

Hepatitis E

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Hepatitis E outbreak on P&O liner

Hundreds of holidaymakers are being tested for Hepatitis E after an outbreak onboard P&O liner Aurora.



The Aurora was at the centre of an outbreak of the Norovirus in 2003

Seven passengers contracted the virus during an 11-week world cruise which ended in Southampton on 28 March.

All the passengers onboard were sent a letter from the Health Protection Agency requesting a blood sample.

Should donor blood be screened for hepatitis E?

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Monday July 28 2014

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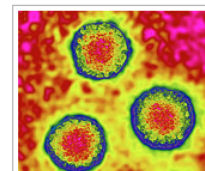
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"One in almost every 3,000 blood donors in England could be infected with hepatitis E, according to a new study," The Times reports.



Researchers screened blood donations for the hepatitis E virus

Hepatitis E normally causes only a mild infection that usually clears up without the need for treatment. It can occasionally lead to more serious complications in more vulnerable groups, such as pregnant women and people with a weakened immune system.

A new study estimated the prevalence of hepatitis E virus in blood donors in England and whether the virus is transmitted to blood recipients.

The prevalence estimate, based on just under a quarter of a million blood donations, was found to be one infection in every 2,848 donors (0.04%). This was higher than expected.

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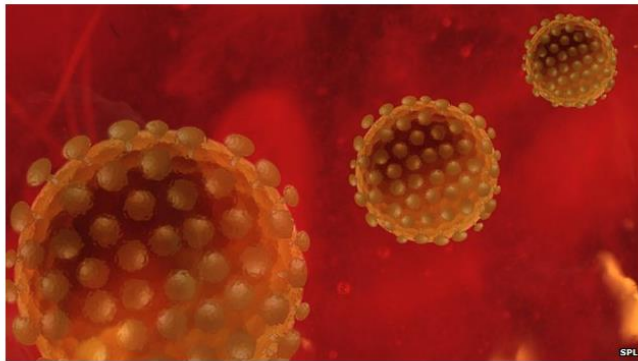
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Blood donors 'passing on hepatitis E'



Around 1,200 people each year are infected with the hepatitis E virus (HEV) through donated blood in England, a large study shows.

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Jamie Doward

The Observer, Saturday 21 September 2013 17.12 BST

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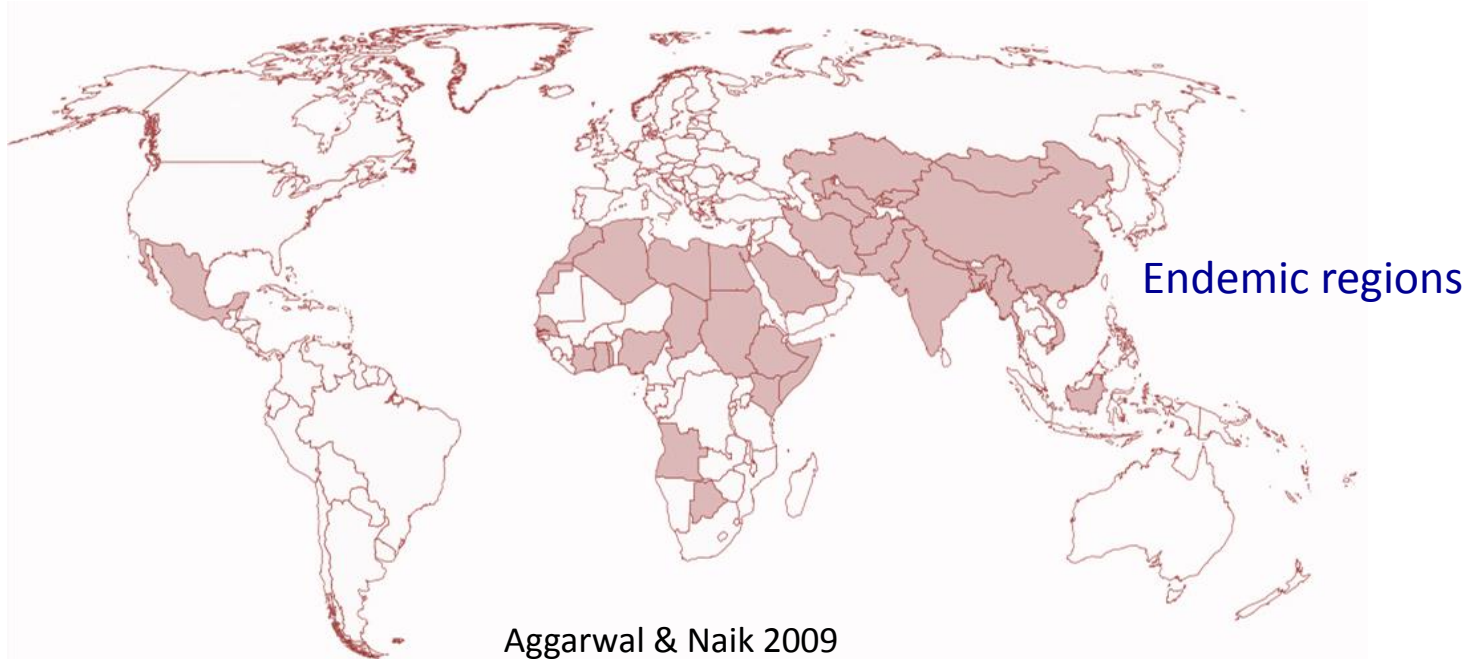
Acute viral hepatitis in SE Scotland

- 3462 bloods for acute hepatitis (2010-12)

		<i>tested</i>		<i>ALT:</i>	<i>jaundice:</i>
EBV	1%	(¼: 4.1%)	24yr	306	rare
HEV	0.7%	(⅛: 6.1%)	48yr	1697	most
CMV	0.6%	(¼: 2.6%)	30yr	141	none
HBV	0.7%	all		2445	most
HCV	0.5%	all	49yr	706	19%
HAV	0.2%	all		1782	most
HDV	0				

Two epidemiologic patterns of infection

- **Endemic in poor water sanitation (30-80% seropositive)**
 - human to human (water borne)
 - frequent sporadic & large outbreaks
 - 3 million symptomatic infections/year
 - 70,000 deaths/year, especially pregnant women WHO, ReinDB Hepatology 2012



Acute hepatitis E (developing areas)

- genotypes 1 & 2
- subclinical mostly
- mild self-limited illness (few weeks)
 - young people (10-40)
 - men predominate
 - pain, fever, vomiting
 - then jaundice (40%), hepatomegaly
 - few: fulminant hepatic failure (7%); acute pancreatitis
 - some: low platelets, haemolysis
 - some: prolonged cholestasis, resolving in several months
 - no chronic hepatitis

Acute hepatitis E (endemic areas)

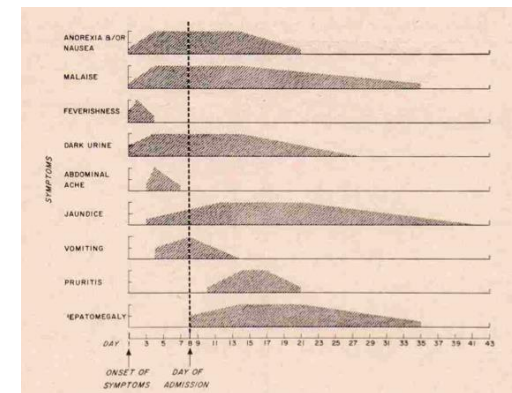
- severe disease settings
 - pregnancy
 - 10-20% get clinical disease: 20-40% of those have **FHF**
 - vertical transmission has a high **perinatal mortality**
 - chronic liver disease (any cause)
 - common cause of cirrhosis **decompensation** (>40%; Kumar A 2004)
 - **superinfection** caused 30% of acute presentations of occult eAg negative Hepatitis B (Kumar M 2008)

Unusual Features of Viral Hepatitis in Accra, Ghana

RICHARD H. MORROW, JR., M.D., M.P.H., F.A.C.P., HANS F. SMETANA, M.D.,
F. T. SAI, M.D., F.R.C.P. (EDIN), M.P.H., and JOHN H. EDGCOMB, M.D.
Accra, Ghana

pathology

- **Delhi 1955/6 waterborne epidemic** GuptaDN1957
- **Kashmir waterborne epidemic 1978/9** KhurooSM1980
 - 31 liver biopsies:
 - 14 **classic** acute viral: ballooning, portal inflam, binucleation, Kupffer hyperplasia, hepatocellular & canalicular bile
 - 10 **cholestatic** hepatitis (dominant canalicular bile, rosettes),
 - variable necrosis (single cell focal/zonal to bridging/submassive).
 - 5 follow-up biopsies: all normal
- **Accra (Ghana) 1962/3 endemic sporadic** MorrowRH1968
 - 158 inpatient bx in 1 yr
 - individual histology pattern maintained over serial bx
 - conventional acute hepatitis
 - variable **triad** of pseudoglands (diffuse 50%, focal 20%), canalicular bile (20% sev), rare acidophil bodies
- **Agrawal: 11 fatal fulminant HEV vs 7 HBV FHF.**
 - necrosis variable
 - pseudoglands, cholestasis, portal/lobular mixed hepatitis
 - lymphocytic cholangitis



