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Infectious Canine Hepatitis (ICH)

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- Canine contagious hepatitis or Rubarth's disease = Infectious, contagious, virulent and inoculable disease, specific to canids, caused by canine adenovirus type 1 (CAV-1).

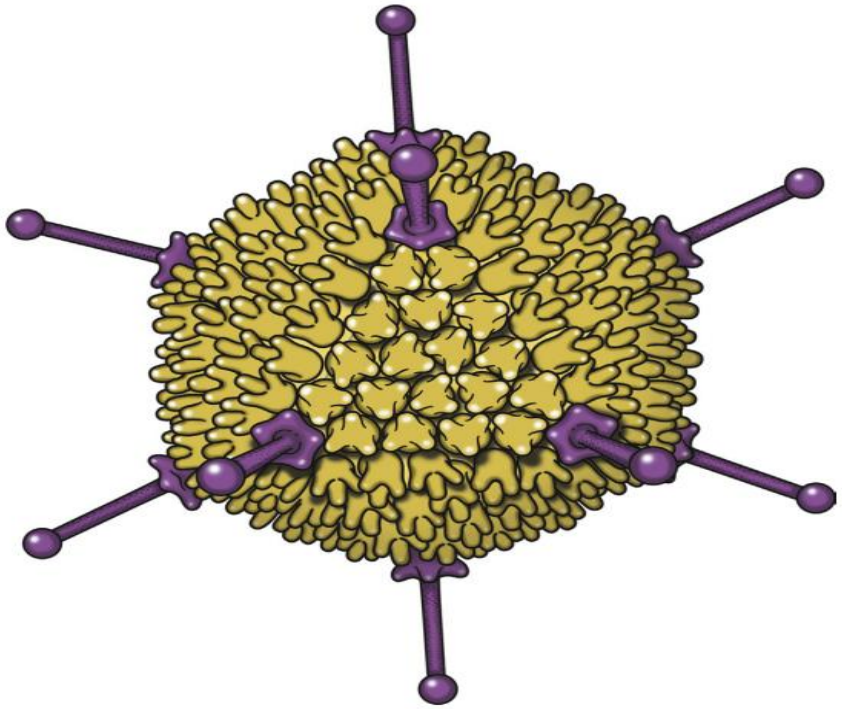
- Infection, very widespread; most often in an inapparent form.
- Very polymorphic general disease with rapid evolution: gastroenteritis, adenitis, hepatic symptoms, and mortality in young puppies.

Etiology

The infectious agent responsible: Canine adenovirus type 1 (CAV-1):

- Family of Adenoviridae, genus Mastadenovirus.
- Double-stranded DNA virus, non-enveloped with icosahedral capsid

Structure of canine adenovirus: Icosahedral, non-enveloped with fibers or spikes (purple) radiating outward from the virion.



- **CAV-1 and CAV-2 have different tropisms; however, they are antigenically related.**
- Canine adenovirus type 2 (CAV-2) = Infectious tracheobronchitis in dogs (Kennel cough) = Canine infectious respiratory disease complex (CIRDC)

Virus resistance

- CAV-1: Very resistant to environmental stresses:
  - Remains infectious for up to 9 months in the external environment; pH=3-9; low temperature (< 4 °C).
  - Ambient temperature: Can survive 3-11 days on contaminated objects.
  - Can survive various disinfectants: Chloroform, Ether, acids, and formaldehyde.
  - Stable under certain UV frequencies.

- Inactivated = 5 minutes at 50 °C-60 °C, making steam cleaning (wet steam) a good means of disinfection.
- Effective chemical disinfection with: Iodine, phenol, and sodium hydroxide (potentially caustic products).

Epidemiological data

➢ **Sensitive species =**

- CAV-1 = Clinical disease in:

✓ **Canids: Dogs, coyotes, foxes, wolves, etc.**

✓ Fox encephalitis.

- Bears (Ursids), weasels (Mustelids) can be infected.
- Skunks are susceptible to CAV-1.
- A fatal infection has been reported in an otter.
- Serum antibodies (virus-specific): Detected in marine mammals: Walruses and sea lions.

Skunk

European Weasel

Otter

Walrus

- **Geographic distribution: Described worldwide: United States, Canada, United Kingdom, Australia, Japan, Brazil, Europe, etc.**

- **At-risk dog population:**

  - **Young < one; although unvaccinated dogs of any age can be affected:**

  - Mortality = 100% for puppies <2 weeks; 10-30% for adults.

➢ Mode of transmission:

- Entry route = oro-nasal route.
- Contagion occurs directly; possible indirectly.
- The virus can cross from mother to fetus through the placenta.

➢ **Virulent materials**

- Urine, feces, saliva from infected animals.
- **Urine is the most important source of the virus.**
- Possibility: Passive vectors (objects: eating utensils), hands of handlers, ectoparasites.

