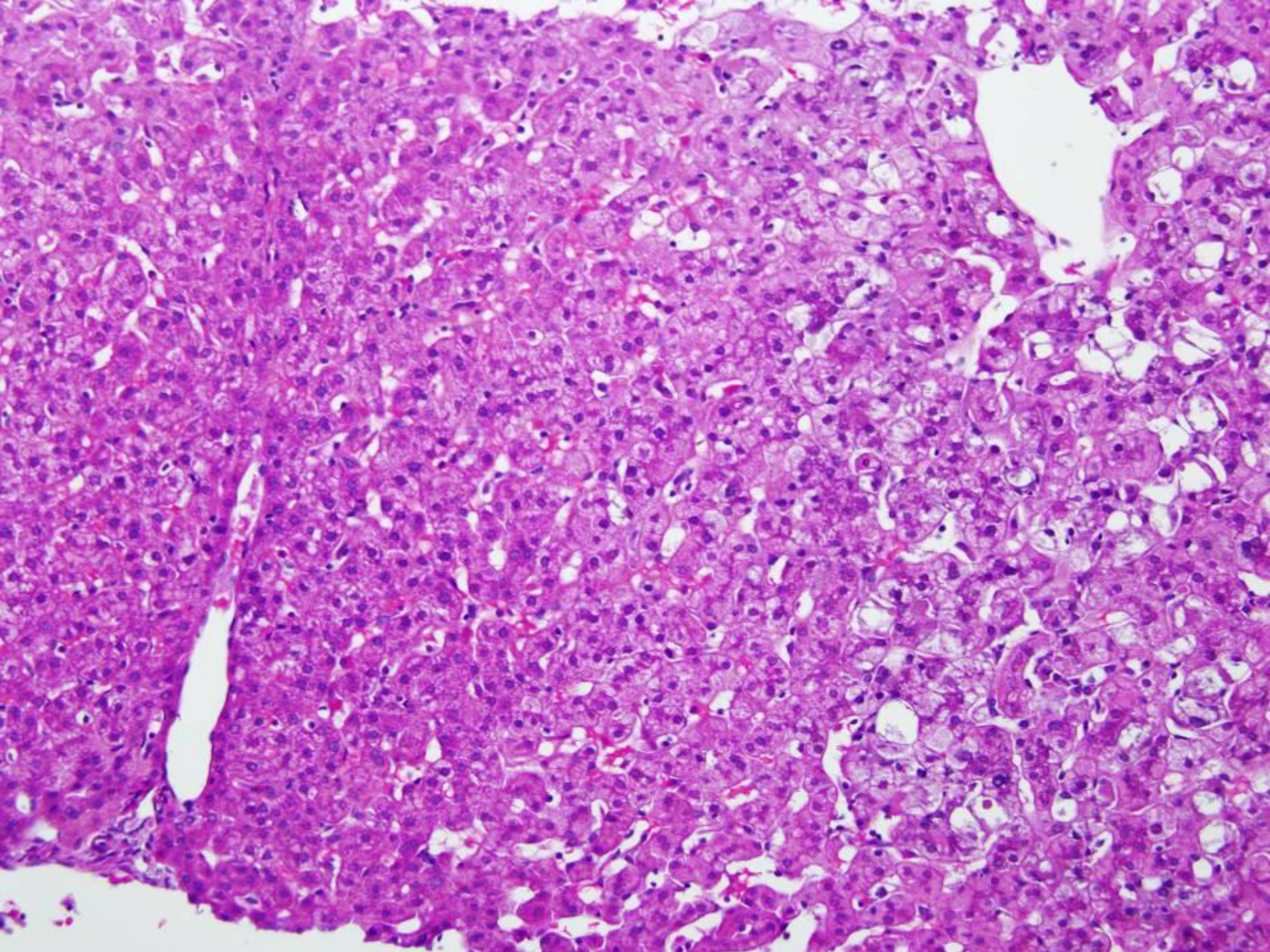
- Low (0.5-2%) incidence of ALT elevations >3x ULN in clinical trials – asymptomatic and generally of little concern
- Statins can be used safely in the presence of chronic liver dx such as NAFLD
- Rare reports of serious hepatotoxicity
  - Acute cholestatic hepatitis
    - Usually develops after 3-4 months of therapy
    - Serum chemistries show hepatocellular jaundice
  - Autoimmune hepatitis pattern, may be a triggering effect of statins, since the hepatitis may persist
    - Usually ANA positive, also ASMA, anti-histone Ab
    - Biopsies show autoimmune hepatitis pattern