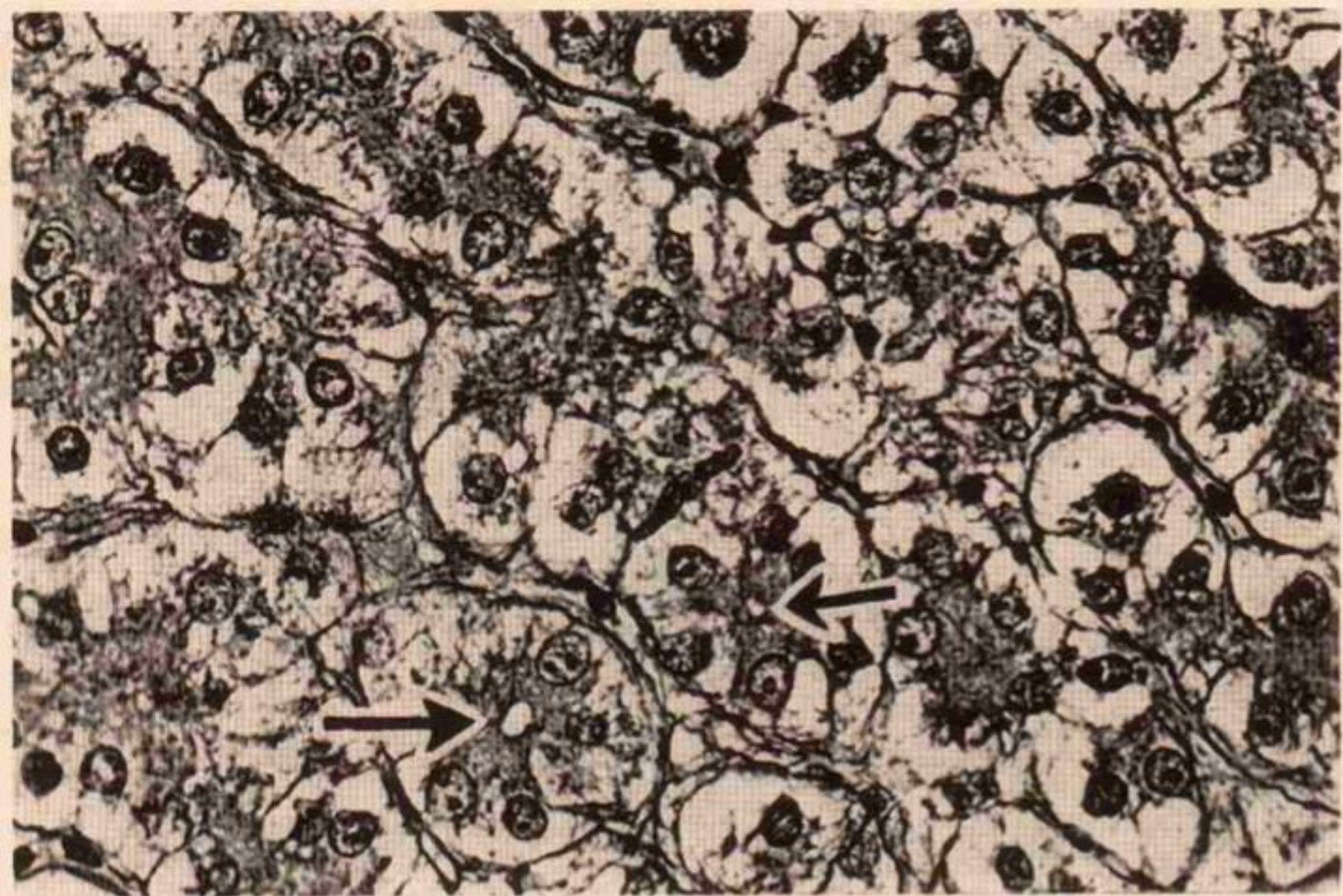
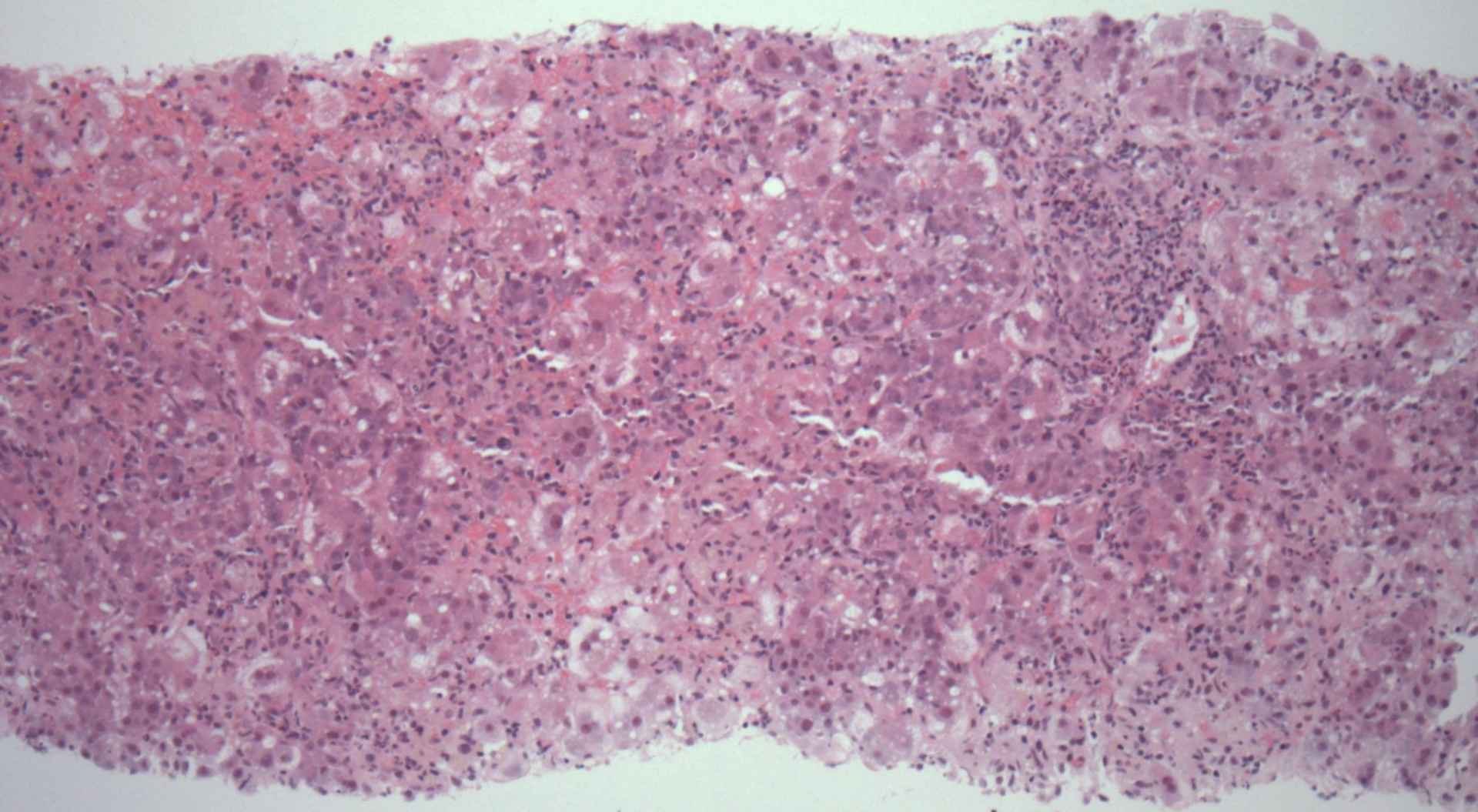
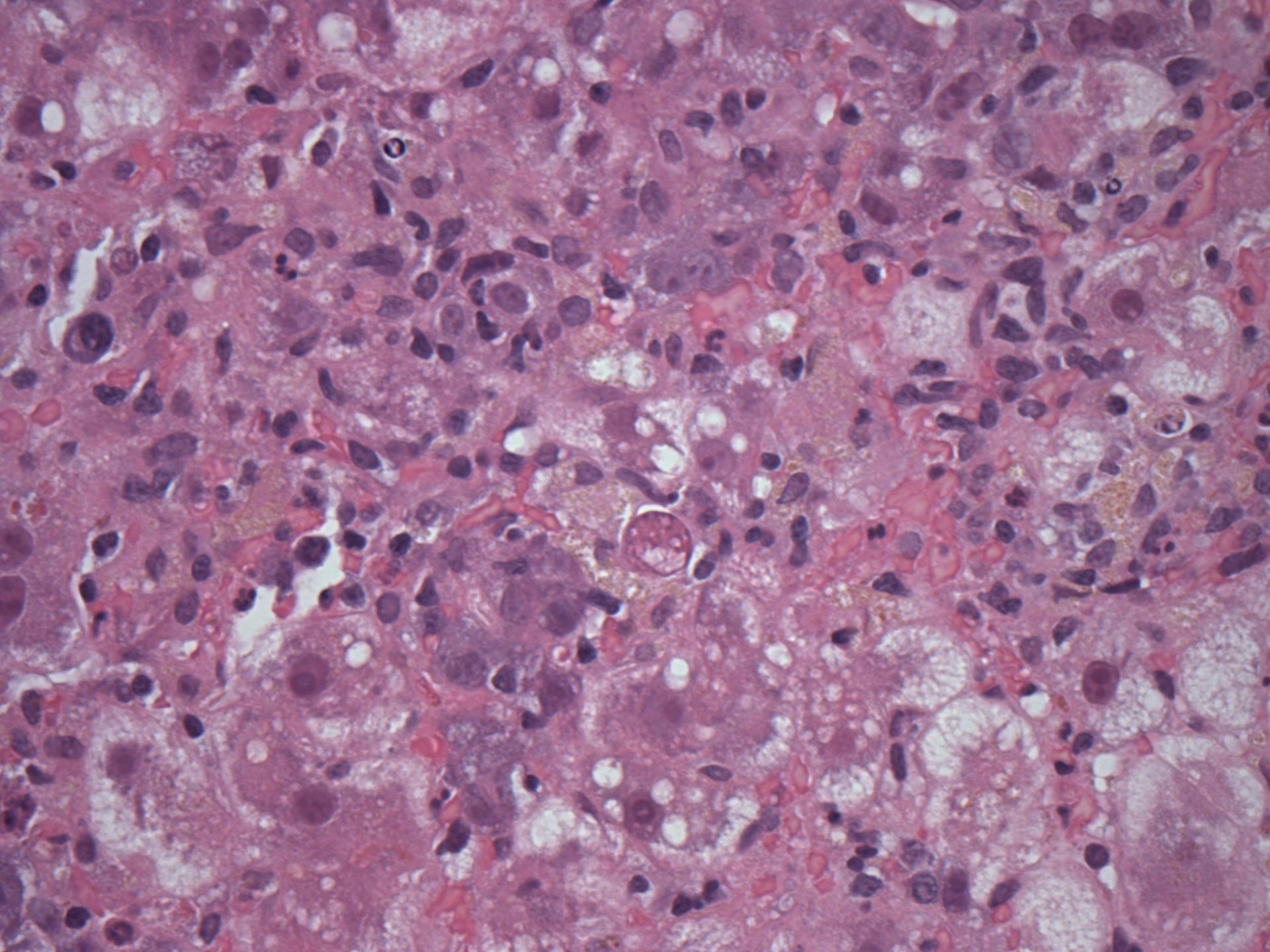
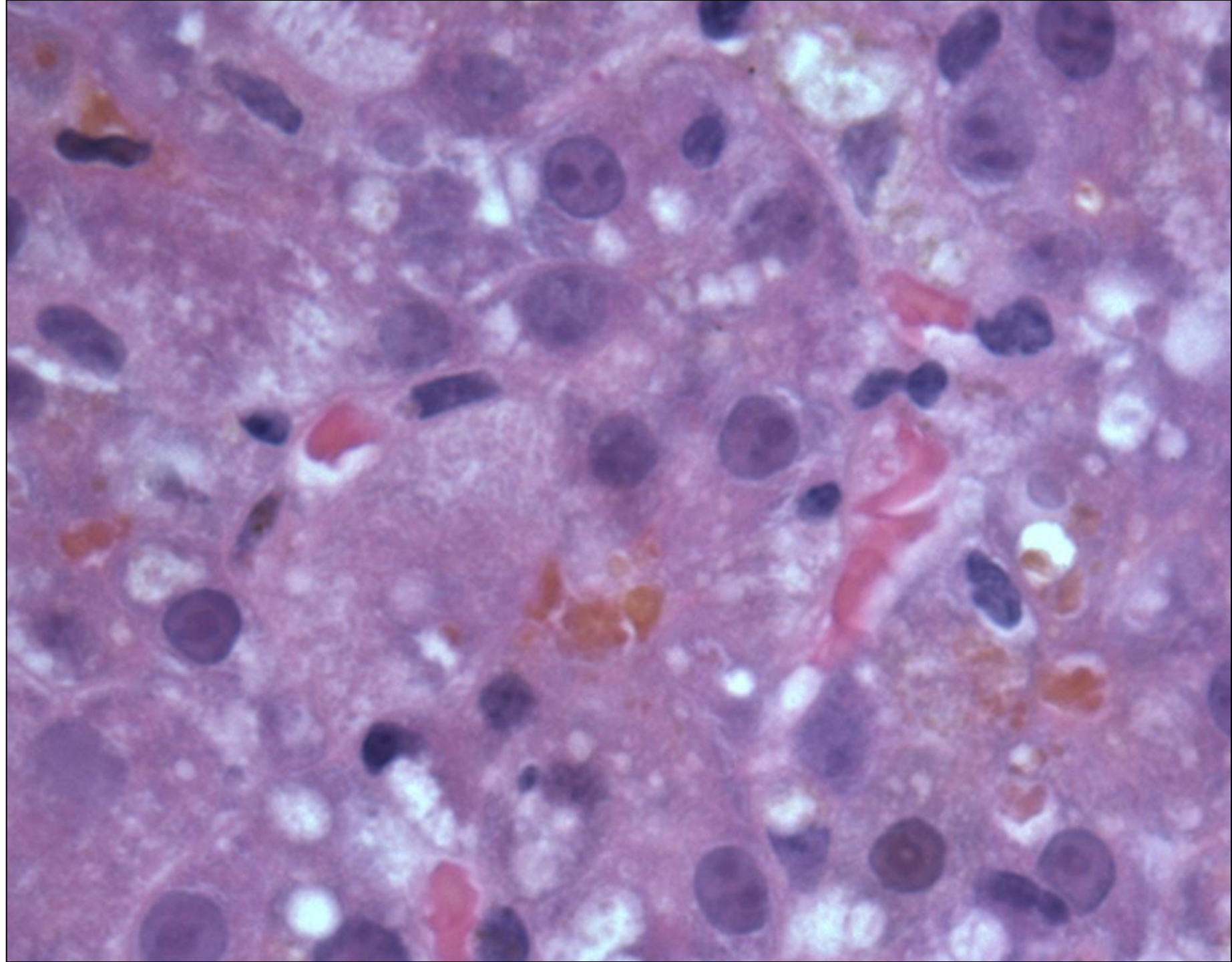
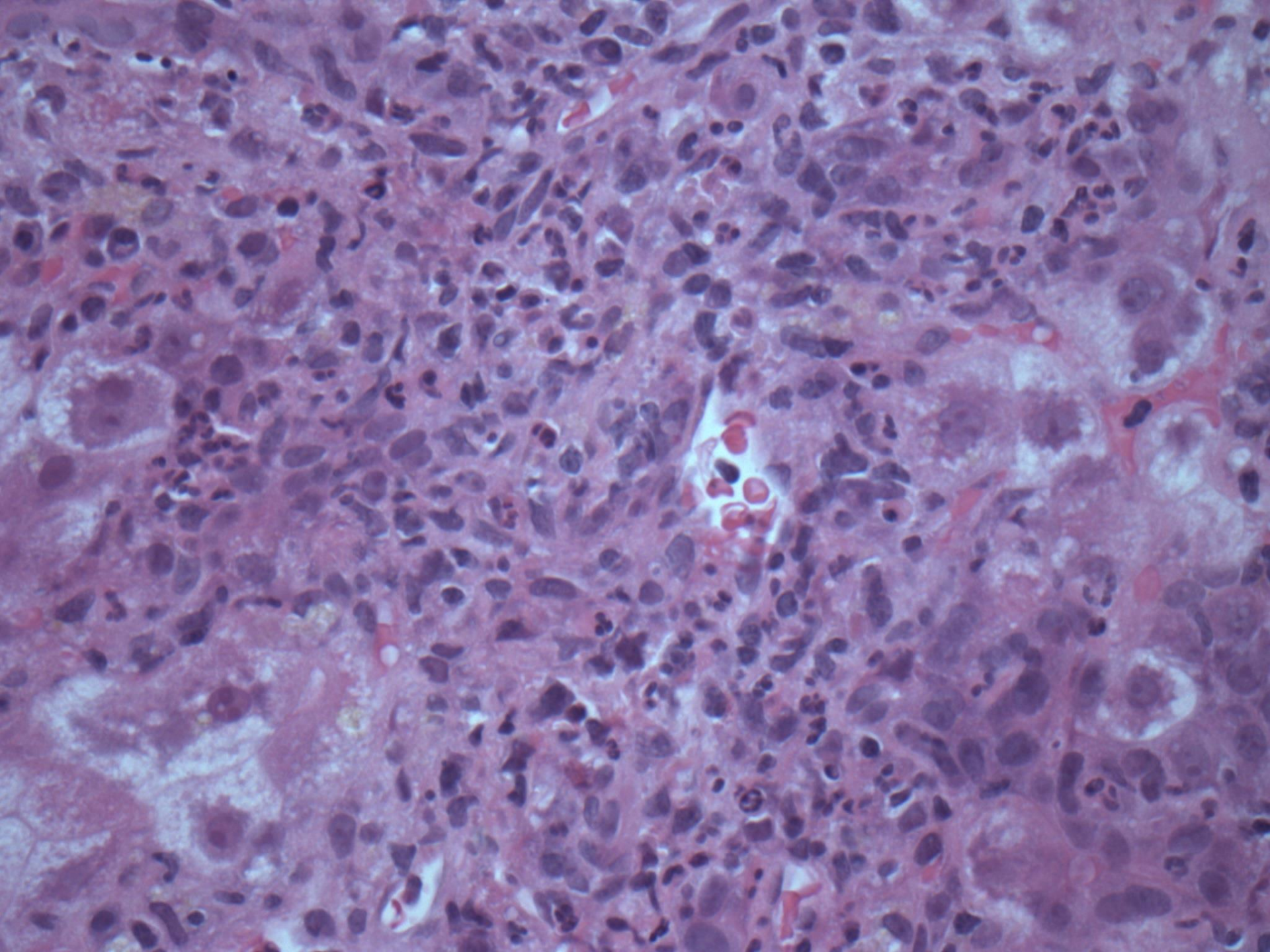