➢ Excretion of the virus

- ❑ Isolated in all body tissues and secretions (urine, saliva, feces) of dogs during acute phases.
- ❑ Between 10 to 14 days PI, the virus is found only in the kidneys = Urinary excretion.
- ❑ CAV-1 = Excreted in urine for at least 6 to 9 months.

Pathogenicity

- After oronasal exposure, the pathway of the virus in the body can be divided into 3 successive phases:

- ***First phase = Local primary replication***

The virus multiplies in epithelial cells, as well as in macrophages of the tonsils and local lymph nodes.

❑*Second phase = Viral dissemination (Viremia)*

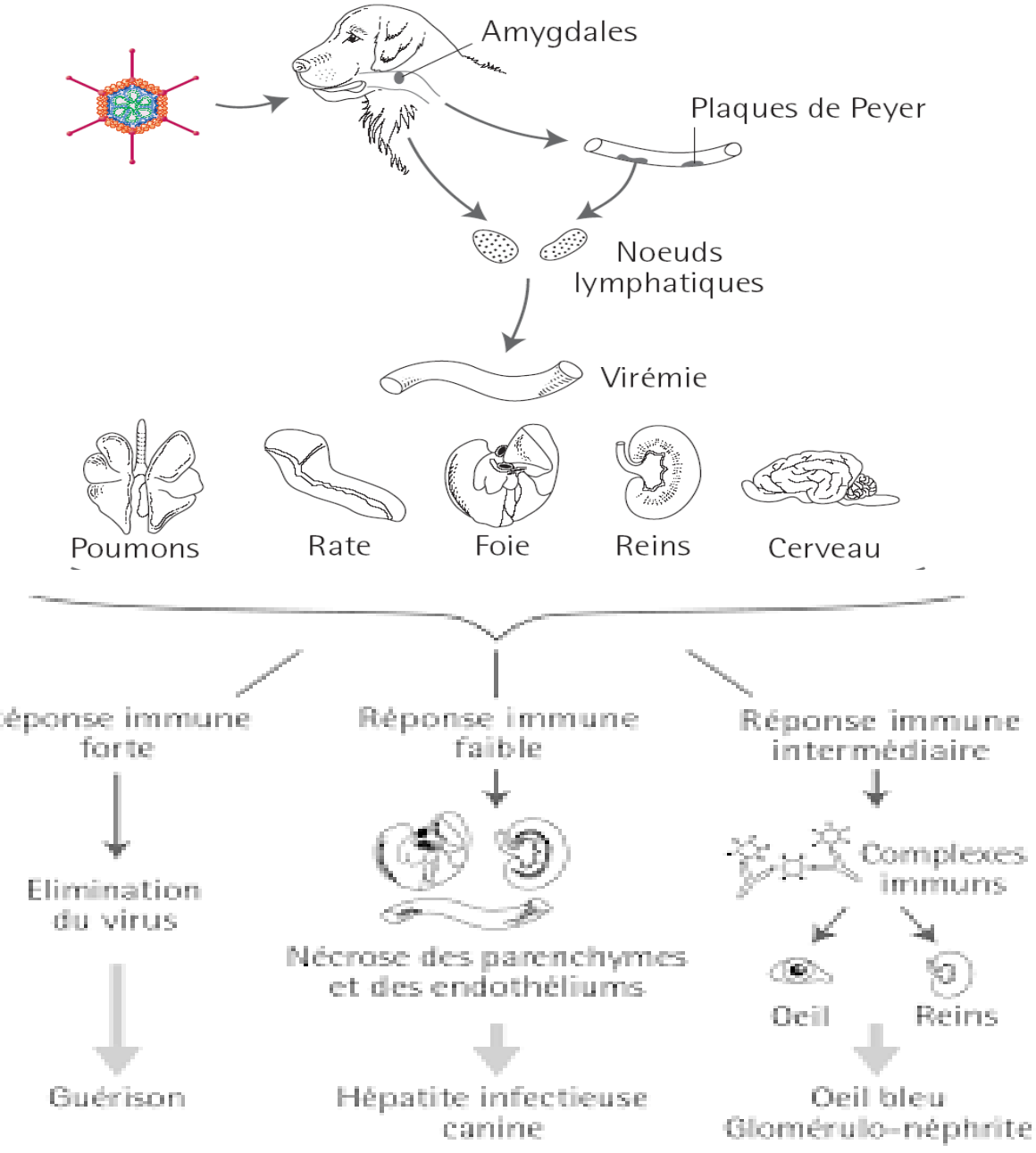
Starting from day 4, the virus reaches the blood through the thoracic duct via lymphocytes.

- Third phase = Secondary replication

The viremia, which lasts 4 to 8 days, leads to the secondary replication of virions in the vascular endothelium of many target organs: liver, kidneys, CNS, digestive tract, eye, lymph nodes.

Note:

- The transition from phase 1 to phase 2 is not systematic and seems to be quite rare, which would explain the large number of asymptomatic or localized forms.
- Tropism = Vascular endothelial cells; renal and hepatic parenchymal cells.