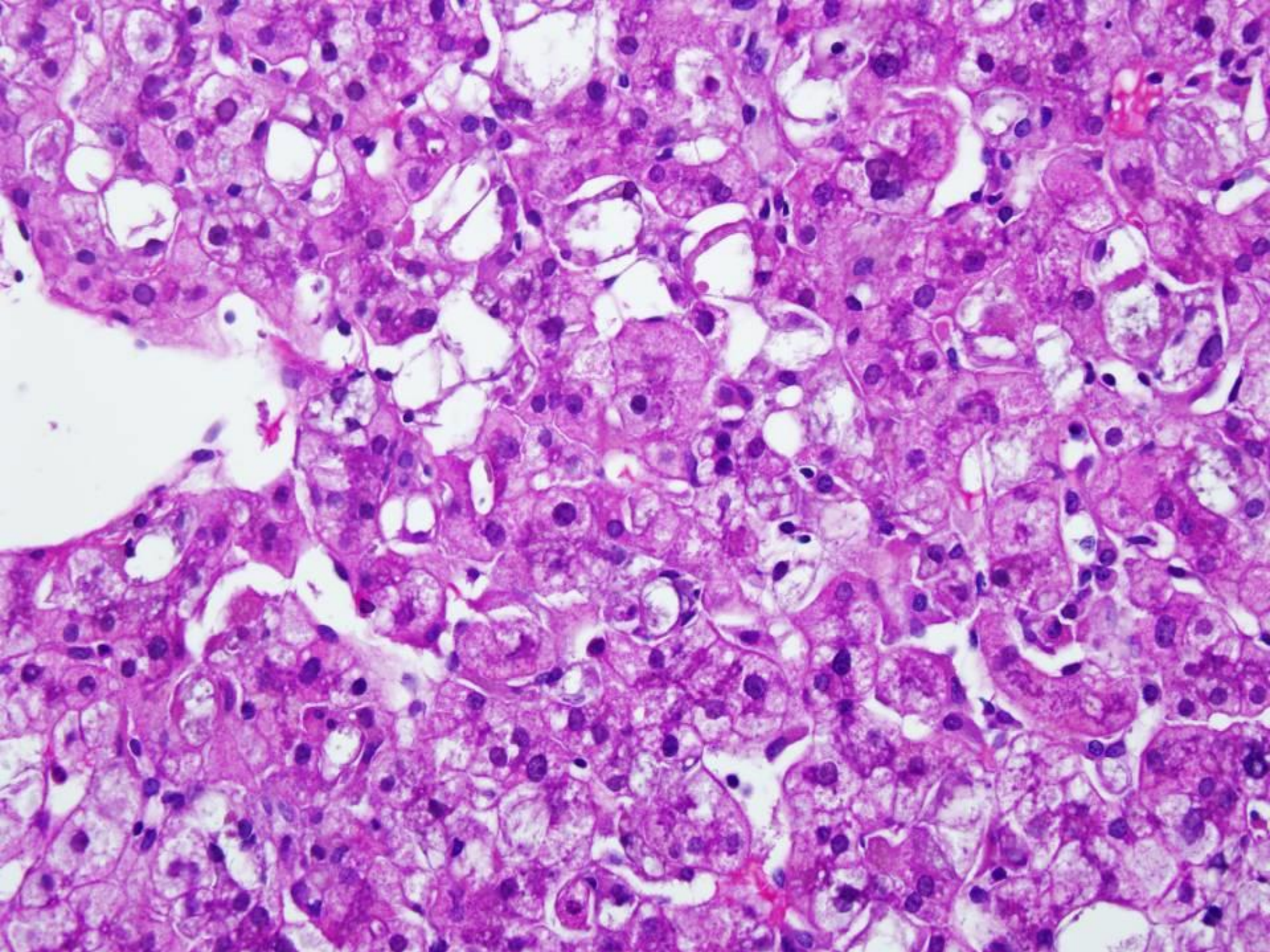
Evaluation of Toxicity – Case 1

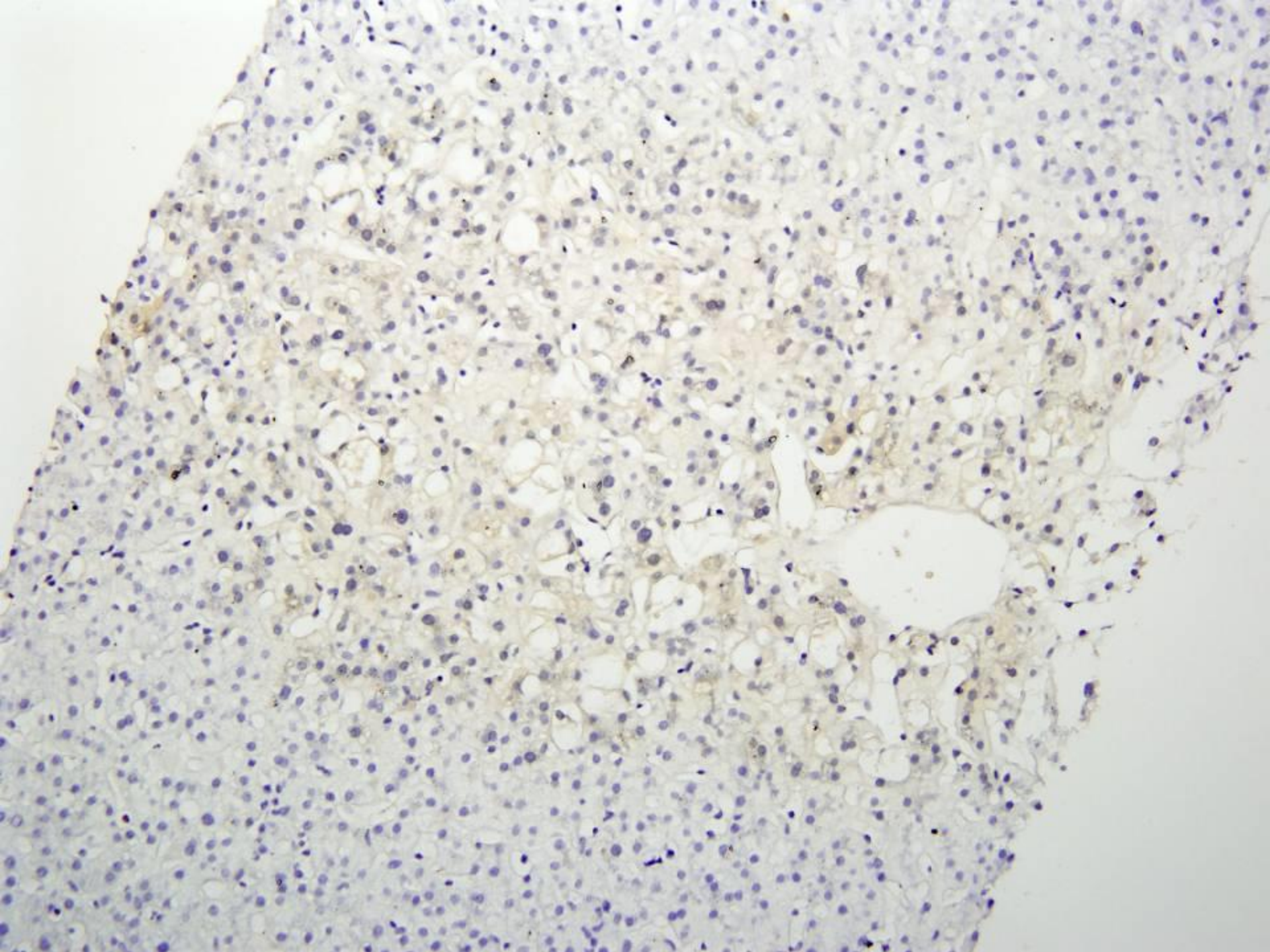
- **Temporal eligibility** – 4 months of statin therapy is median for injury cases. Metformin, bupropion and escitalpram also rarely cause DILI, with lag time of 1-3 months, wrong for this case
- **Exclusions** – Viral and autoimmune hepatitis, obstruction excluded, other drugs less likely
- **Known potential** – Rare, but well documented reports of hepatocellular jaundice due to statins
- **Precedent** - Biopsies of statin-induced injury have shown cholestatic hepatitis in multiple reports
- **De-challenge/Re-challenge** - Biochemical evidence of injury resolved over the next six weeks after stopping medication
- **Toxicology** – Not performed
- **Conclusion** – DILI very likely due to simvastatin