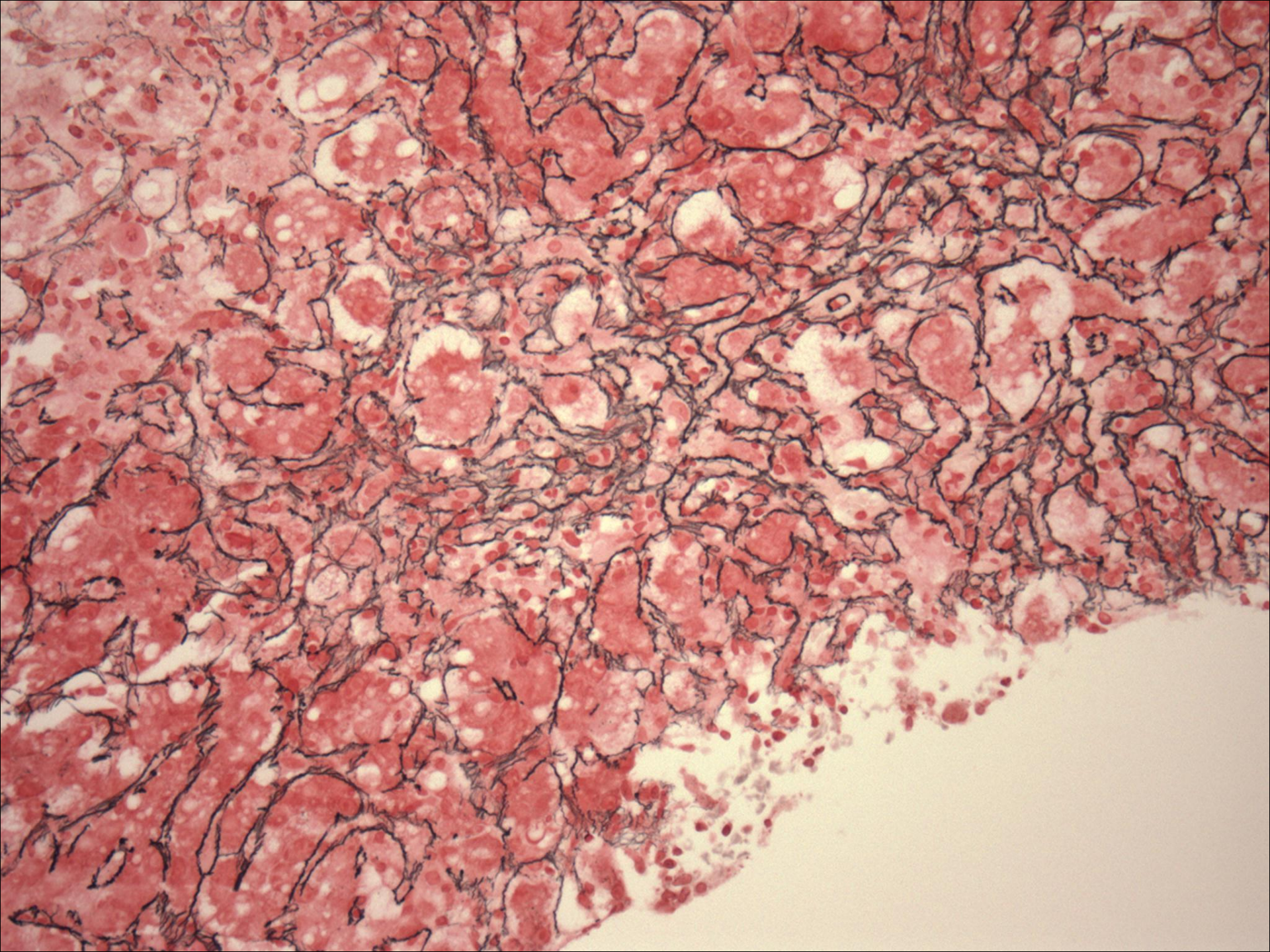
FIGURE 1. Patient Z. Y. (Spl. 105), a 26-year-old Ghanaian man, developed severe viral hepatitis and died 6 months later after an unrelenting, slowly progressive clinical course, complicated in





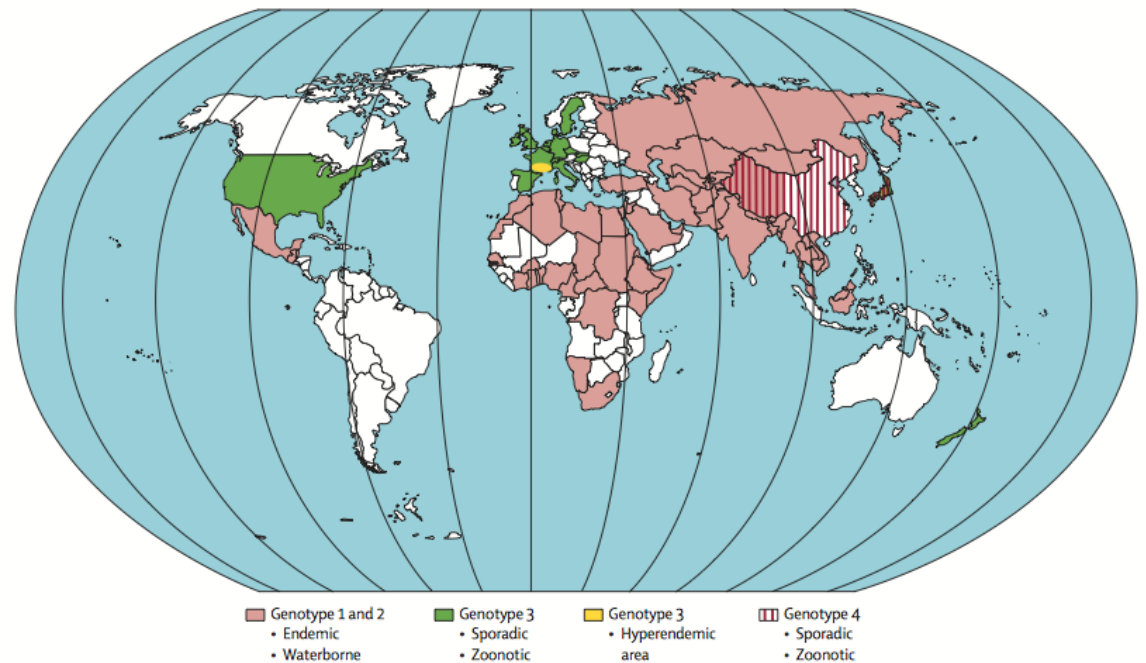






Acute hepatitis E (developed areas)

- Europe/USA/Japan/New Zealand (10-50% seropositive)
 - travel to endemic region
 - ‘locally’ acquired
 - sporadic & small cluster outbreaks
 - zoonosis
 - human blood products



Locally acquired Hepatitis E

- genotypes 3 or 4
- subclinical mostly
- mild self-limited illness (few weeks)
 - older men (median 50-65 years, 3x women)
 - alcohol >21u/wk
 - jaundice + transaminitis (75%)
 - some: fever, arthralgia, myalgia, abd pain, vomiting, rash
 - monoclonal gammopathy (usually resolves) Woolson2014
 - 5%: neurological presentation

Genotype 3 mini-cluster

Hepatitis E outbreak on P&O liner

Hundreds of holidaymakers are being tested for Hepatitis E after an outbreak onboard P&O liner Aurora.

Seven passengers contracted the virus during an 11-week world cruise which ended in Southampton on 28 March.

All the passengers onboard were sent a letter from the Health Protection Agency requesting a blood sample.