Amygdales
Plaques de Peyer
Noeuds lymphatiques
Virémie
Poumons
Rate
Foie
Reins
Cerveau
Réponse immune forte
Réponse immune faible
Réponse immune intermédiaire
Elimination du virus
Nécrose des parenchymes et des endothéliums
Complexes immuns
Oeil
Reins
Guérison
Hépatite infectieuse canine
Oeil bleu
Glomérulo-néphrite

- The disease includes 2 categories of symptoms slightly staggered in time:

- Primary: Related to the lesions caused by the secondary replication of virions in the endothelium of target organs, particularly the digestive tract = Hemorrhagic.

- Secondary symptoms: Possible consequences of ocular and renal hypersensitivity phenomena.

- Disseminated intravascular coagulation (DIC): A common complication = Begins at the onset of the viremia phase:

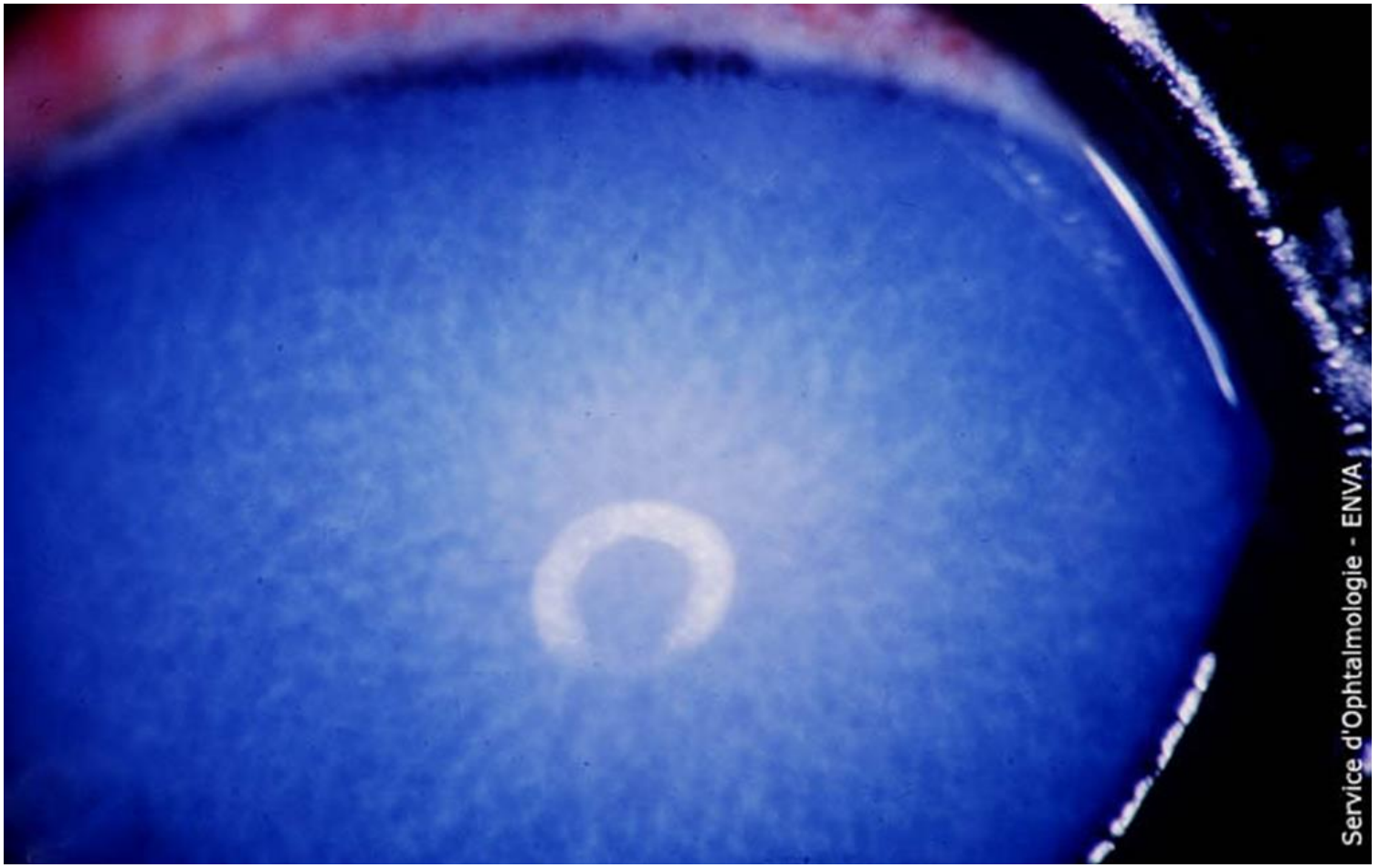
❖ Lesions of endothelial cells = a widespread activation of the coagulation mechanism.

❖ Inability of the diseased liver to eliminate activated coagulation factors.