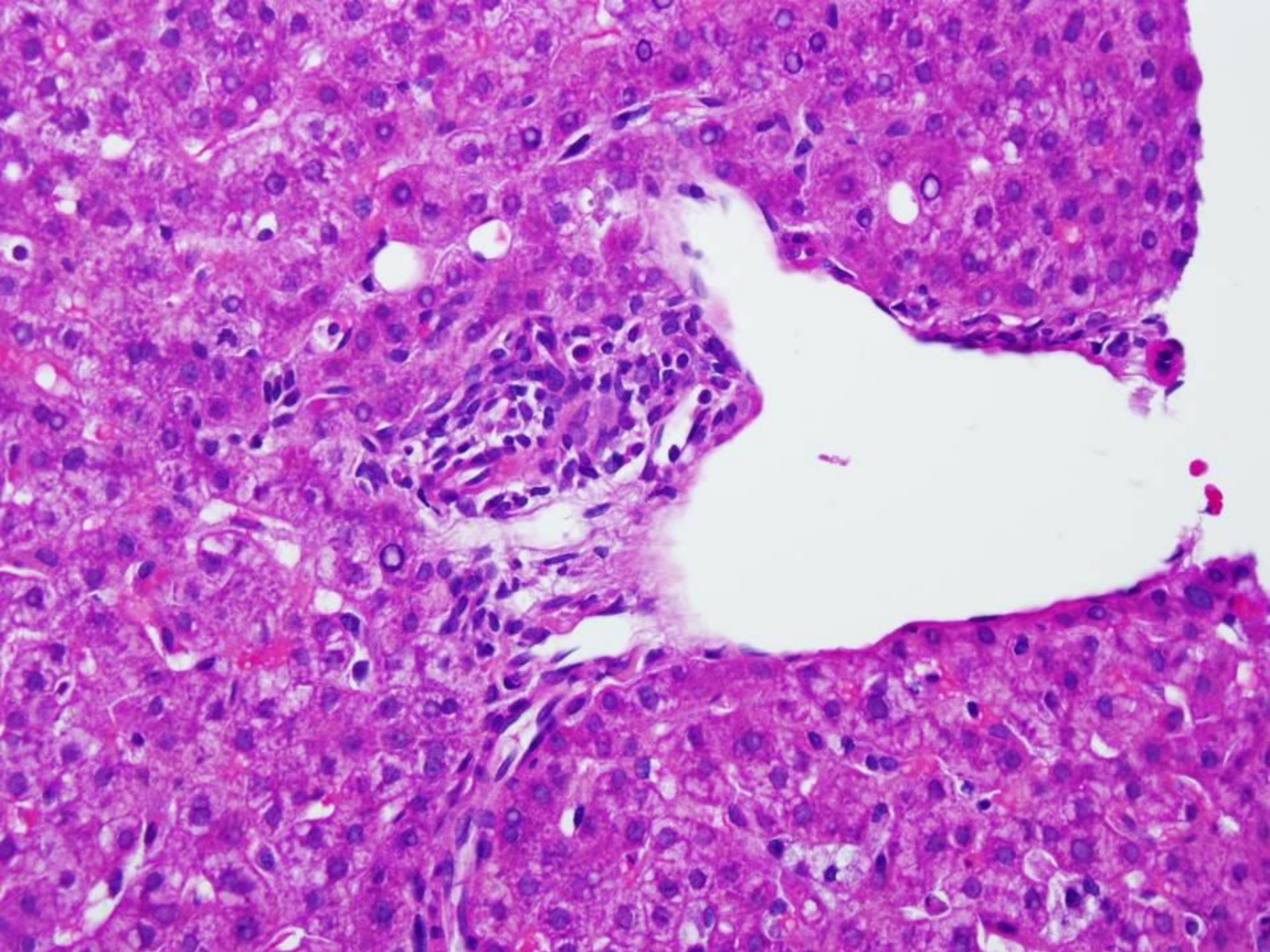
DILI Case Example # 2

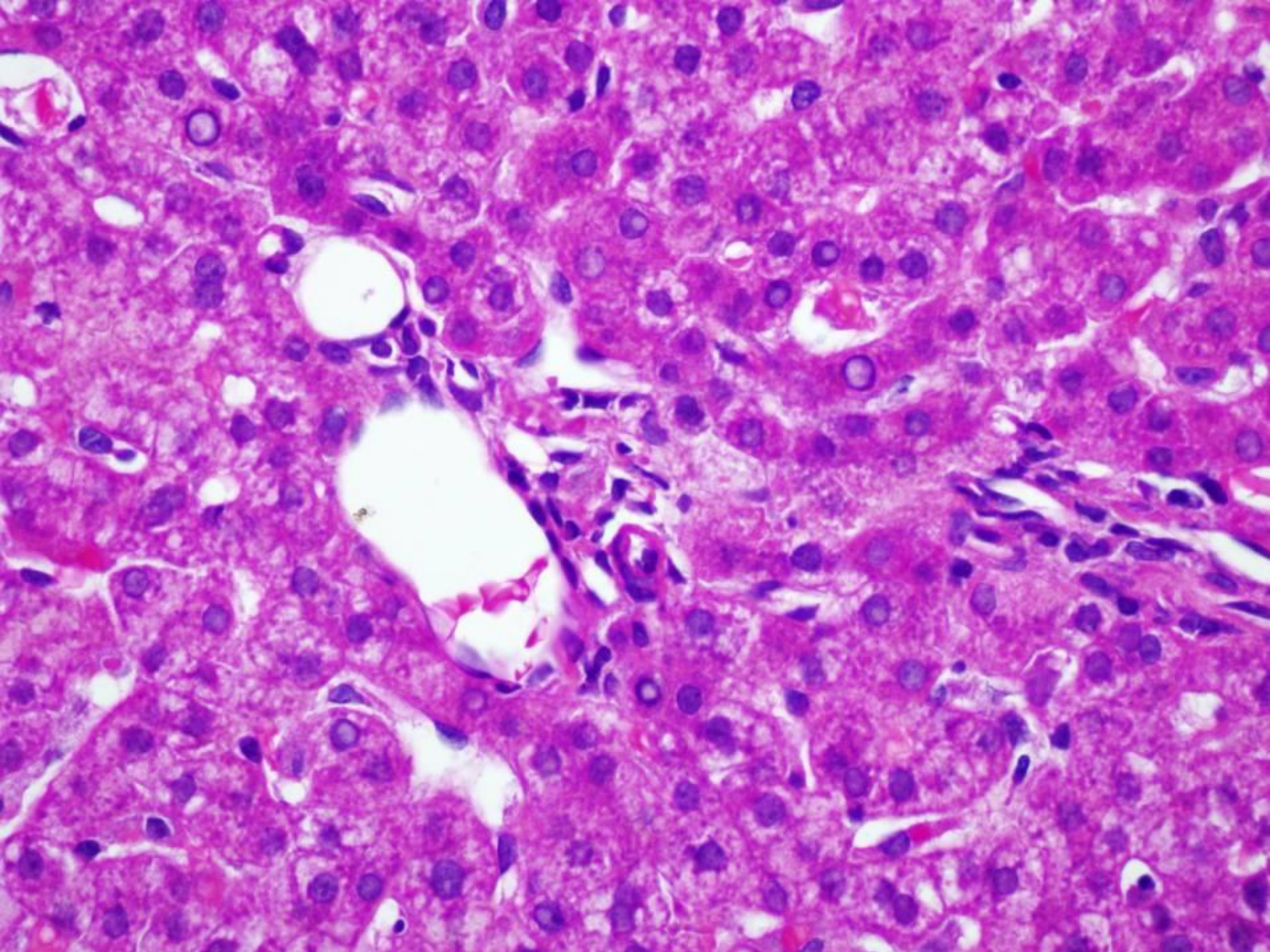
- 10 y.o. girl developed a punctate rash over chest, trunk and neck 7 weeks after 5 day course of azithromycin
- Over next week developed cough, fever and sore throat – she was given cephtriaxone in ER and another 5 day course of azithromycin from which she took 2 doses
- Rash worsened, involving oral and conjuctival mucosa, admitted to hospital
- ALT 411, AST 376, AP 460, tBili 3.4
- Abd U/S normal, viral and autoantibody serologies negative
- Skin biopsy confirmed Steven-Johnson syndrome
- Liver biopsy performed











Pathology Evaluation

- Overall pattern – Bile ductopenia (vanishing bile duct syndrome), one 1 of 18 portal areas had ducts
- Features of chronic cholestasis (copper accumulation, pseudoxanthomatous change) not yet present, probably because injury is still in acute phase
- VBDS is a rare pattern of DILI, associated with many drugs, many of which more typically cause cholestatic hepatitis
- Duct paucity may also be the result of chronic liver disease (PBC, PSC, Sarcoidosis) or other immunologically mediated injuries (GVHD, transplant rejection, HIV infection)

Evaluation of Toxicity – Case 2

- **Temporal eligibility** – Latency of 2 months after taking azithromycin is longer than most reported cases, but within the 1 to 3 month window for immunoallergic reactions
- **Exclusions** – Viral and autoantibody studies were negative. Imaging did not identify an obstructive cause; other causes of ductopenia (PBC, PSC, hepatic sarcoidosis) excluded on biopsy and by clinical evaluation
- **Known potential** – Azithromycin is a rare cause of cholestatic hepatitis
- **Precedent** – One reported case of azithromycin associated ductopenia, which also involved Stevens-Johnson syndrome
- **Re-challenge/De-challenge** - With short course antibiotic therapy, the course is usually over by the time the symptoms begin. The patient was "rechallenged" with 2 doses of azithromycin after which her symptoms worsened. Consistent with a ductopenic injury her AP and bilirubin took 5 months to resolve and her transaminases remained abnormal a year later.
- **Toxicology** – Not done
- **Conclusion** – Vanishing bile duct syndrome probably due to azithromycin

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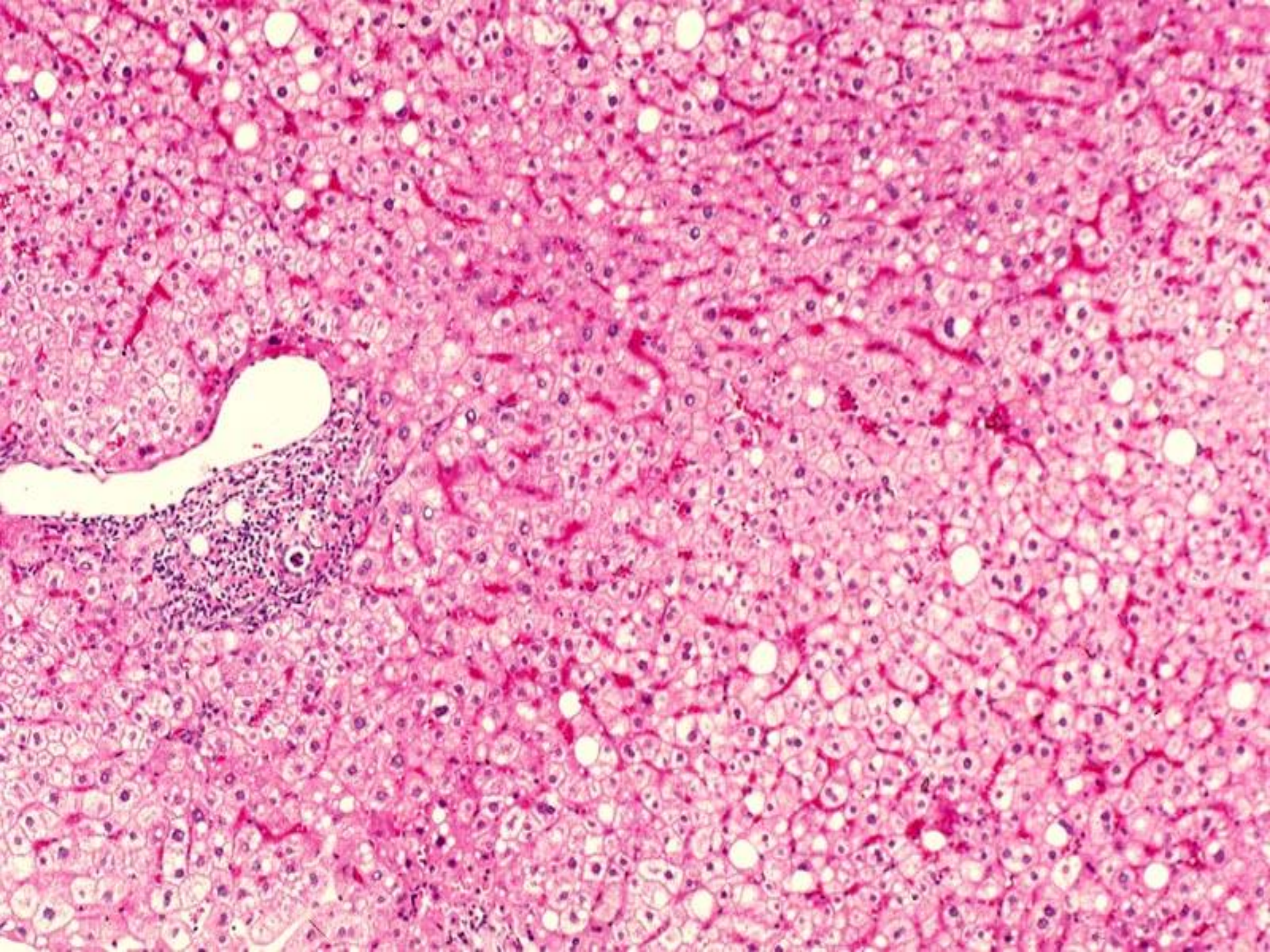
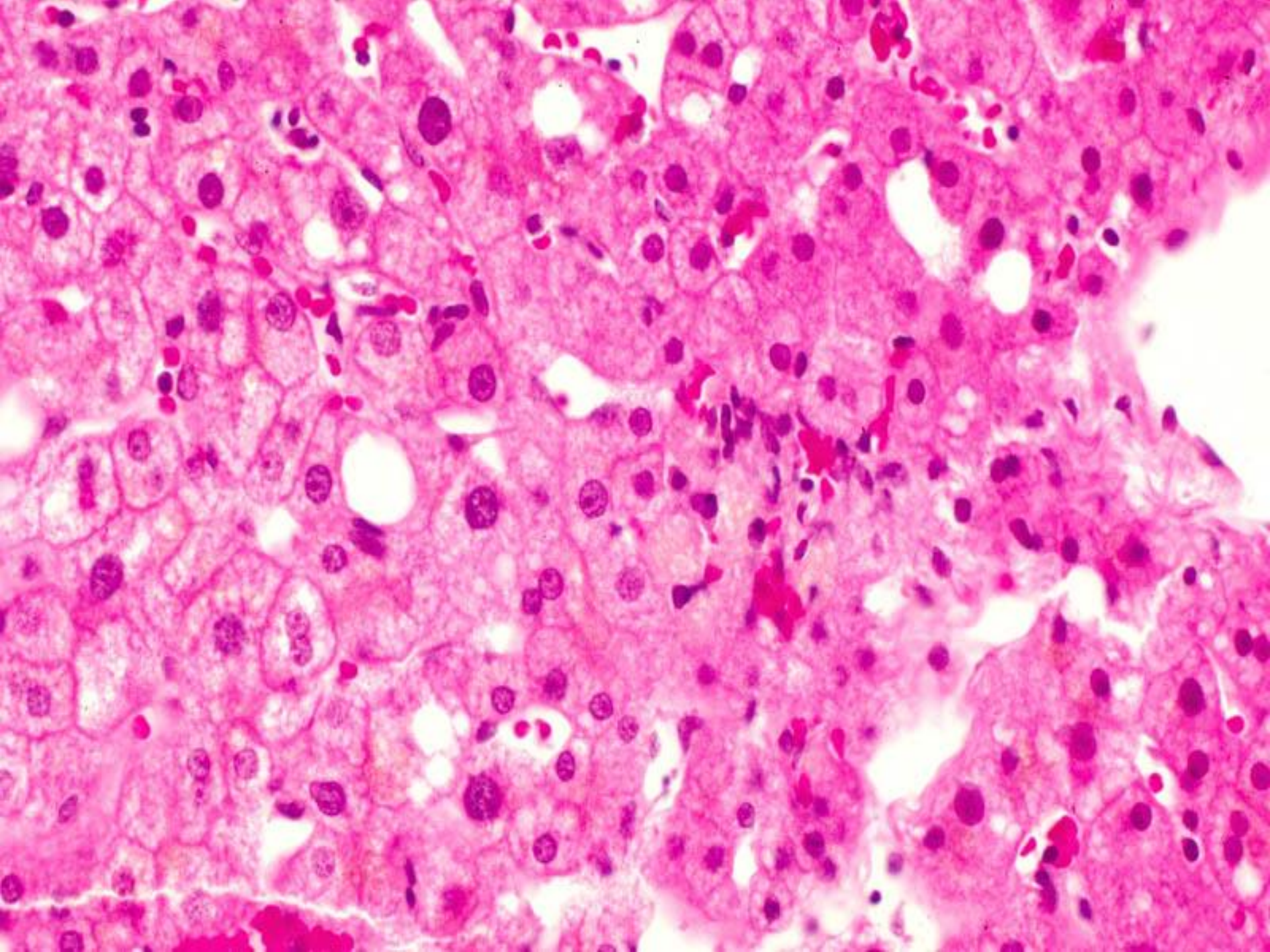
Case 3 57F