The Aurora was at the centre of an outbreak of the Norovirus in 2003

RESEARCH

Hepatitis E Outbreak on Cruise Ship

Bengü Said, Samreen Ijaz, George Kafatos, Linda Booth, H. Lucy Thomas, Amanda Walsh, Mary Ramsay, and Dilys Morgan, on behalf of the Hepatitis E Incident Investigation Team¹

- 4 symptomatic elderly patients returned from a world cruise
- 30% passengers studied:
 - 4% (33/789) had acute HEV (IgM+)
 - associations: male, alcohol, shellfish consumption
 - only 11/33 symptomatic
 - 74% male (54% females on board)

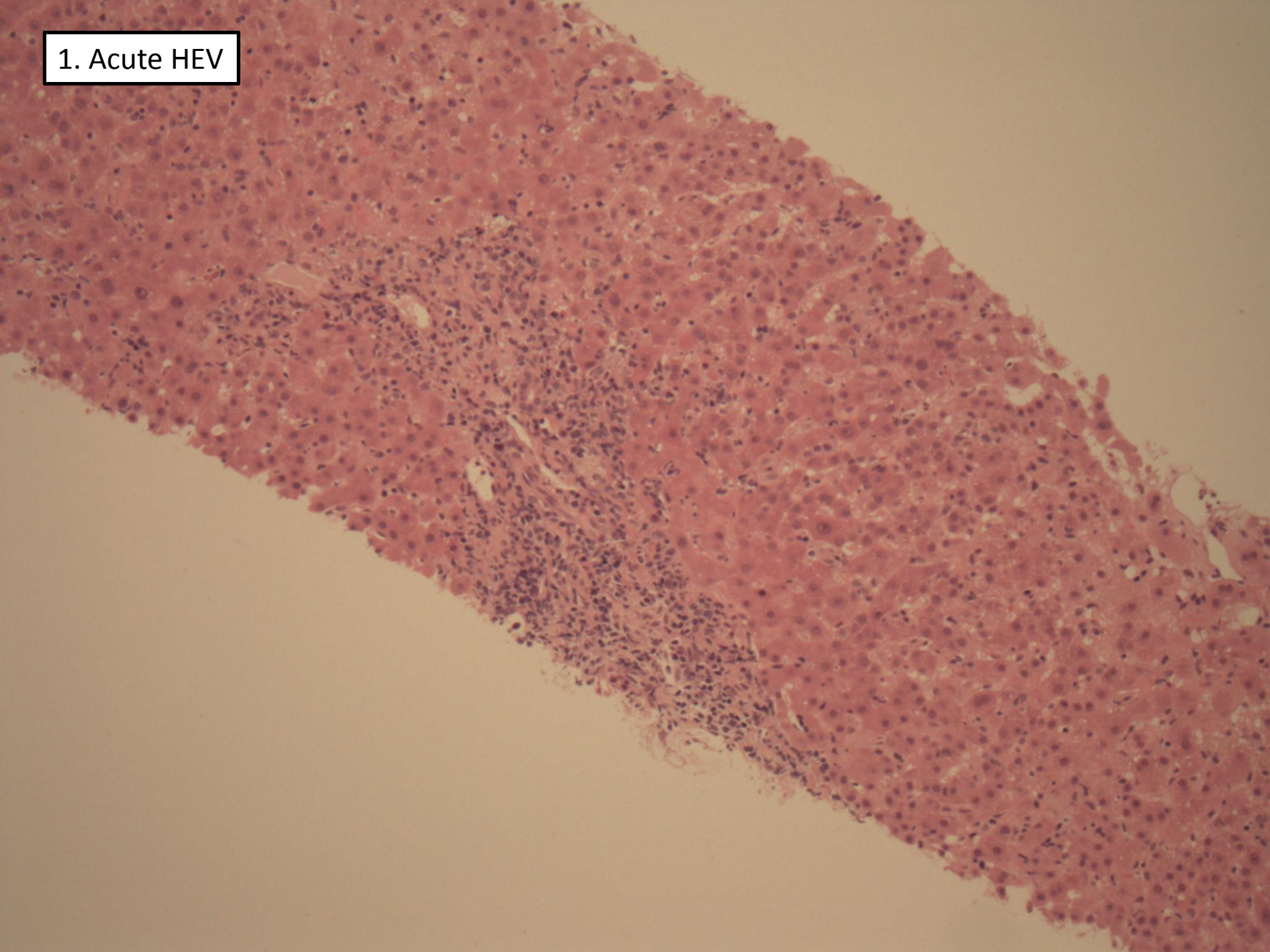
Locally acquired Hepatitis E

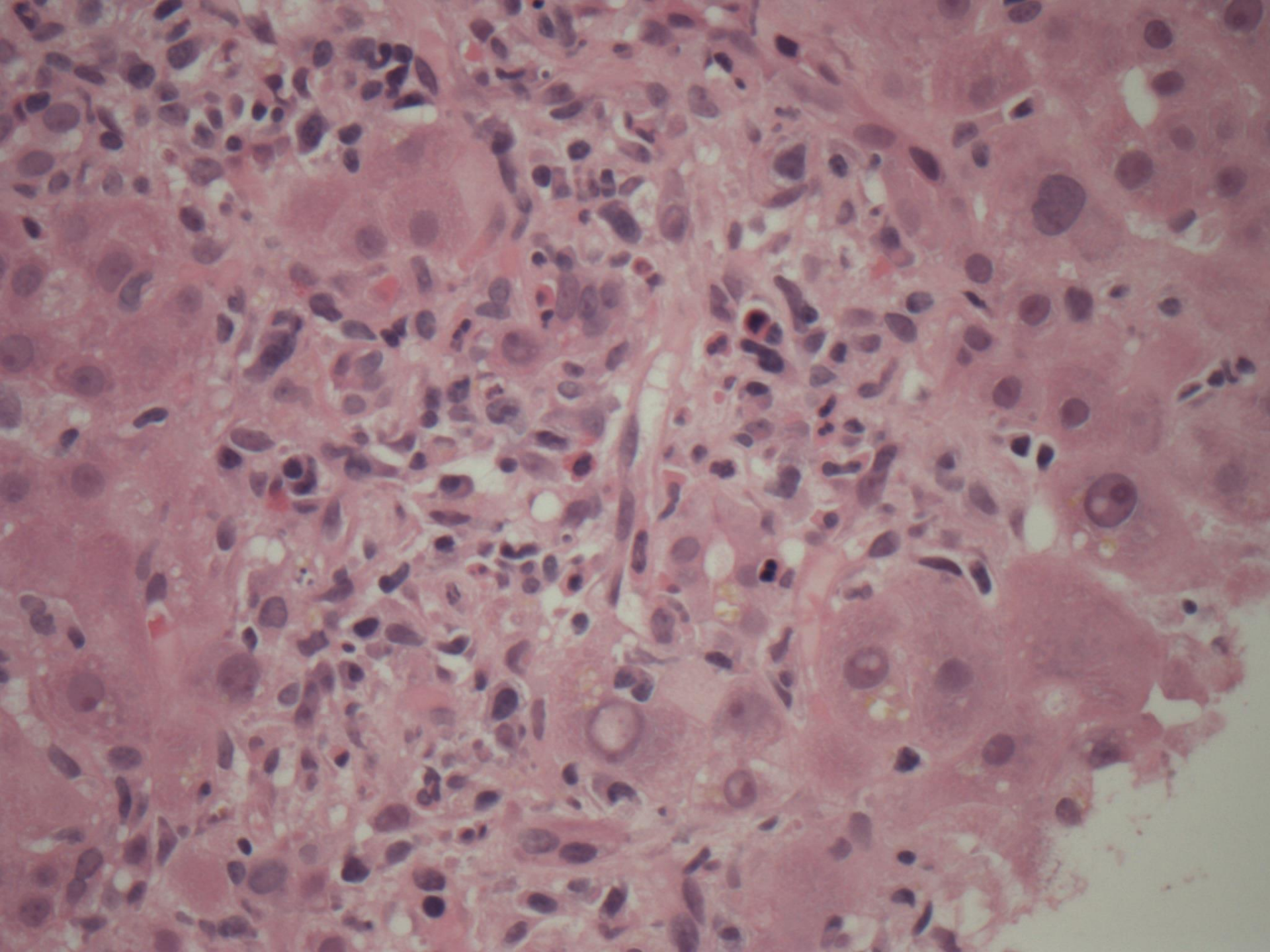
- severe disease settings
 - chronic liver disease Dalton2007
 - alcohol hepatitis Peron2007
 - decompensated cirrhosis
- diagnosis overlooked
 - suspected drug-induced liver injury
 - 13% of 47 meeting drug injury criteria Dalton2007
 - 3% of 318 retrospective cases Davern2011
 - atypical presentations
 - neurologic-dominated presentations
 - polyarthrititis + rash Al-Shukri2013