- Infection leads to the production of antibodies, which react secondarily with viral origin components and can cause neutralization reactions but also delayed hypersensitivity:

- Type III (Arthus reaction) in the eye that can cause a particular corneal edema = Blue keratitis.
- Type IV in the kidney: Nephritis that manifests as isolated proteinuria.

Blue keratitis



Clinical study

- Different clinical forms.
- Incubation = 4 to 5 days PI.
- Severity of the disease depends on:
  - **Age of the animal.**
  - **Immune status.**

Peracute form

- Very brutal; more often in puppies, exceptional in adult dogs.
- Generally observed in communities where other animals are introduced.
- Rapid evolution: Healthy animal in the evening, found dead the next morning without any alarming signs having attracted the owner's attention.

- Death in 24-48 hours without prodrome or characteristic clinical picture following severe hepatic injury (hepatitis) and a state of collapse.
- Owners often believe their dogs have been poisoned.
- Lesions: Vascular origin = hemorrhages + hemorrhagic effusions in large cavities (thoracic, abdominal).

Acute form

- Acute form progresses in 6 to 10 days.
- Mortality: 10-30% in 2 weeks.
- One can achieve recovery after a convalescence period (of approximately 15 days).

- During the first 48 hours:
  - Severe lethargy, dehydration, fever (40 - 41 °C).
  - Fever may be transient or biphasic at the onset of the disease.
  - Tachypnea and tachycardia.
  - Conjunctivitis and inflammation of the mucous membranes.

- After 48 hours:
- Temperature decreases.
- Onset of the state of hepatitis.
- Liver dysfunction leads to digestive disorders = Anorexia, intense thirst, frequent yellowish mucous liquid vomiting, and foul-smelling yellow diarrhea with dehydration and electrolyte imbalance.

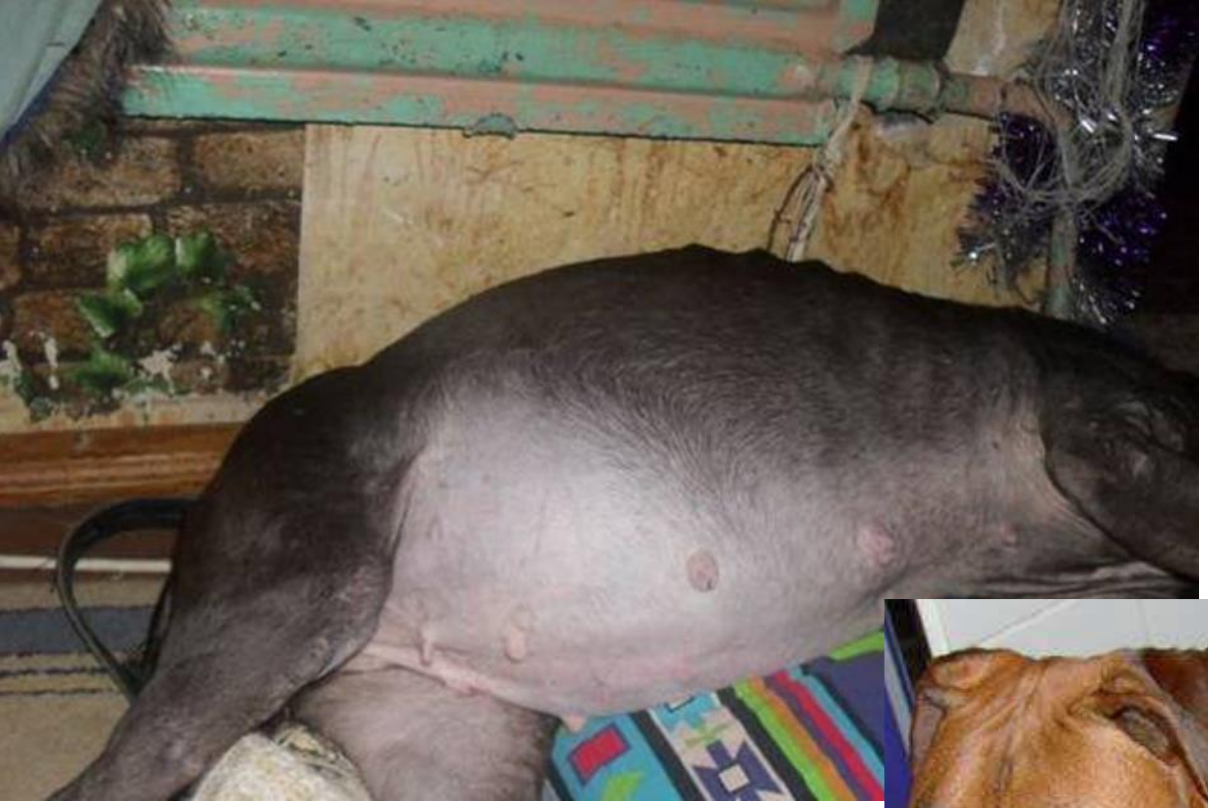
- Abdominal palpation: Hepatomegaly (Pain in the upper right hypochondrium = Projection of the gallbladder), splenomegaly.