- Rheumatoid arthritis X 10 yrs
- Methotrexate X 3 yrs
  Total dose 2.34 gm
- No liver symptoms or signs
  Normal liver tests





Methotrexate

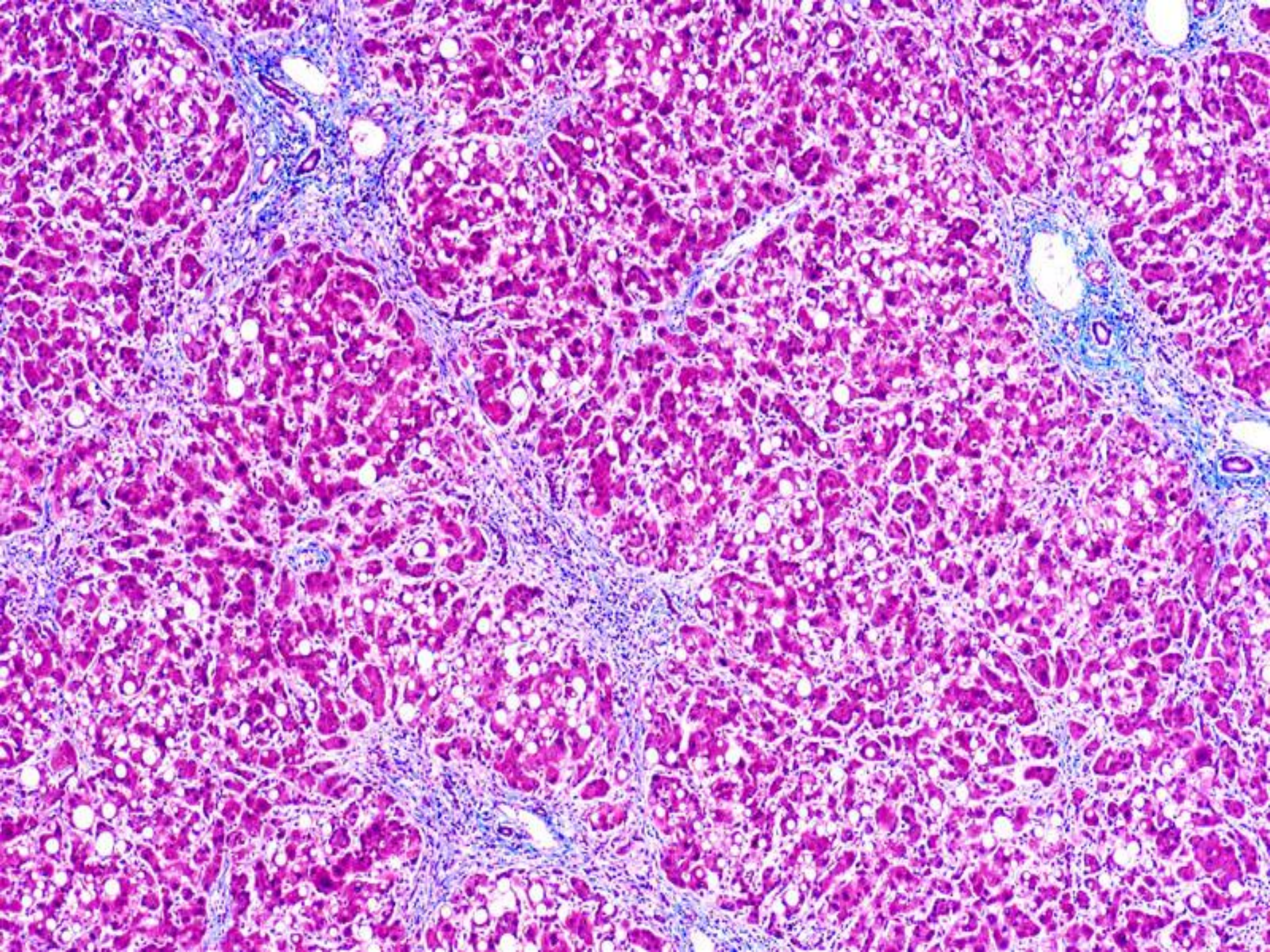
- Antimetabolite folic acid antagonist
- Leukemia, solid tumors
- Inflammatory diseases - psoriasis, rheumatoid arthritis, PBC
- Toxic to most tissues