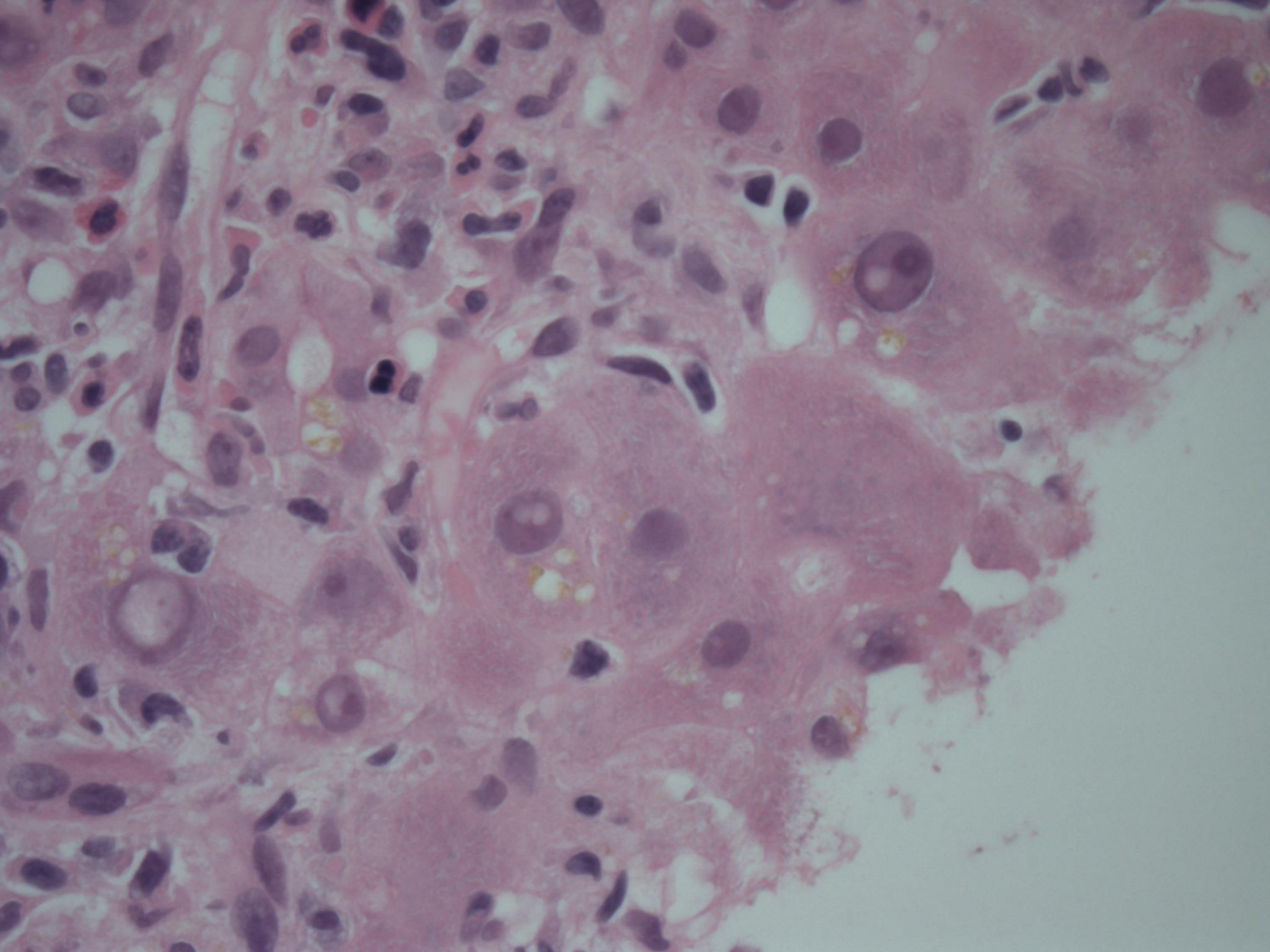
pathology

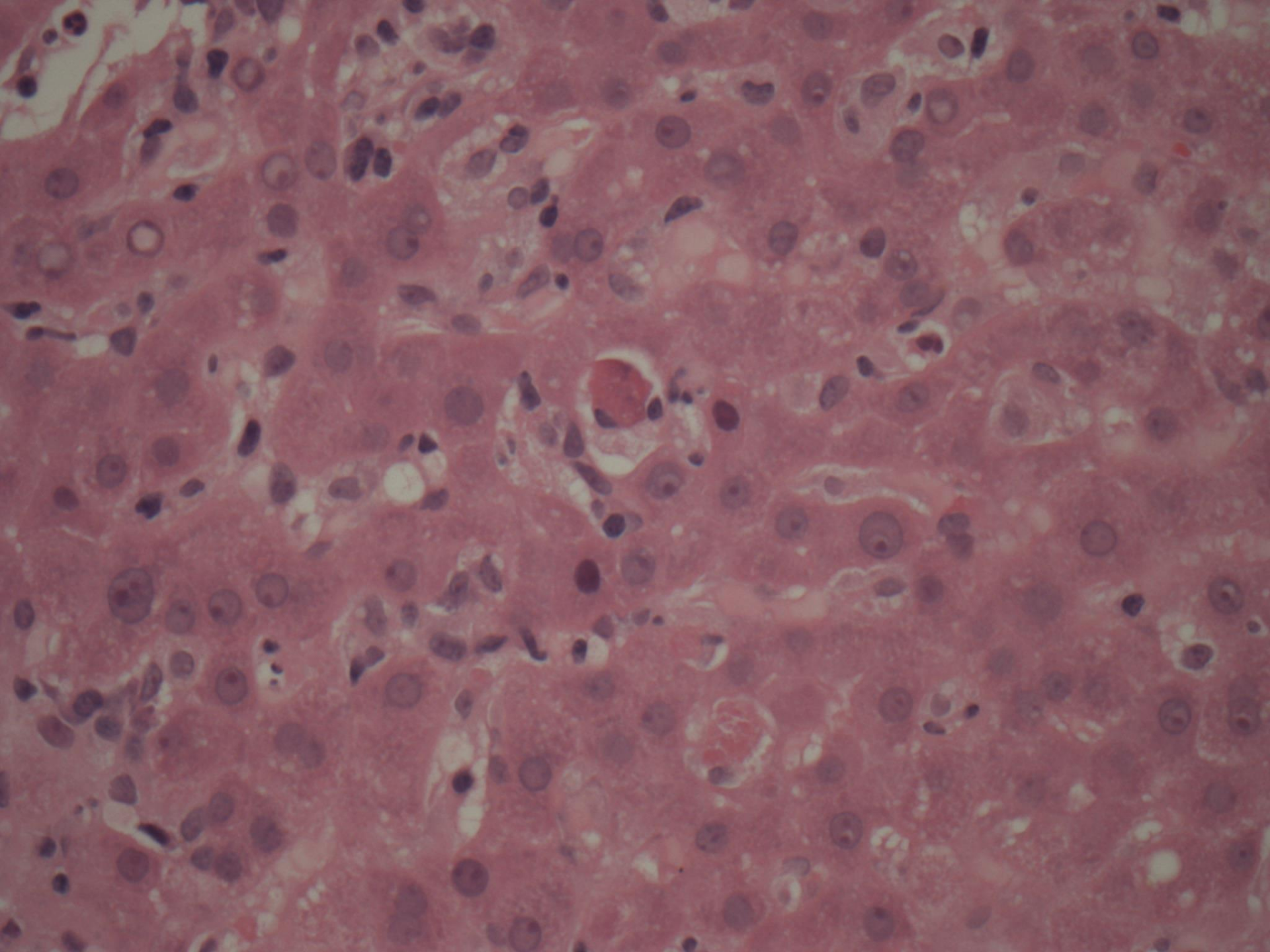
- mixed neutrophil-rich cholestatic hepatitis
 - **Malcolm2007 (3 local SW England vs 1 Chinese endemic)**
 - no CLD
 - marked inflammation:
 - portal lymphoplasmacytic inflam, neutrophil cholangiolitis
 - ballooning, lobular disarray, anisonucleosis/binucleates, some acidophils, mitosis
 - neutrophil-rich mixed lobulitis, canalicular cholestasis, some rosettes
 - some necrosis, perivenular dropout & oedema
 - **Peron2007**
 - 5 cirrhotics (4/4 RNA+)
 - 4 ASH, 1ANA++
 - 6 other (2/4 RNA+)(F0-2)
 - neutrophilic spotty & confluent necrosis, neutrophil-rich mixed portal inflammation,
 - some: mild cholangiolitis, mild cholangitis, mild cholestasis
 - **Drebber2013 (7 RNA+ of 221 unexplained acute hepatitis bx [excluded alcohol, drugs, ANA])**
 - 4/4 genotype 3
 - no CLD
 - classic hepatitis: ballooning, portal & lobular lymphocytic hepatitis
 - also cholestatic features: neutrophils (portal, lobular), cholangiolitis, canalicular & cytoplasmic bile, lymphocytic cholangitis
 - some confluent/bridging necrosis (5/7)
 - **non-HEV cases** showed less portal inflammation, more eosinophils, similar lobular inflammation but less necrosis
 - **Haim-Boukoba2014 (only 4% of 84 alcohol hepatitis were HEV+)**
 - The 3 bx showed cirrhosis, mild-sev steatohepatitis, no sepsis reaction
 - 1 showed sinusoidal lymphoplasmacytic infiltrate, but no other clear sign of viral hepatitis.