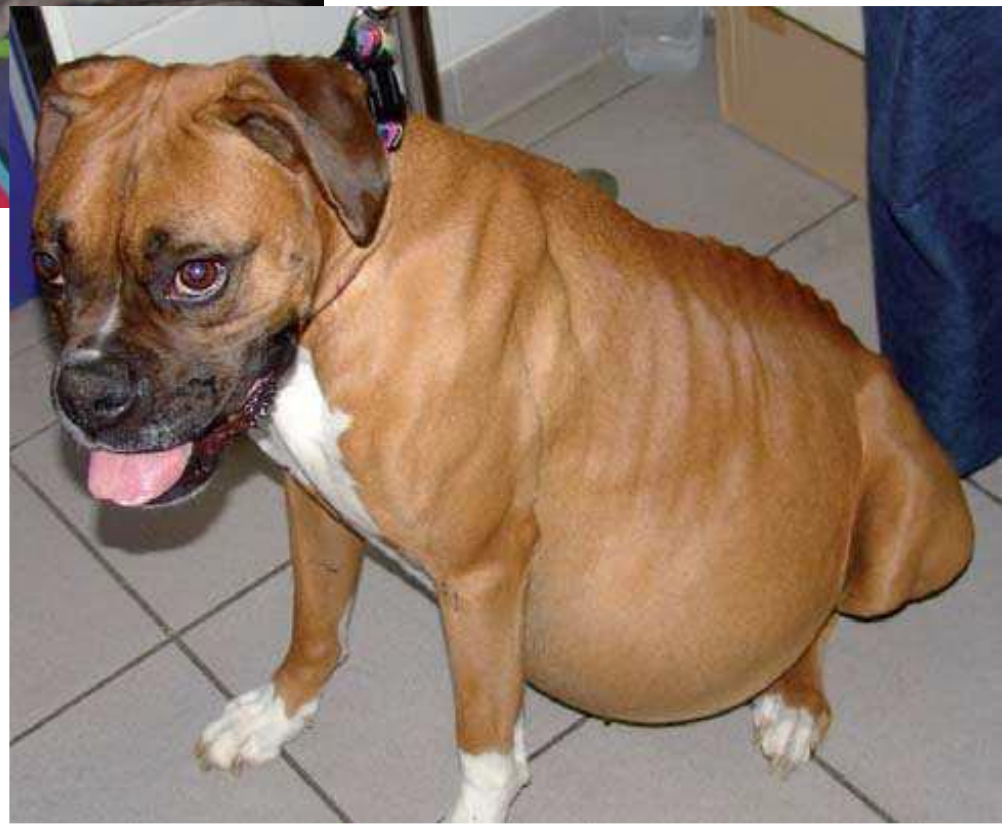
- Hypertrophy and congestion of the tonsils, generally associated with pharyngitis and laryngitis.
- Coughing and auscultated sounds from the lower respiratory tract are manifestations of pneumonia.
- Serous to mucopurulent ocular and nasal discharge (co-infections = respiratory viruses and/or bacteria).

- Peripheral cervical lymphadenopathy:
  - Submandibular, retro-pharyngeal, pre-scapular, etc. = Hypertrophy clearly perceptible on palpation.
  - Associated with subcutaneous swelling of the head and neck.

- Coagulopathies (DIC) = Hemorrhagic disorders:

- Pallor of the mucous membranes (hemorrhages).
- Cutaneous or mucosal petechial hemorrhages (gingival hemorrhages); epistaxis; prolonged bleeding from venous puncture sites.
- Peripheral bleeding, in the thorax or abdomen = Ascites (abdominal distension due to the accumulation of serosanguineous or hemorrhagic fluid).





Ascites

- Jaundice:
  - Rare.
  - May occur in dogs whose progression of the disease is longer.
  - It can be found in some dogs that survive the acute fulminant phase of the disease.

- The acute form is still characterized by signs:

- Ocular (20% of cases).