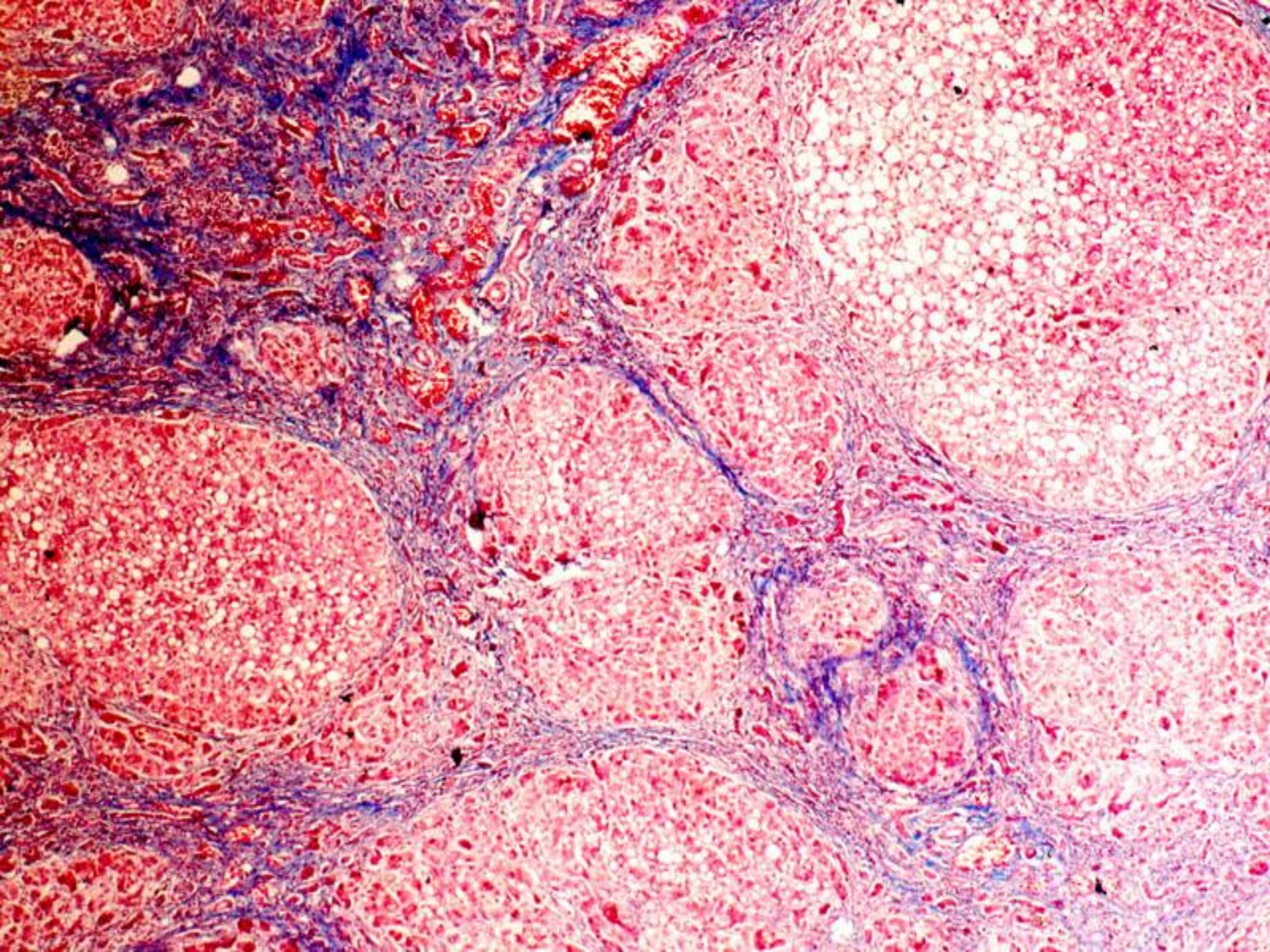
Methotrexate
Hepatotoxicity

- Threshold at 1500 mg & 2 years
- Increased susceptibility
  Daily doses
  Psoriasis
  Alcohol
  Renal failure
  Obesity/diabetes
- Progression in 27%
  Bridging fibrosis/cirrhosis in 5%

Methotrexate
Hepatotoxicity

- I - Fat, nuclear pleomorphism, mild inflammation
- II - Portal inflammation, fibrosis, focal parenchymal necrosis
- III A - Early fibrous septa
  B - Bridging fibrosis
- IV -Cirrhosis