1. Acute HEV

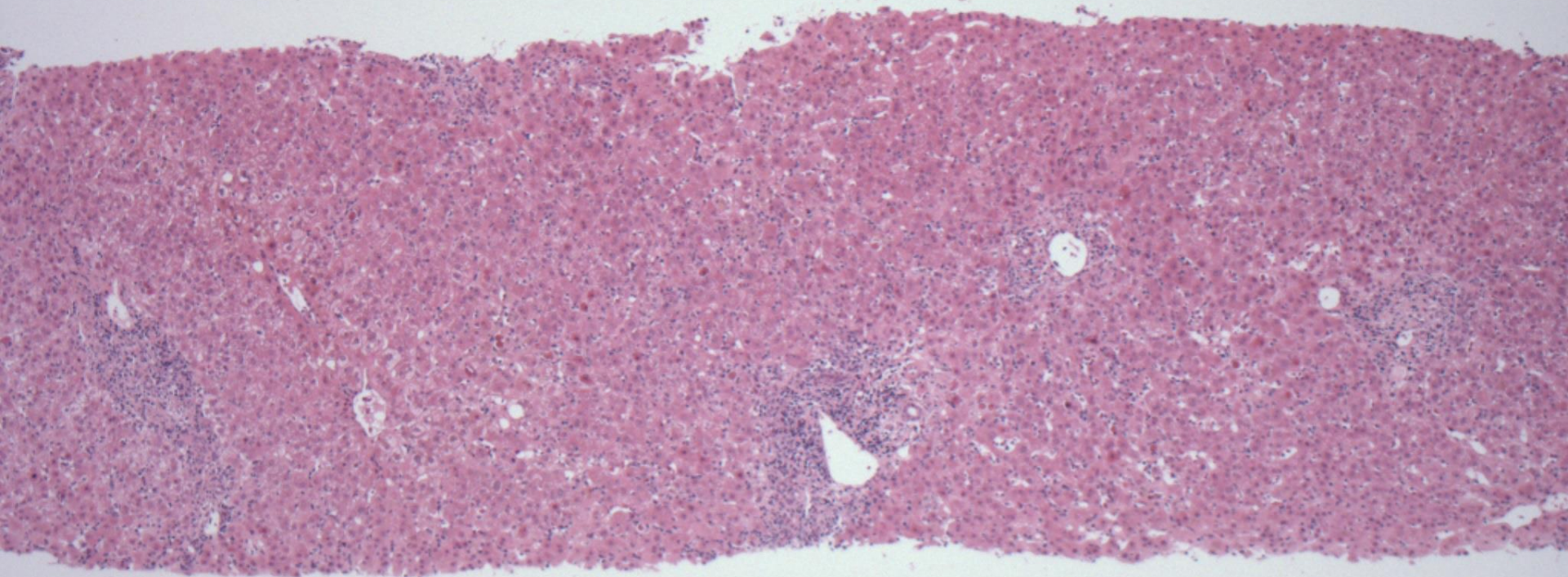


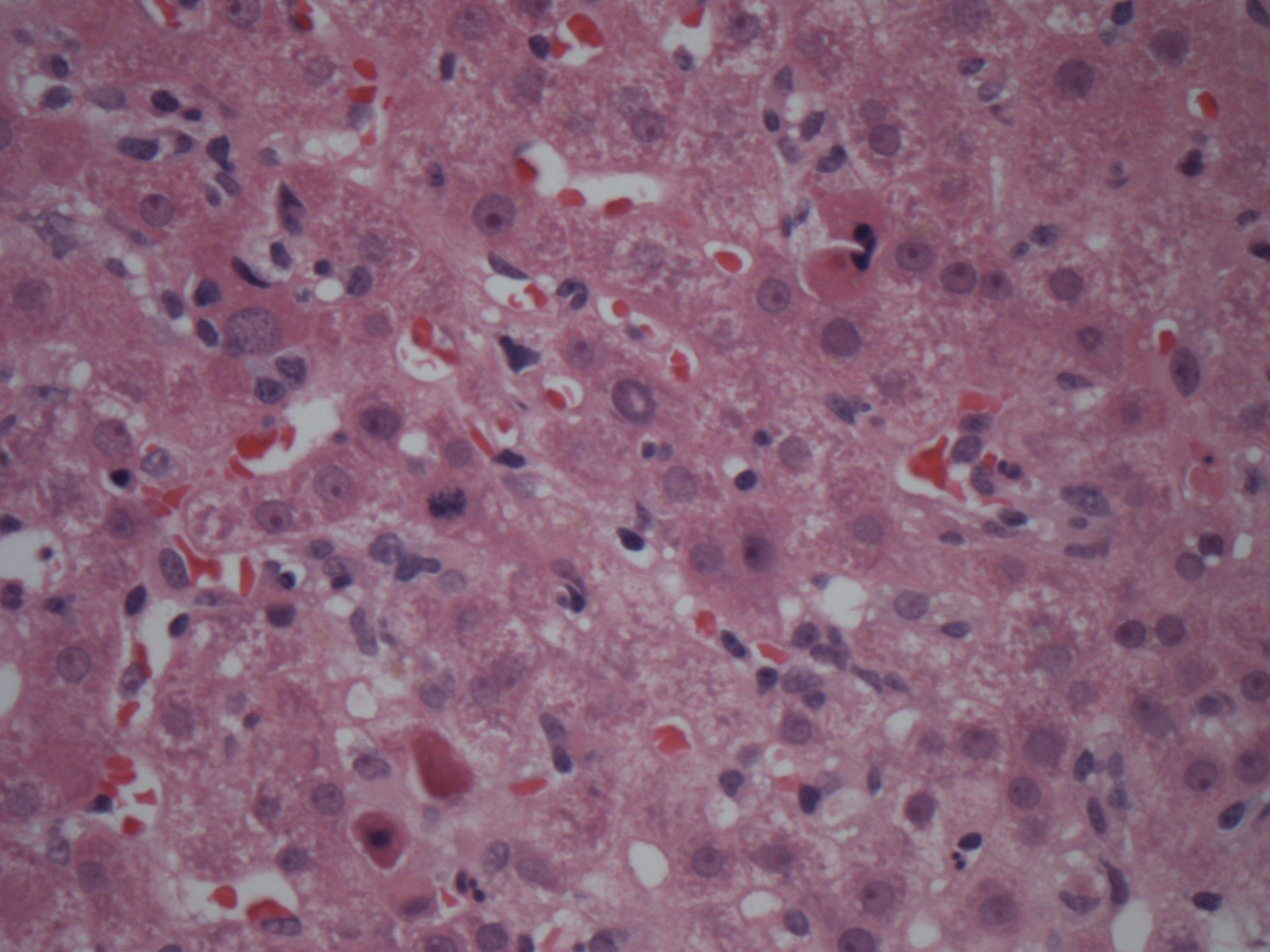


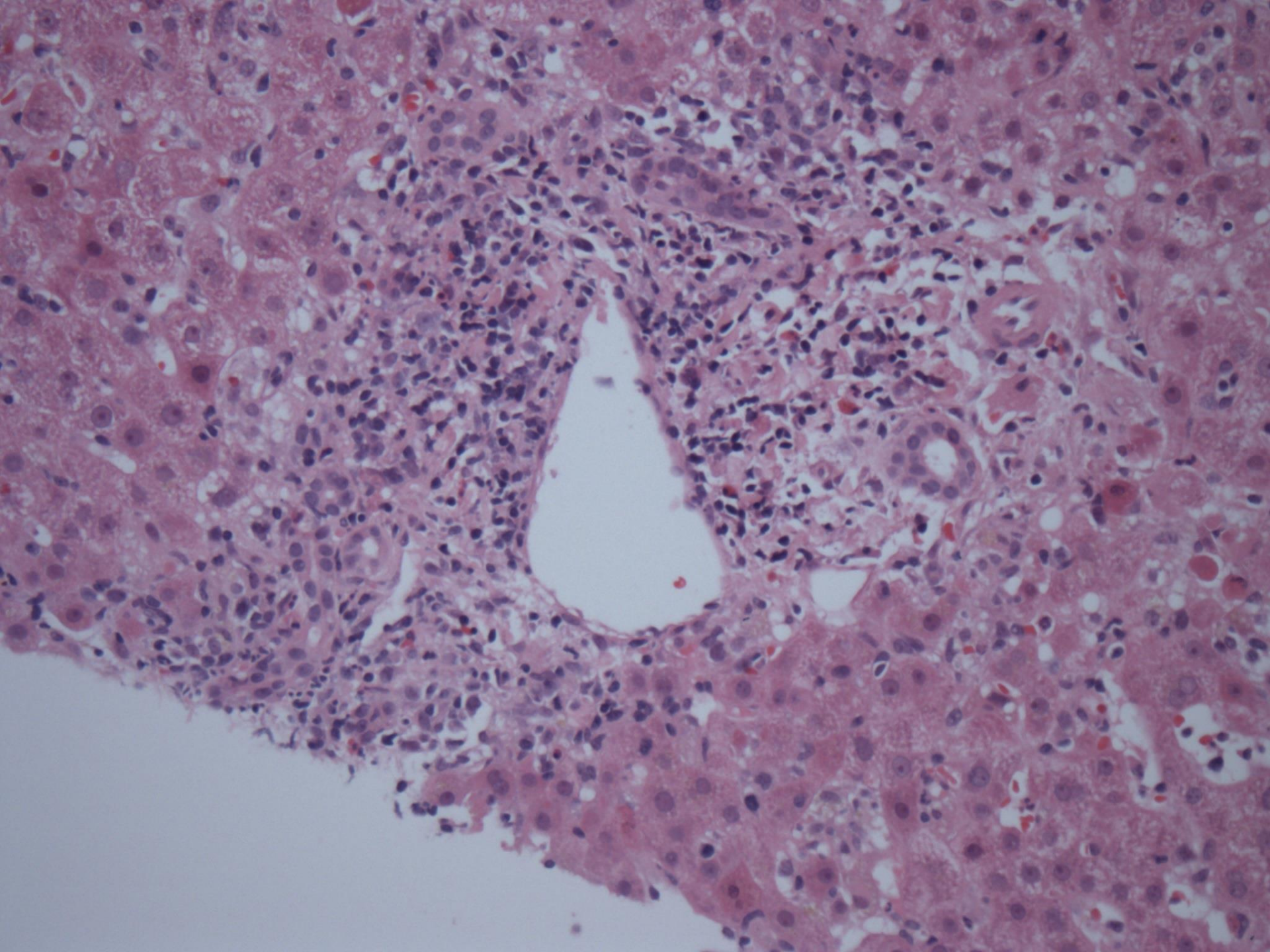




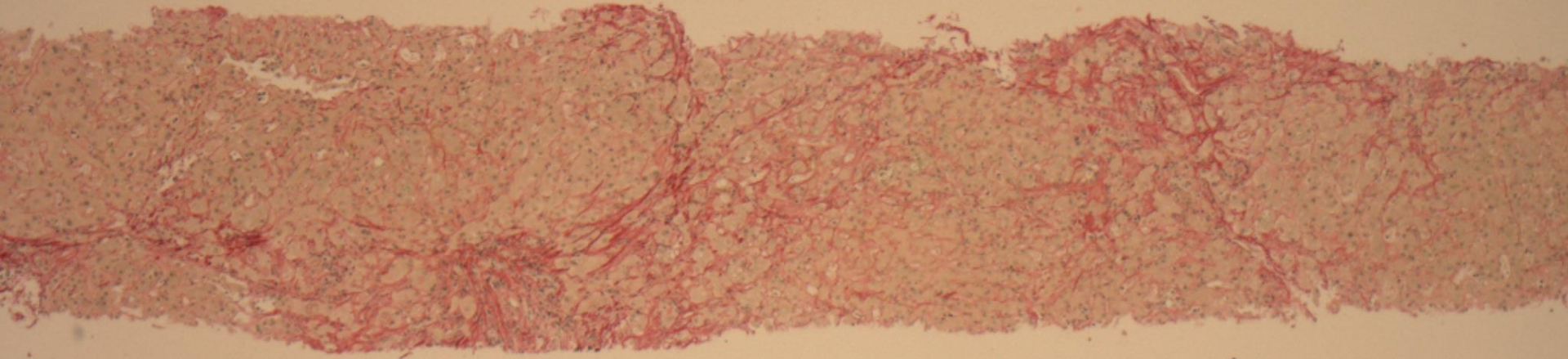
2. Acute HEV

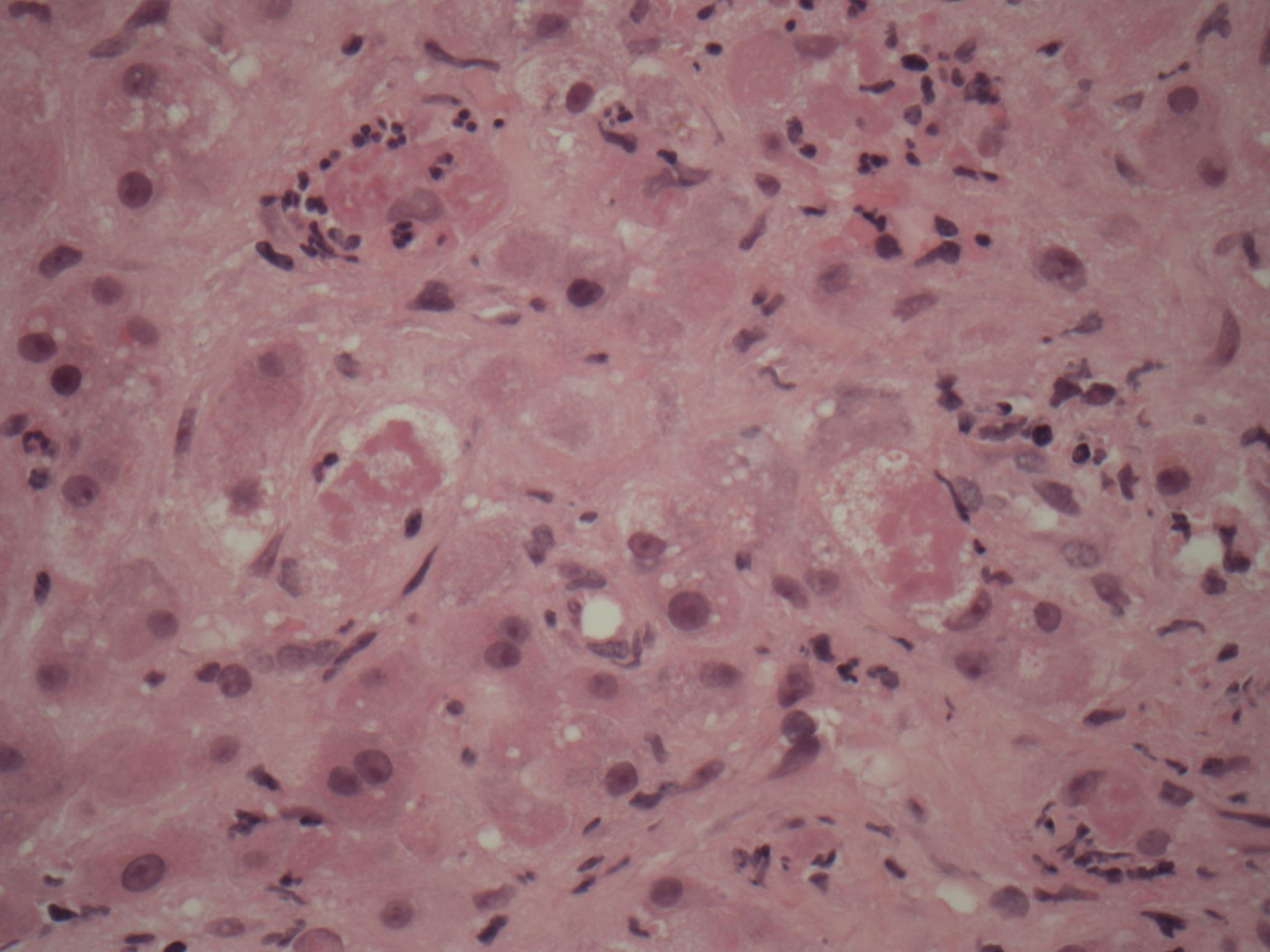


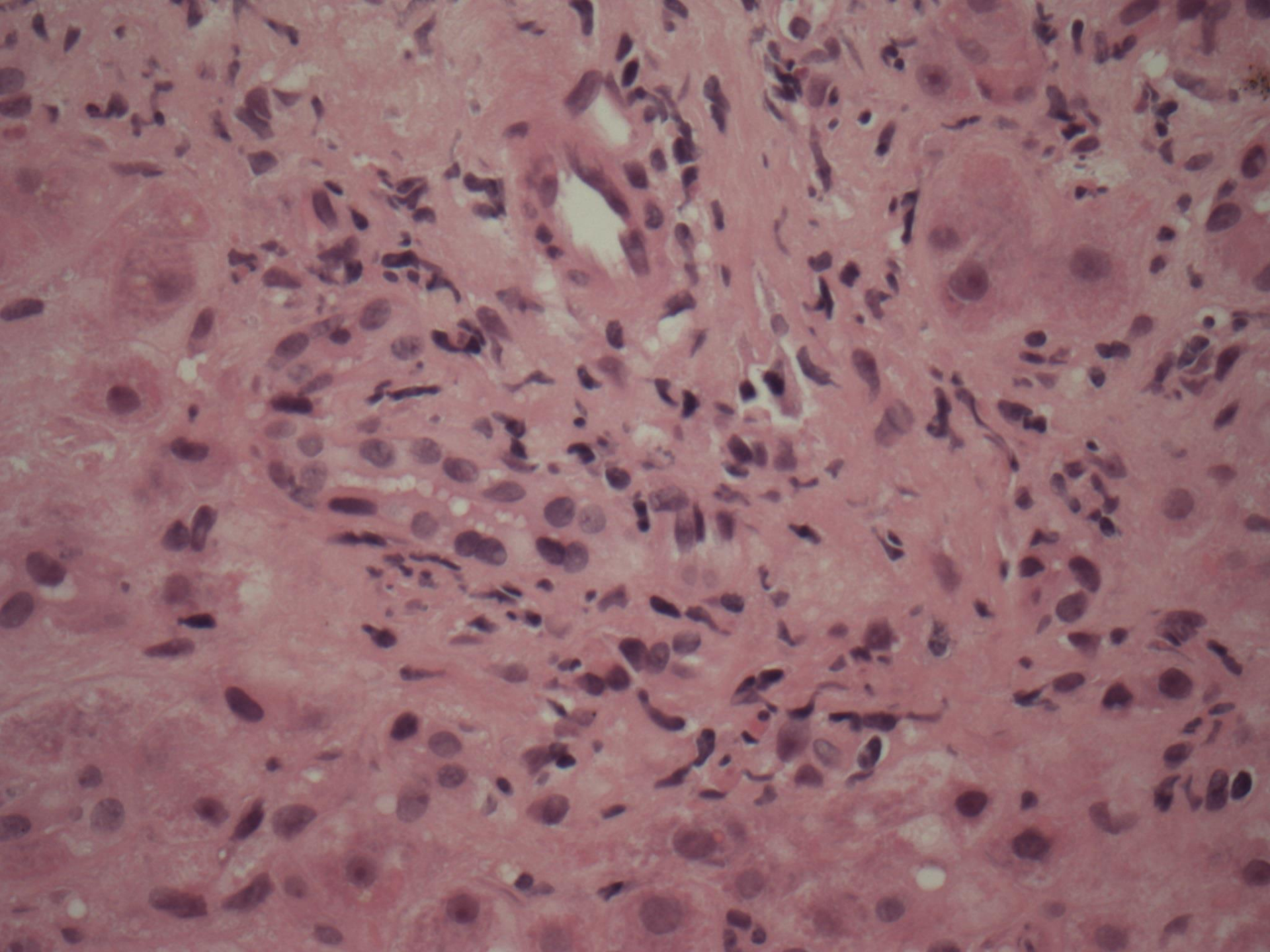


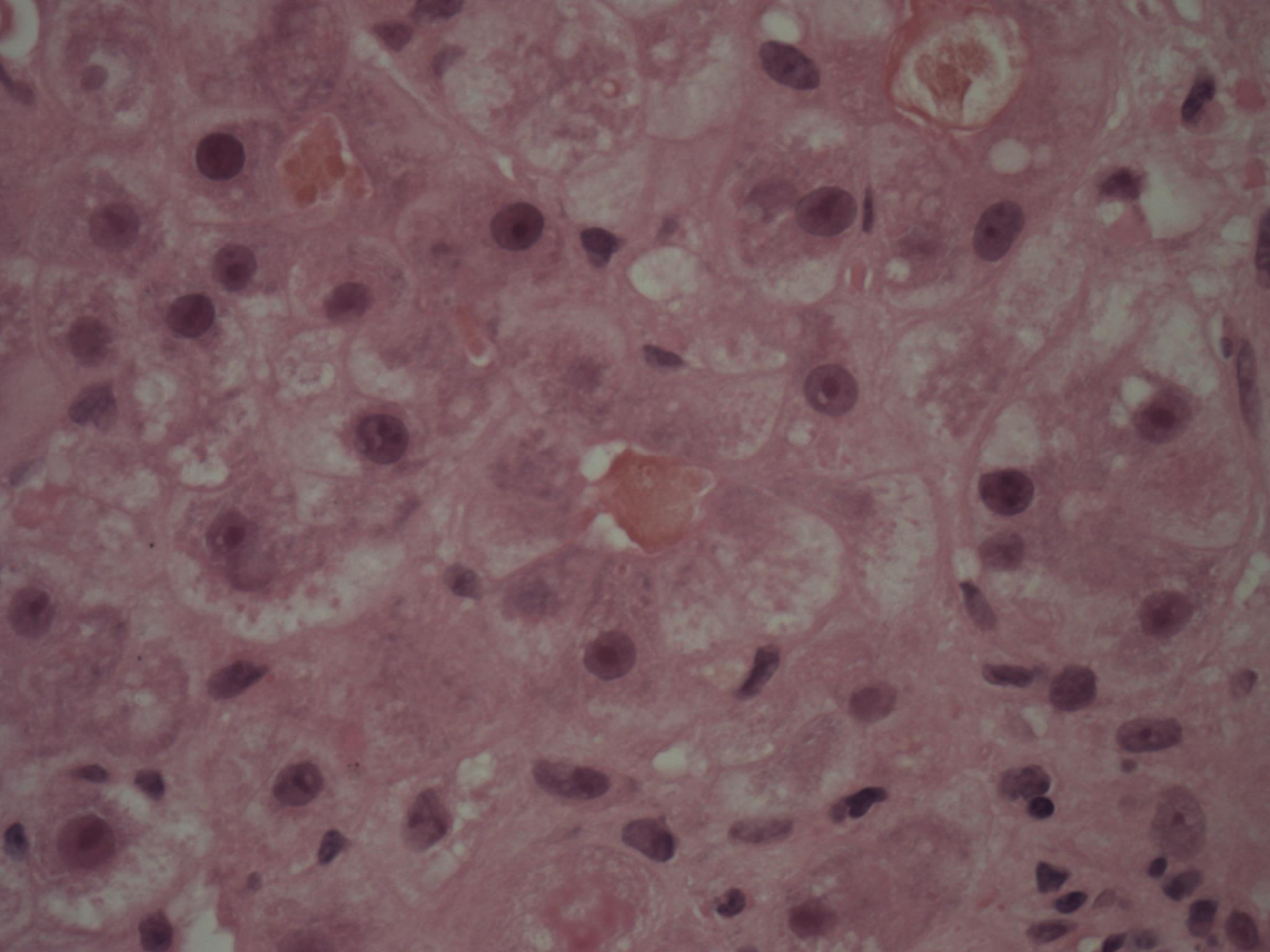


3. Acute HEV









HEV-associated **neurologic** diseases

- diverse central & peripheral injuries Kamar2011
 - Guillain-Barre (5%, van den Berg 2014)
 - neuralgic amyotrophy (10%, van EijkJJ 2014)
 - meningoencephalitis, Bell's palsy...
- neurological signs **dominate**
 - 5% of symptomatic HEV (acute HEV1/3 or chronic)
 - mild or no transaminitis
 - pathogenesis unknown
 - ? neurotropic forms Kamar2010

Virology

- non-enveloped ssRNA
 - resistant to
 - heat (<71°C 20 mins) Barnaud2012
 - acid/alkali, cleaning agents
 - reinfection possible
 - no viral determinants of FHF Smith2014
- mammalian (also bat, avian, fish) Smith2013, Kamar2014
 - human (g1,2)
 - late 18th century: jaundice outbreaks targeting young adults and fatal to pregnant women. ? shifting east after WWII
 - swine, human, deer (g3,4). (rabbit)
 - common mammalian ancestor 500-1400 yrs ago Purdy2010
- cytoplasmic replication

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Life & style > Meat

Chefs fight for the right to serve their pork pink

Gourmets say rare meat tastes better as inspectors warn of potentially fatal virus in undercooked meat

Jamie Doward

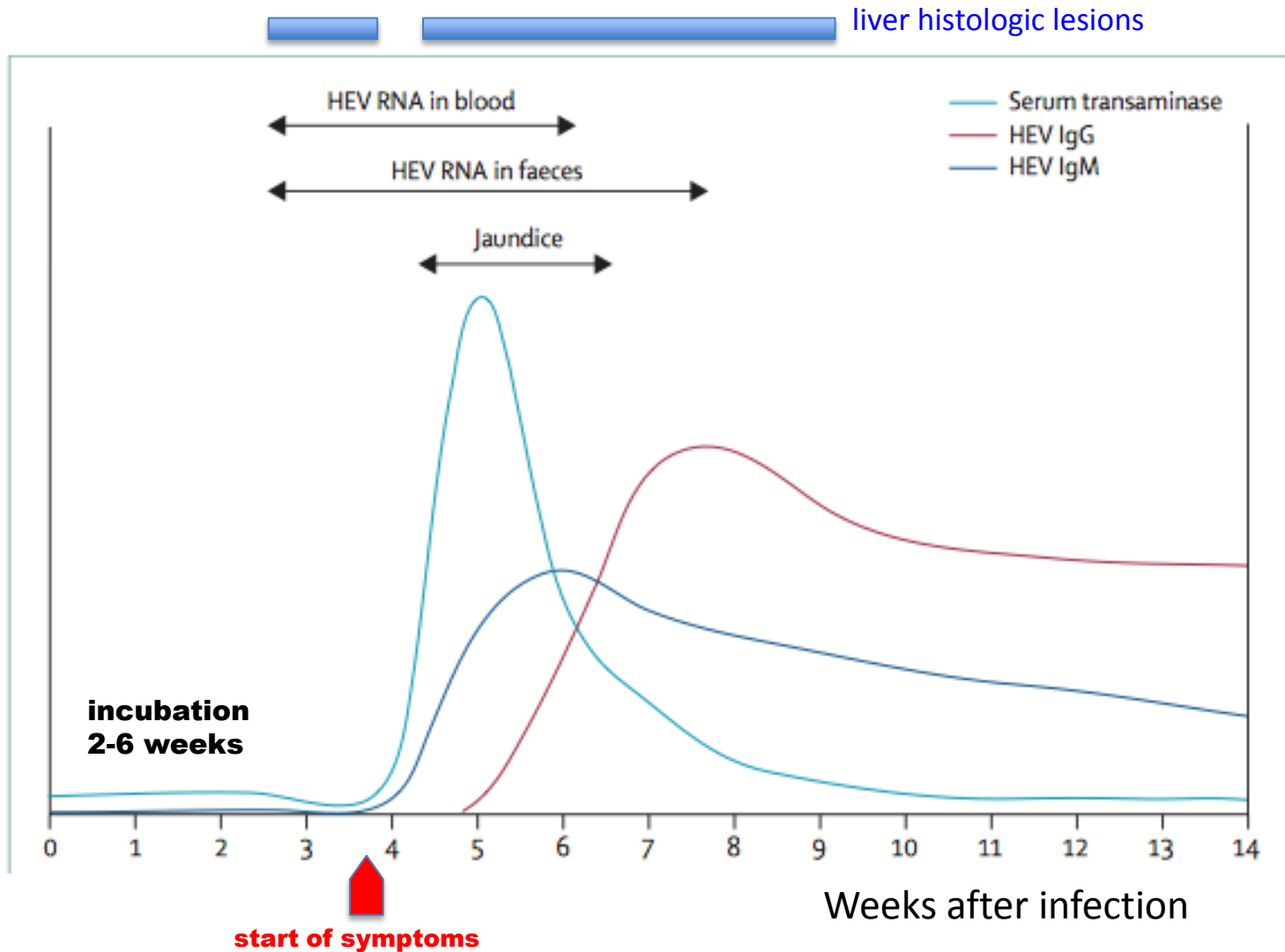