and

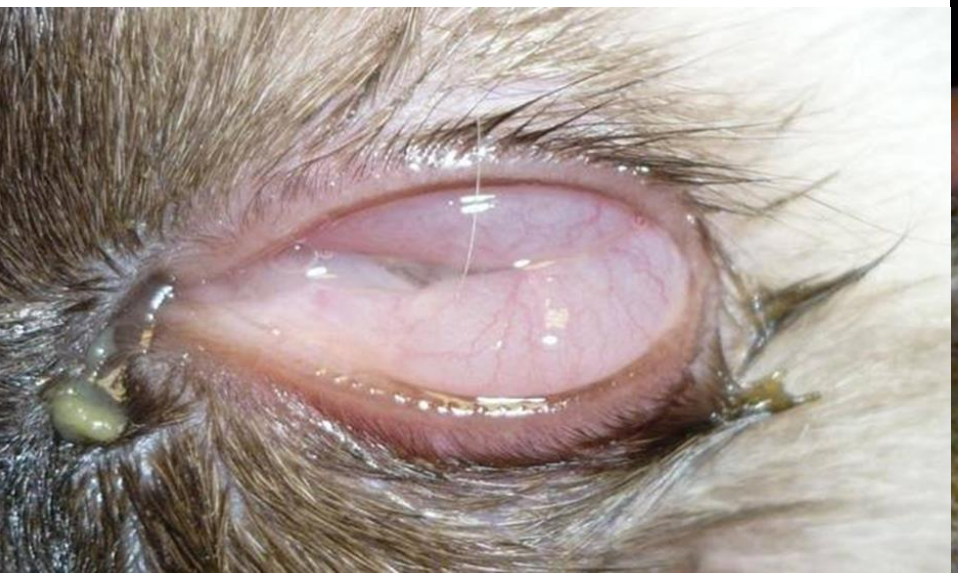
- Nervous (less common).

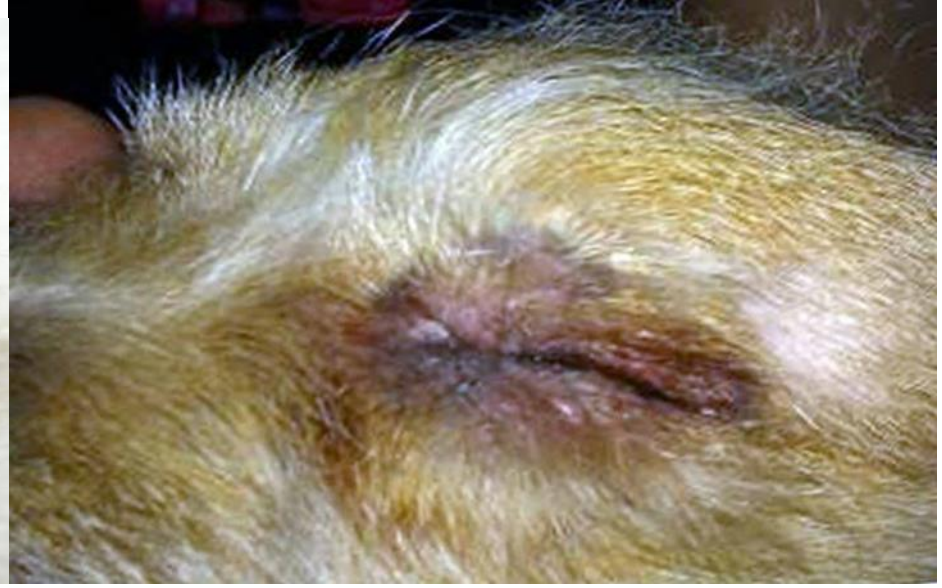
- Ocular symptoms:

- Evocative.

- Anterior uveitis or iridocyclitis (iris + ciliary body) = can manifest as photophobia; Conjunctival edema (chemosis)

- unilateral or bilateral corneal edema (blue keratitis) = Bluish corneal opacity (following damage to the corneal endothelium).
- Corneal ulceration.
- Blepharospasm, serous ocular discharge.