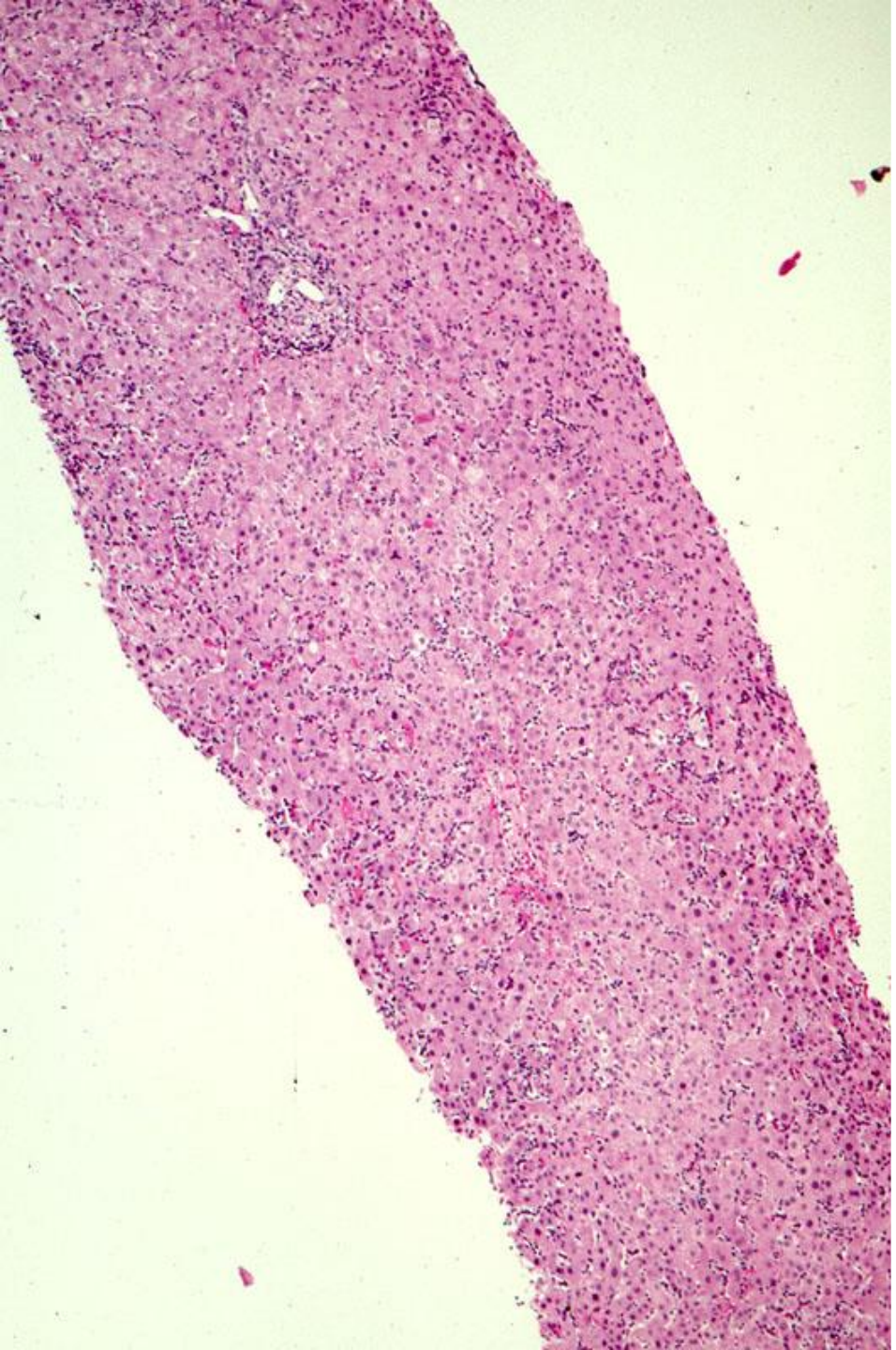


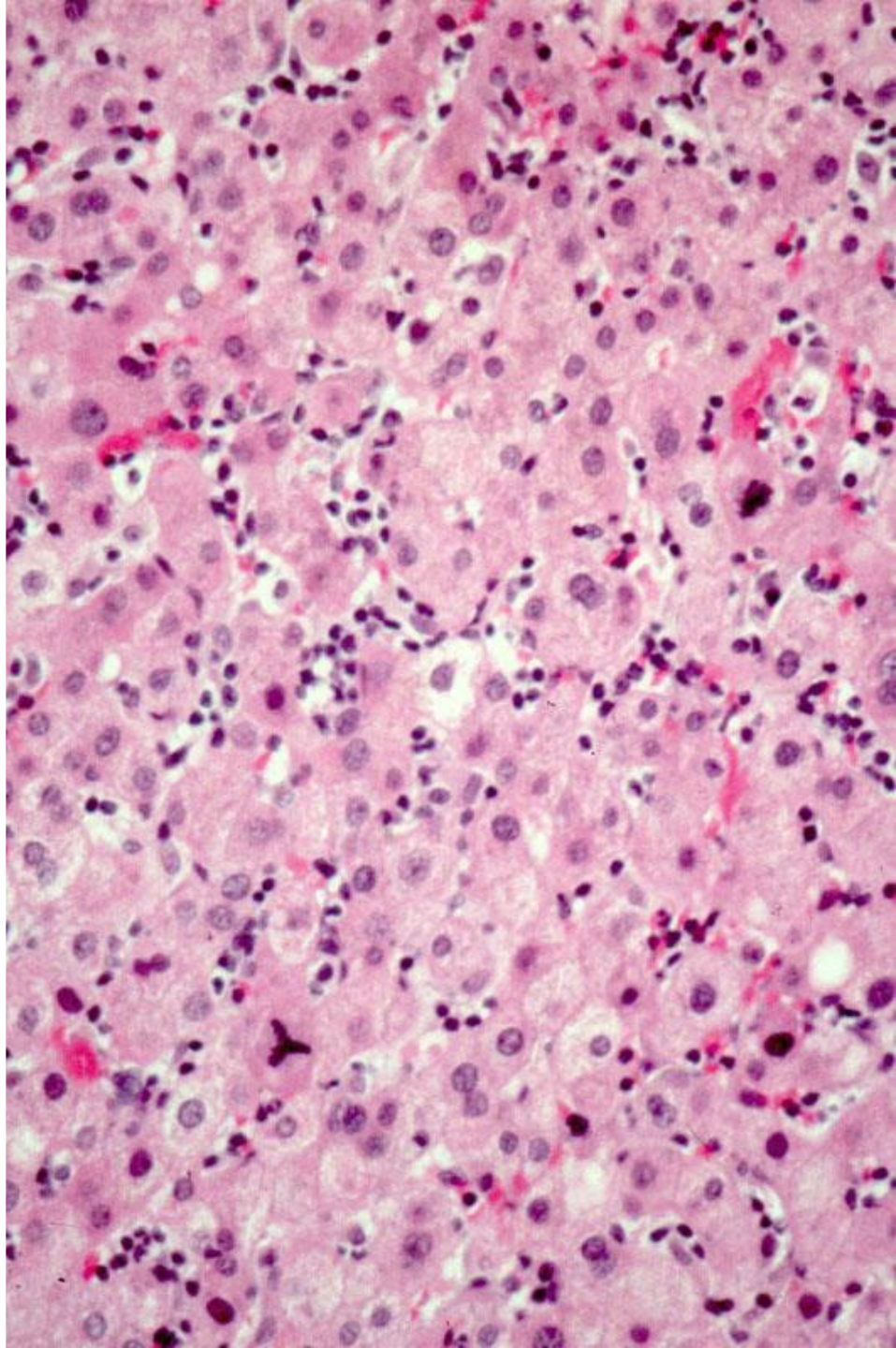
Case 3

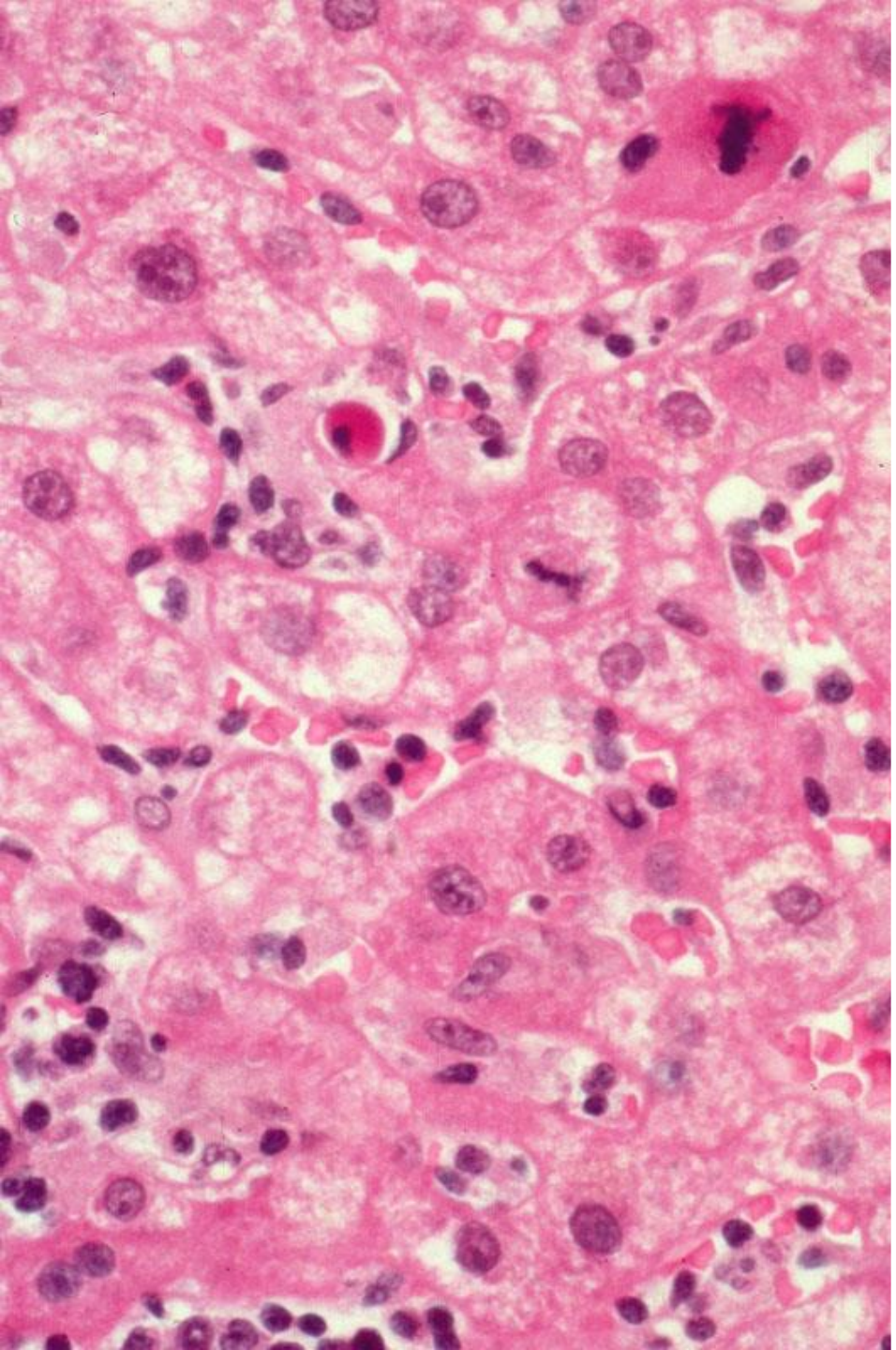
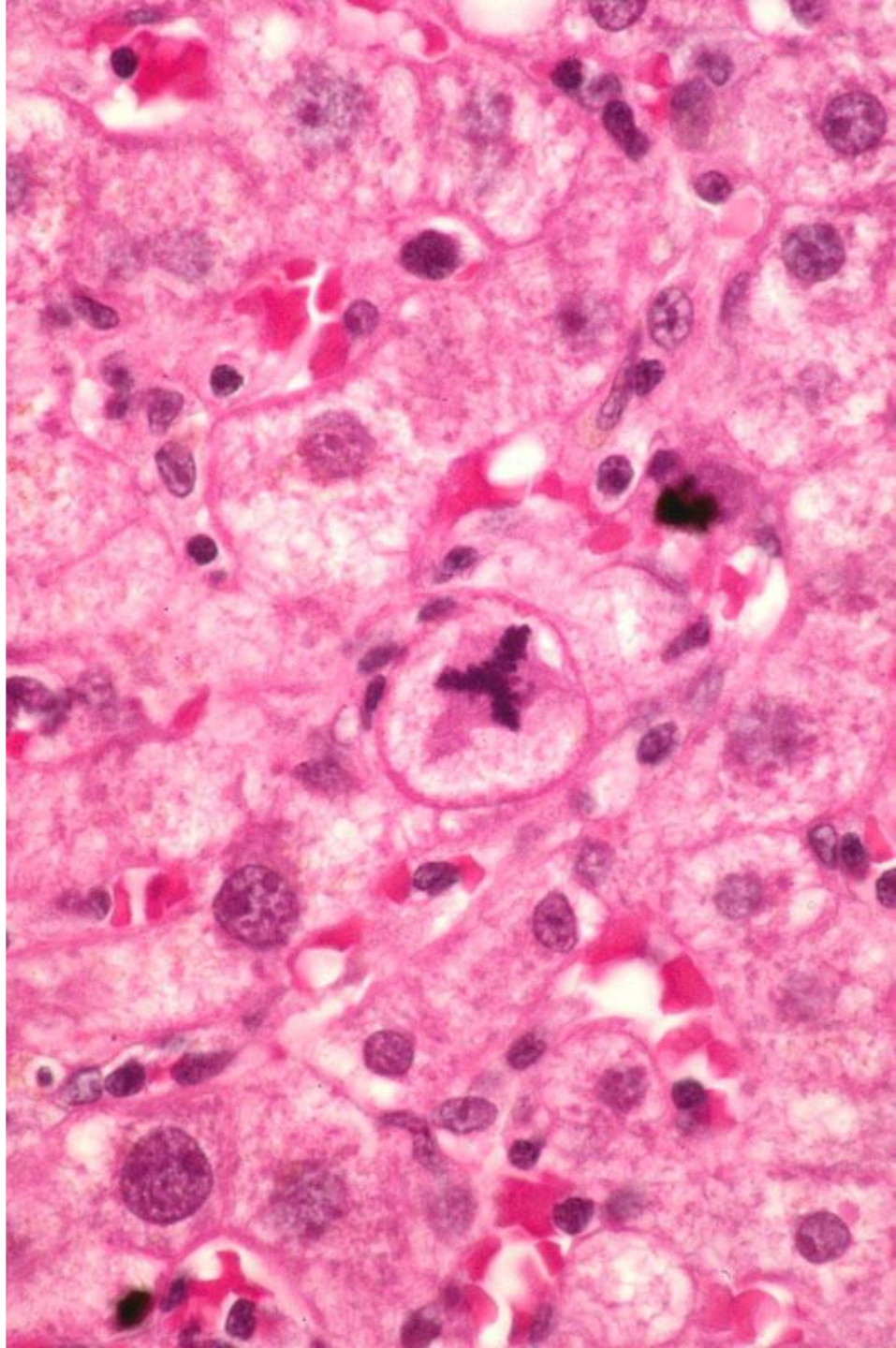
- Temporal eligibility - Latent period
  Analgesics, nonsteroidals - 10 yrs
  Methotrexate - 3 yrs
- Pattern of Injury - Nonspecific
  (fat & nuclear pleomorphism)
- Precedent - Methotrexate
- Conclusion - Trivial methotrexate injury

Case 4 31 M

- H/O seizures following head trauma
- Phenobarbital, carbamazepine X 1 yr
- Diphenylhydantoin (Dilantin) X 3 wks
- Fever, rash, eosinophilia, atyp lymphs
- AST 315 ALT 360 Bili 2.1
  HAV, HBV, monospot negative





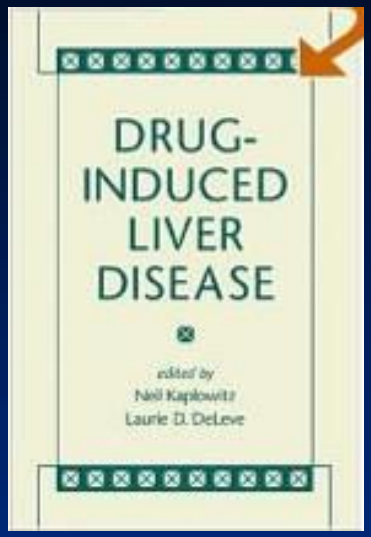
Diphenylhydantoin

- Subclinical - 1%
- Hypersensitivity - 75% of symptomatic cases
- Patterns of injury
  Acute hepatitis - 60%
  Classic, mono-like, (sub)massive
  Hepatocellular-cholestatic - 20%
  Granulomatous hepatitis - 20%