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Transmission

- waterborne from humans
- infected animals
 - undercooked pork, pig liver, venison, (rabbit)
 - contamination (salad, fruit)
 - animal slurry: shellfish Crossan2012
 - occupational risk: vet, pig farmer, butcher...
- blood products
 - pooled plasma Baylis2012
 - transfusion Khuroo2004, Matsubayashi2008
 - SE England Hewlitt2014
 - 1:2800 donations viraemic (5x SE Scotland)
 - 129 components (esp platelets): 60 patients received
 - 42% recipients infected
 - 10/18 had mod/sev immunosuppression (aplastic anaemia, malignancy, 1 transplant) and showed **prolonged or chronic** infection (median 18w, 30w vs 10w infection)



Diagnosis



Diagnosis of recent infection

- single serotype
 - IgM
 - sustained ~8wks
 - rising IgG of low avidity
 - peak ~4wks after symptom onset, sustained years Huang2010
- RNA
 - peak during incubation & early symptomatic
 - 3 wks after symptoms (blood)(5wks stool)
 - rtPCR or LAMP
 - large **variability** of in house assays (Baylis2011)
 - WHO standard (Baylis2013) g3a
 - » commercial assays show good concordance

Estimation of past infection

- seroprevalence: one serotype

- kit differences Bendall 2010, Wenzel2013

- 3 vs 16% (SW England);
- 4 vs 18 vs 29% (Germany);
- 16 vs 53% (SW France)

- age increase

- geographic variation

- 2% West Japan (6% East Japan)
- 4% New Zealand
- 5% Scotland (28% if >55yrs)
- 10-16% England/Wales
- 14% Germany
- 27% Holland
- 32% China (heterogeneous)
- 52% South-West France (4x North France)