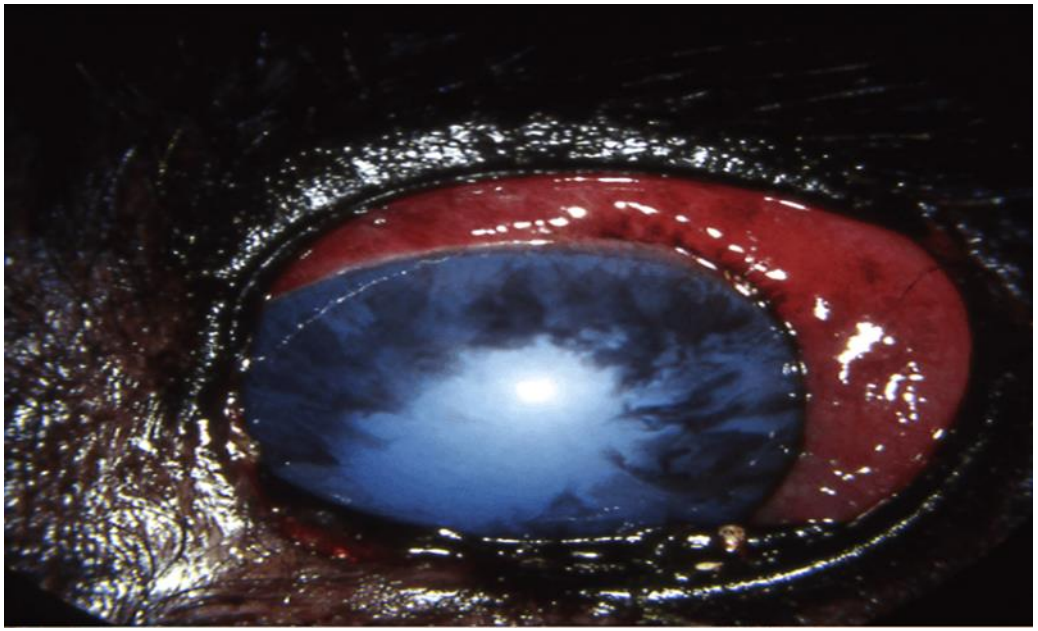




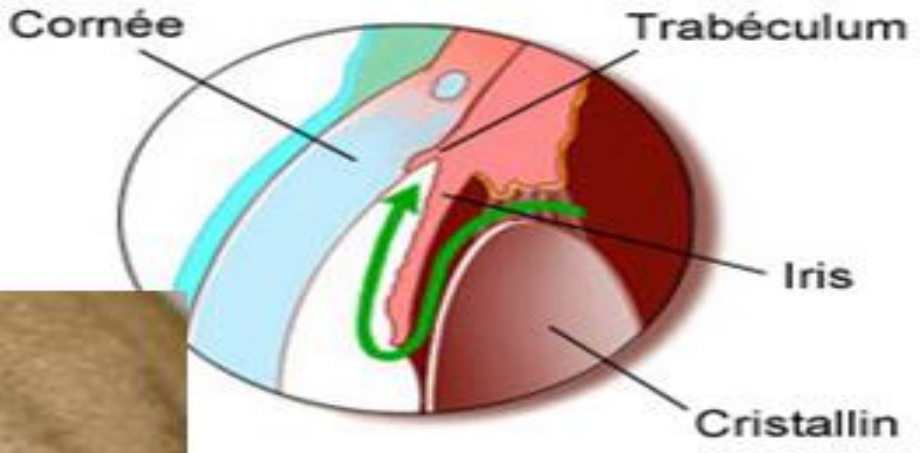
Chemosis.

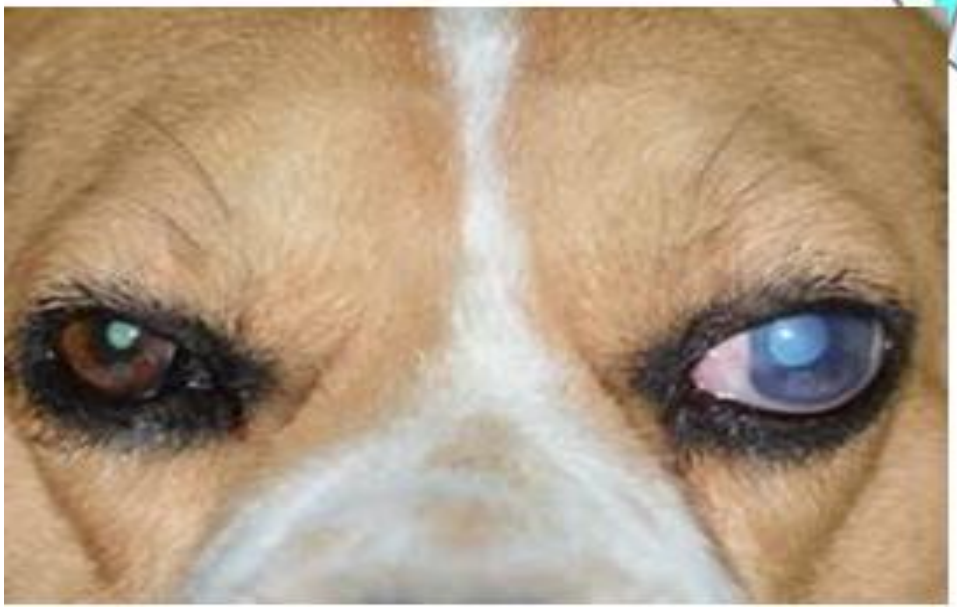
Blepharospasm.

Diffuse edema of the cornea in a dog with Rubarth disease (blue keratitis).



- It can be noted:
- ✓ Hydrophthalmos = Glaucoma = Increase in intraocular pressure (IOP) = Blindness.
- ✓ Phthisis = Ocular hypotonia.





- Neurological disorders.
  - Rare.
  - Encephalitis: Circling behavior, vocalization, pressure on the head (coma, convulsions), ataxia, and blindness.

Mild or benign forms

- Discrete: Gastroenteritis + transient hyperemia.
- Uncomplicated clinical signs = often last 5 to 7 days before improvement.
- Concurrent infections (e.g. canine distemper) can worsen benign forms.
- Sometimes: Blue keratitis and/or anterior uveitis occur; they may be the only clinical abnormalities observed.

Subclinical forms

- High prevalence of neutralizing serum antibodies (of natural origin) in the population of wild dogs and unvaccinated dogs suggesting:

Subclinical infection is very common.

Atypical forms

- Nervous: rare.
- Respiratory: Laryngo-tracheitis or rhino-tracheobronchitis: runny nose, strong and paroxysmal cough, bronchial rales.