Case 4

- Temporal eligibility - Latent period
  Phenobarbital - 1 year
  Carbamazepine - 1 year
  Diphenylhydantoin - 3 weeks
- Pattern of Injury - Mono-like hepatitis
- Exclusion - Neg hepatitis & mono tests
- Precedent - Diphenylhydantoin
- Conclusion - Prob. diphenylhydantoin

Standard References



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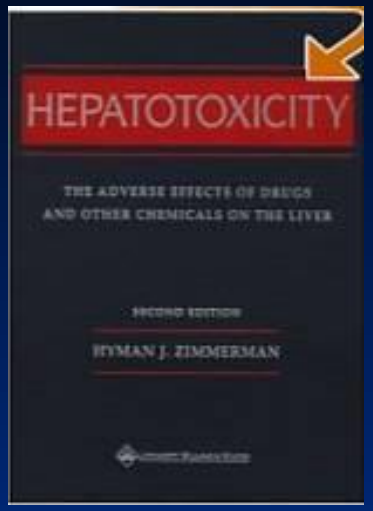

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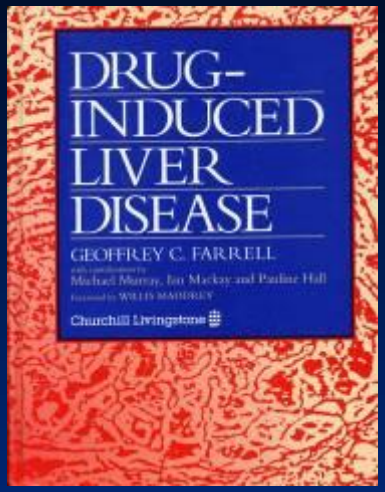

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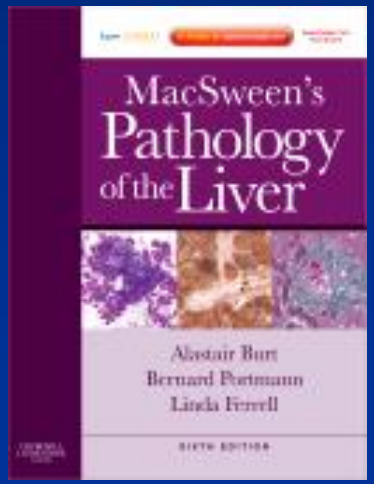

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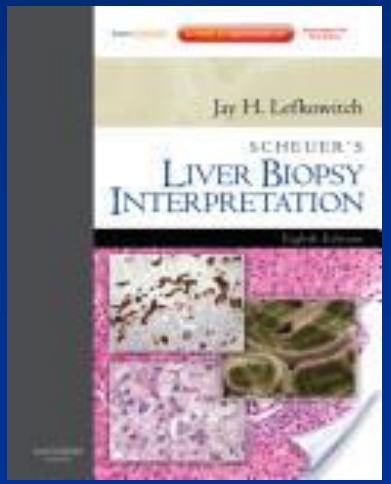

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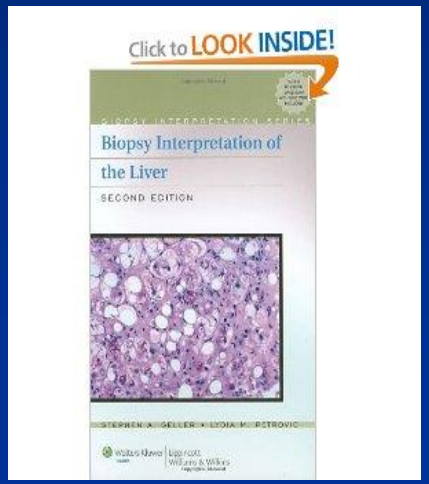

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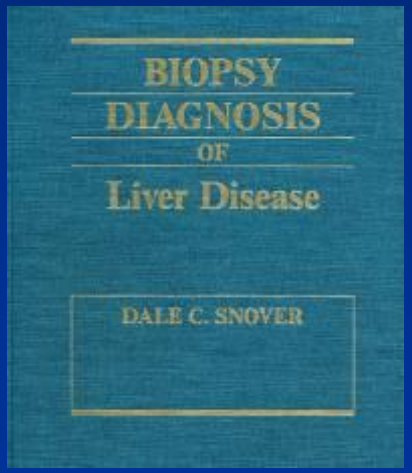

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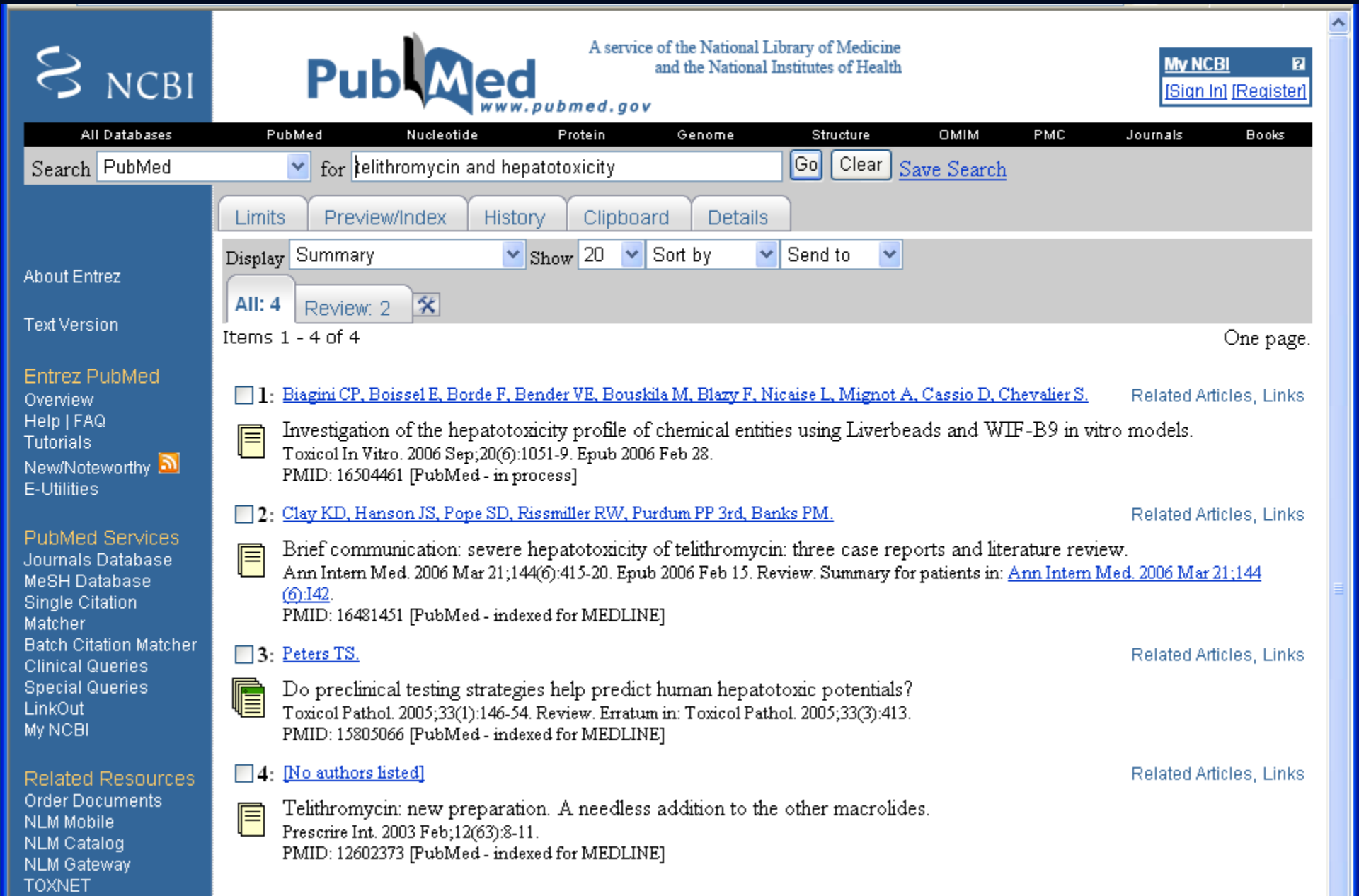

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telithromycin and hepatotoxicity Search Advanced Search Preferences

The "AND" operator is unnecessary -- we include all search terms by default. [details]

Web Results **1** - **10** of about **10,500** for **telithromycin and hepatotoxicity**. (**0.14** seconds)

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We present 3 cases of drug-induced **hepatotoxicity** thought to be secondary to **telithromycin**. One case required liver transplantation, and 1 resulted in death ...
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(2) **Telithromycin** is a macrolide antibiotic derived from erythromycin. ... mainly gastrointestinal disturbances, headache, dizziness, and **hepatotoxicity**. ...
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Infectious Disease News - FDA issues advisory about Ketek and ...
The FDA has issued a public health advisory after three reports of a possible risk of serious **hepatotoxicity** in patients who use **telithromycin** (Ketek, ...
www.infectiousdiseasenews.com/200602/ketek.asp - 9k - Cached - Similar pages

www.micromedex.com (subscription)