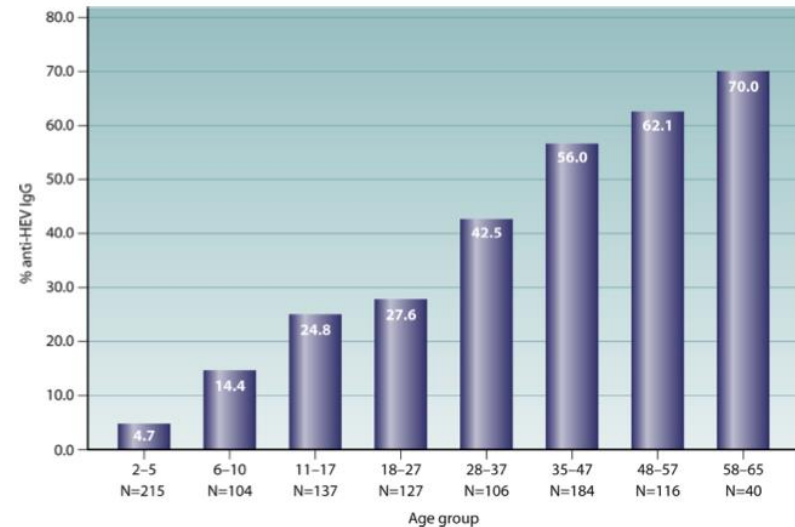
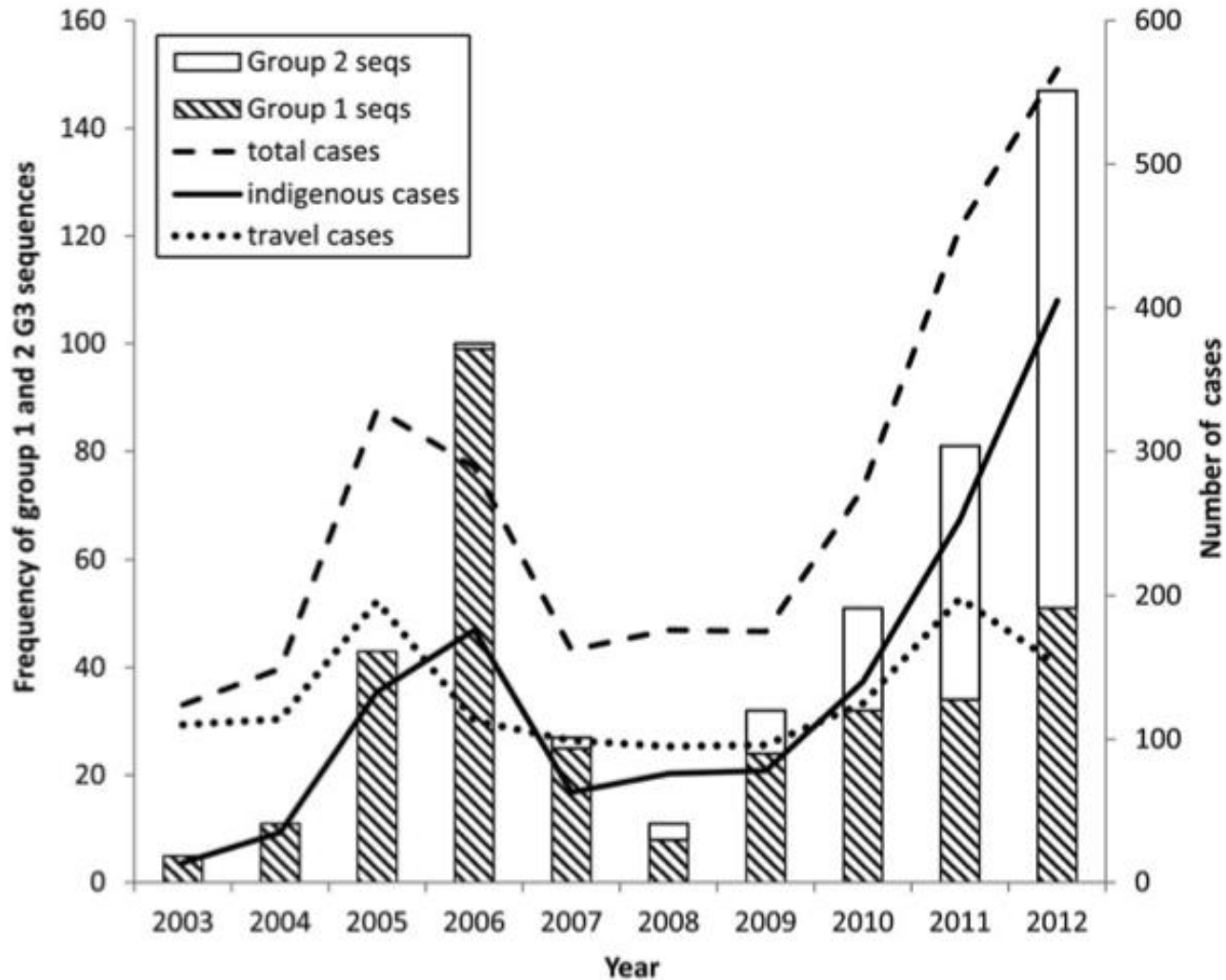


FIG 3 Anti-hepatitis E virus IgG distribution in Midi-Pyrenees area of France, according to age.

Kamar2014

HEV infection trends



Chronic hepatitis E

- **genotype 3 only**
 - prolonged viraemia (6m; transplant patients don't clear after 3m)
 - **serology unreliable: may not seroconvert**
 - mild transaminitis, few/no symptoms
- **transmission**
 - as general population
 - transfusion (not CVID)
 - occult donor infection Schlosser2012
 - reinfection of 2nd liver graft
 - reactivation after stem cell transplant
- **course/complications**
 - rapid, aggressive progression including early cirrhosis in 10%
 - neurologic
 - membranous GN
 - human recombinants (Wang2010)
 - ribosome gene fragment: selective advantage in culture (Shukla2011, Nguyen2012)

Chronic hepatitis E

- **clinical setting**: impaired cellular immunity
 - **solid organ transplants**
 - ~1% (5% if abnormal LFT) Kamar2014.
 - ± brief fatigue, mild transaminitis. Jaundice rare
 - ~60% of infections become chronic Kamar2011
 - no spontaneous clearance after 3 months viraemia Kamar2013
 - » 32% cleared after immunosuppression decreased
 - liver biopsy
 - acute: no ballooning, mild hepatitis
 - chronic: chronic hepatitis,
 - » 10% cirrhosis, often in 2-3 years

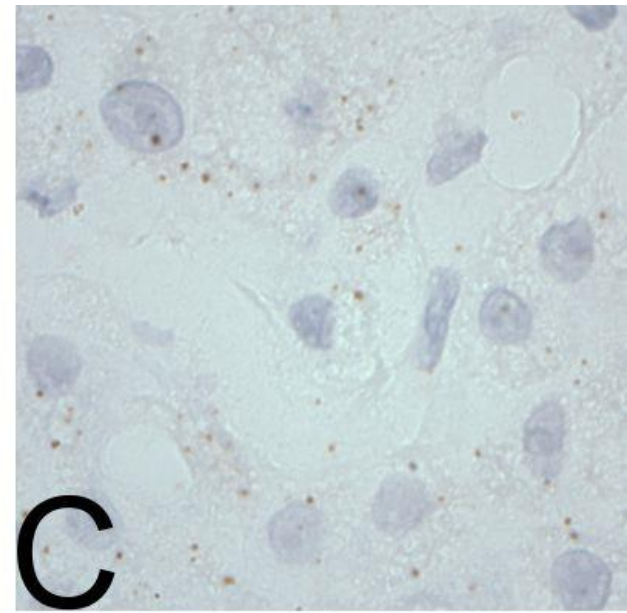
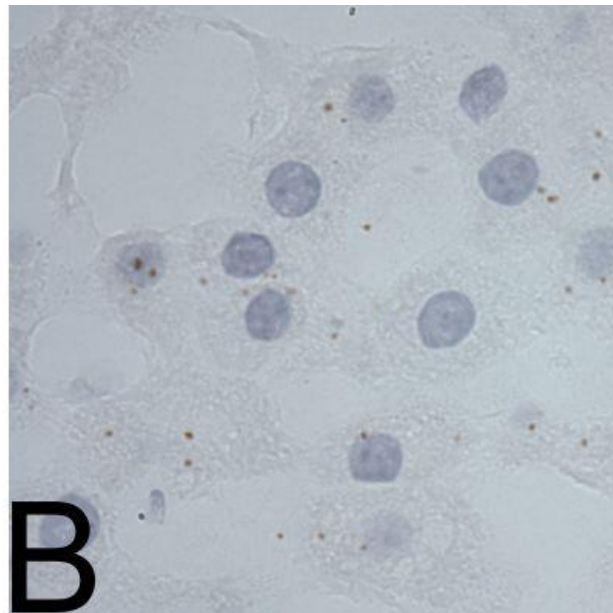
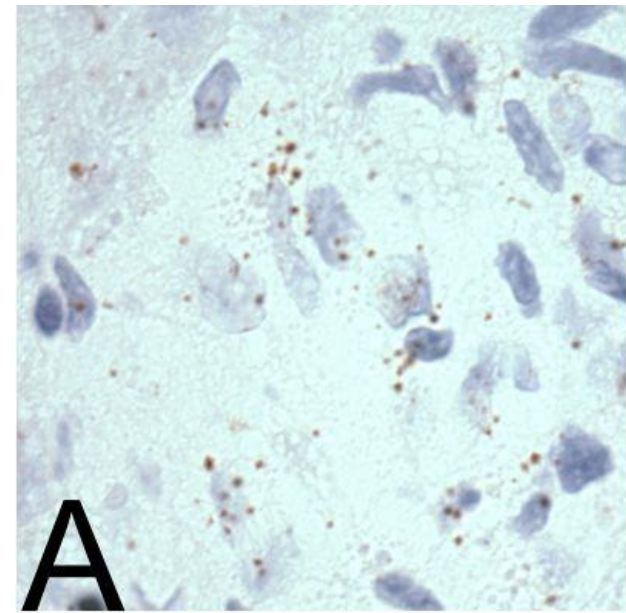
Chronic hepatitis E

- other clinical settings
 - haematological malignancy Tamura2007, Tavitian2010
 - stem cell transplantation Peron2006
 - including reactivation
 - pauci-immune vasculitis
 - SLE on treatment Grewal2014
 - retroperitoneal fibrosis HonerZuSiederdisen2014
 - HIV with low CD4 count Dalton2009, Kaba2011
 - CD4 T cell defect HonerZuSiederdisen2014

Pathology of chronic HEV

- [Kamar2008](#)
 - 9 acute liver bx:
 - no ballooning, some acidophils, mild portal/interface/lobular lymphocytic hepatitis
 - chronic viraemia & transaminitis (6 bx, 10-18m after acute HEV)
 - chronic lymphocytic hepatitis: dense portal, varied interface, mild/mod lobulitis
- [Gerolami2008](#):
 - cirrhosis with portal/interface hepatitis after 15months chronic HEV
- [Haagsma2008](#)
 - Husband got acute g3 HEV, recovered.
 - She had mild fatigue + transaminitis, sero-negative (later shown RNA+).
 - Mild hepatitis on bx. Seroconverted by 1 year later.
 - Mild lobular/portal hepatitis evolving to cirrhosis with retransplant 5 years later (4bx, explant),
 - recurred after retx (mild portal, mod lobular hepatitis with mild fibrosis)
- [Kamar2008](#)
 - cirrhosis 22 & 38 months after acute HEV
 - portal & lobular hepatitis then chronic hepatitis with lymphocytic cholangitis
- [After clearance](#) (4 cases) [Kamar2010](#)
 - less activity than the viraemics, but no clear improvement of fibrosis after 9-20m

Thank you



management

- prevention
 - water sanitation
 - avoid partly cooked pork products (<71c 20 mins) & raw shellfish
 - better pig effluent disposal
 - (? blood product screening for immunosuppressed)
- vaccination?
 - HEV239 licensed in China (genotype 1: protects 4 also)
 - pig vaccines
- treatment of chronic HEV
 - reduce immunosuppression
 - ribavirin (3m) Kamar2014
 - SVR in 78%