DRUGDEX DRUG EVALUATIONS

TELITHROMYCIN

- CAUTIONS
  - ADVERSE REACTIONS
    - **3.3.6 Hepatic**
      - **A) Hepatotoxicity**
        - 1) Incidence: rare
        - 2) Severe hepatotoxicity associated with the use of telithromycin was reported in three patients. In the first case, a 46-year-old male developed malaise and darkened urine after receiving two days of telithromycin therapy for the treatment of an ear and sinus infection. On the third day of therapy, the patient developed slight jaundice and laboratory testing revealed abnormal liver function test results (eg, alanine aminotransferase level of 948 Units/Liter). Telithromycin was discontinued, and the jaundice resolved within two weeks. Within eight weeks his alanine aminotransferase level returned to normal. In the second case, a 51-year-old white female with a history of drinking two glasses of wine daily, developed jaundice during the week in which she began on a 5-day course of telithromycin for the treatment of cough and rhinorrhea. Laboratory studies revealed abnormal liver function test results (eg, alanine aminotransferase level of 730 Units/Liter). The woman eventually required an orthotopic liver transplantation; massive hepatic necrosis was evident via the histologic findings of the explanted liver. In the final case, a 26-year-old hispanic male with a history of drinking eight 12-ounce beers every two weeks, presented with an 8-day history of jaundice, fever, hematemesis, and melena after completing a 5-day course of telithromycin (800 milligrams/day). Upon laboratory investigation, markedly abnormal liver function test results were observed (eg, alanine aminotransferase level of 2200 Units/Liter). Despite aggressive therapy, the patient died on the third day following admission. Hepatomegaly and massive hepatic necrosis with lymphocytic inflammatory response characteristic of a hypersensitivity reaction were noted in the autopsy. According to the Naranjo probability scale, the chance that these cases were related to an adverse drug reaction was considered to be probable in all three cases (Clay et al, 2006).
      - **B) Liver finding**
        - 1) Reversible HEPATITIS occurred in 0.07% of patients treated with telithromycin in phase III clinical studies. Abnormal liver function tests were also reported. Post-marketing surveillance has also produced reports of infrequent hepatocellular and/or cholestatic hepatitis with or without jaundice (Prod Info Ketek(TM), 2004s).

Herbal and Supplements may also cause liver injury

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AltMedDex

BLACK COHOSH

- CAUTIONS
  - ADVERSE REACTIONS
    - **3.3.7 LIVER**
      - **1. HEPATOTOXICITY**
        - A. A woman taking black cohosh for one week developed acute JAUNDICE and required a LIVER TRANSPLANT. Biopsy revealed severe zone three hepatocyte loss and some bridging necrosis (Whiting et al, 2002).
      - **2. AUTOIMMUNE HEPATITIS**
        - A. Autoimmune hepatitis was associated with the consumption of black cohosh in a case report of a 57 year-old female who presented with a two-week history of lethargy and fatigue following the use of black cohosh for three weeks. Following an unremarkable physical exam, laboratory examination reveled an elevated alkaline phosphatase: 170 Units per Liter (U/L), aspartate aminotransferase (AST): 509 U/L, alanine aminotransferase (ALT): 1234 U/L and an antinuclear antibodies (ANA) titer of 1:640. Hepatitis A, B and C antibodies and smooth muscle antibody titer were negative. Albumin, bilirubin, international normalized ratio (INR), complete blood count (CBC) were all within normal limits. Liver biopsy revealed piecemeal necrosis and lobular infiltrates with extensive plasma cells and eosinophils. The patient's liver function tests nine months previous were within normal range (Conner et al, 2003).
  - **3.4 TERATOGENICITY/EFFECTS IN PREGNANCY**
    - **A. TERATOGENICITY**
      - 1. SUMMARY:
        - a. Black cohosh may have estrogenic activity and may interfere with pregnancy maintenance. No teratogenic effects were noted in examination of three pregnancies (Baillie & Rasmussen, 1997; Mellin, 1964).

Consult the Experts

DILIN (http://dilin.dcri.duke.edu/)

Drug-Induced Liver Injury Network

Cooperative research network funded by the NIDDK for the purpose of prospectively studying DILI

- The relationship between exposure to the drug and hepatic toxicity is not always clear.
- There is no specific serum biomarker or characteristic histologic feature that reliably identifies a drug as the cause of toxicity.

The Council for International Organizations of Medical Sciences (CIOMS)
FDA Drug Hepatotoxicity Steering Committee
Roussel-Uclaf causality assessment method (RUCAM) scale
Maria & Victorino (M&V)

Danan et al, J Clin Epidemiol. 1993 Nov;46(11):1323-30.
Kaplowitz, N. Hepatology 2001; 33:308
Maria et al ,Hepatology 1997 Sep;26(3):664-9.

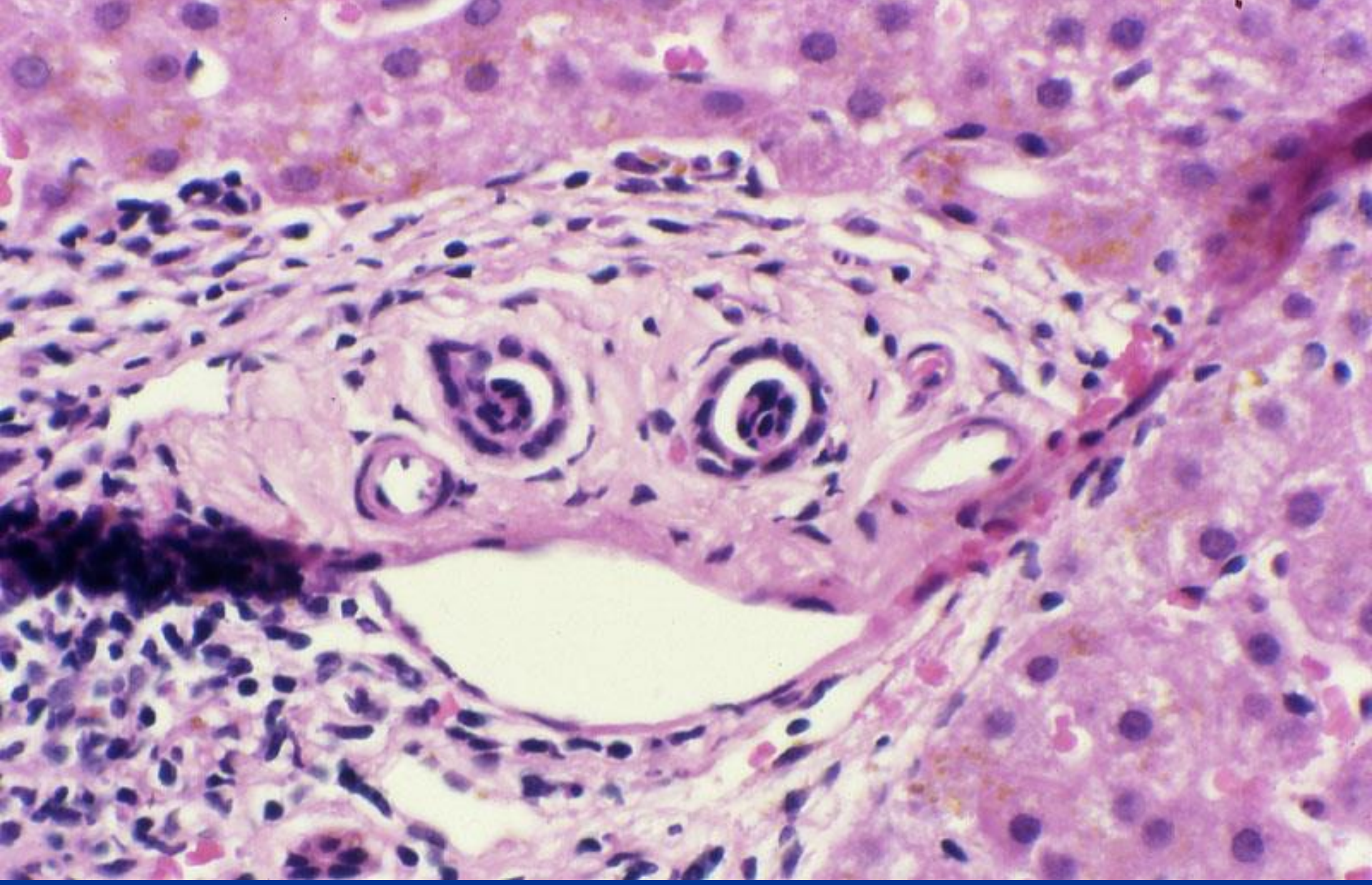
Treatment

- The main treatment is withdrawal of the offending drug.
- Early recognition of drug toxicity is important to permit assessment of severity and monitoring for acute liver failure.
- Few specific therapies have been shown to be beneficial in clinical trials.
- Two exceptions are the use of N-acetylcysteine for acetaminophen toxicity and L-carnitine for cases of valproic acide overdose

Polson J, Hepatology. 2005 May;41(5):1179-97
Bohan et al,Neurology 2001 May 22;56(10):1405-9.

A Final Reminder

1. Think ahead at the grossing bench
2. Identify the pattern(s) of injury
3. Carefully evaluate the clinical history
4. Ask specifically about Herbal medications
5. Assign a degree of certainty to the evaluation of DILI
6. Help is always available if you look for it



THANK YOU