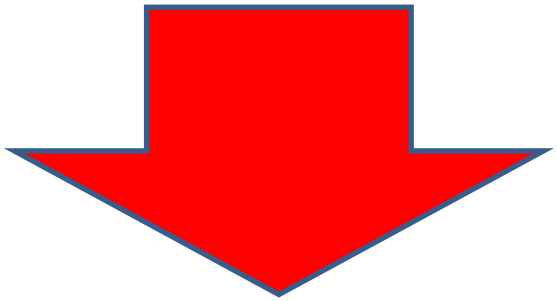
Evolution of affected animals

- Acute forms: 100% mortality.
- Acute forms: Healing in 10 days or death after a short period of coma.

Lesional study

Acute form

Acute form



Macroscopic and microscopic lesions are highly pathognomonic

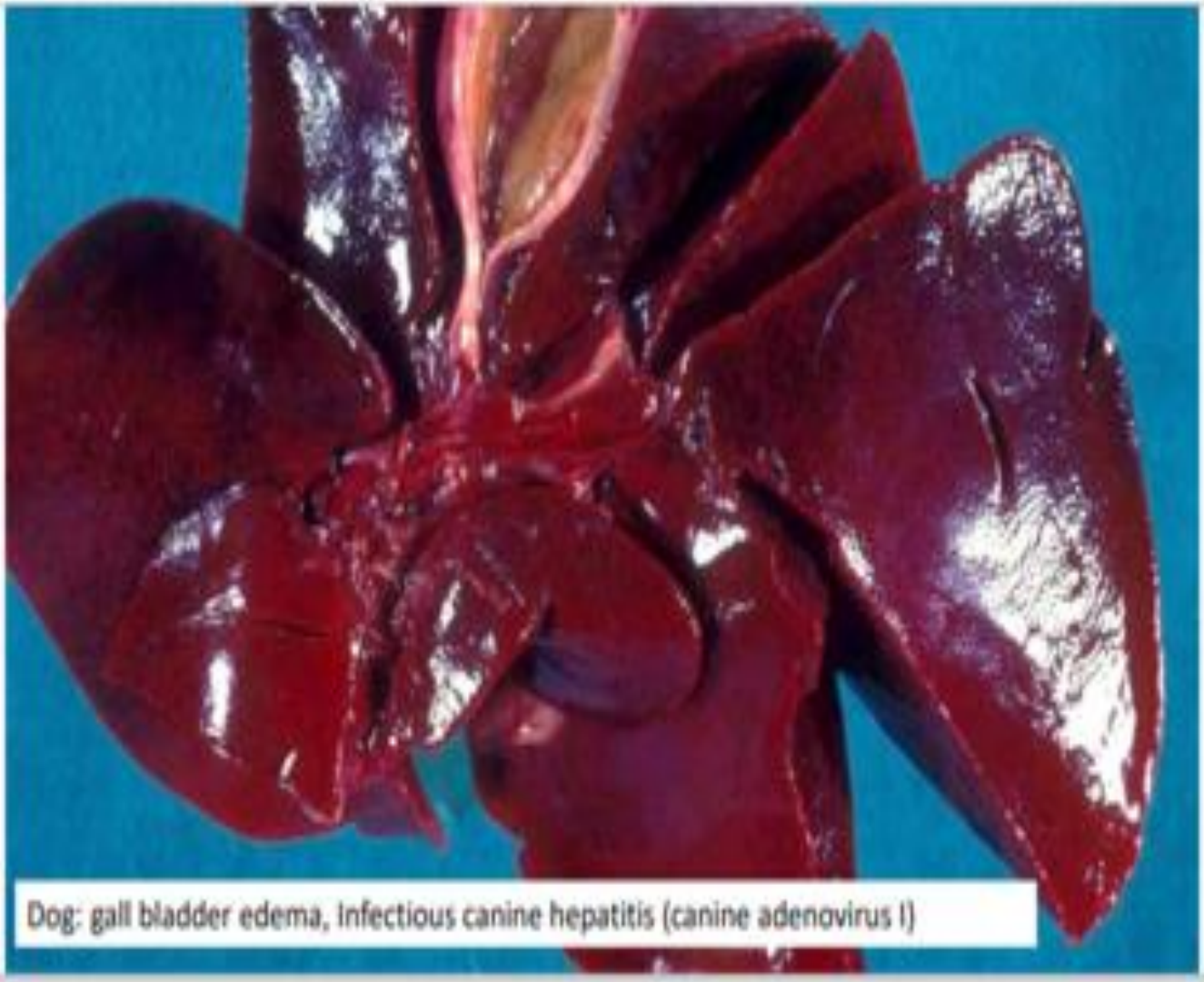
➢ **Macroscopic**

- ❑ Vascular damage:
  - ❖ Edema, congestion, various hemorrhages in the form of petechiae, suffusion or even effusion.

= Peritoneum, mediastinum, lymph nodes, rarely = Renal cortex, lungs.

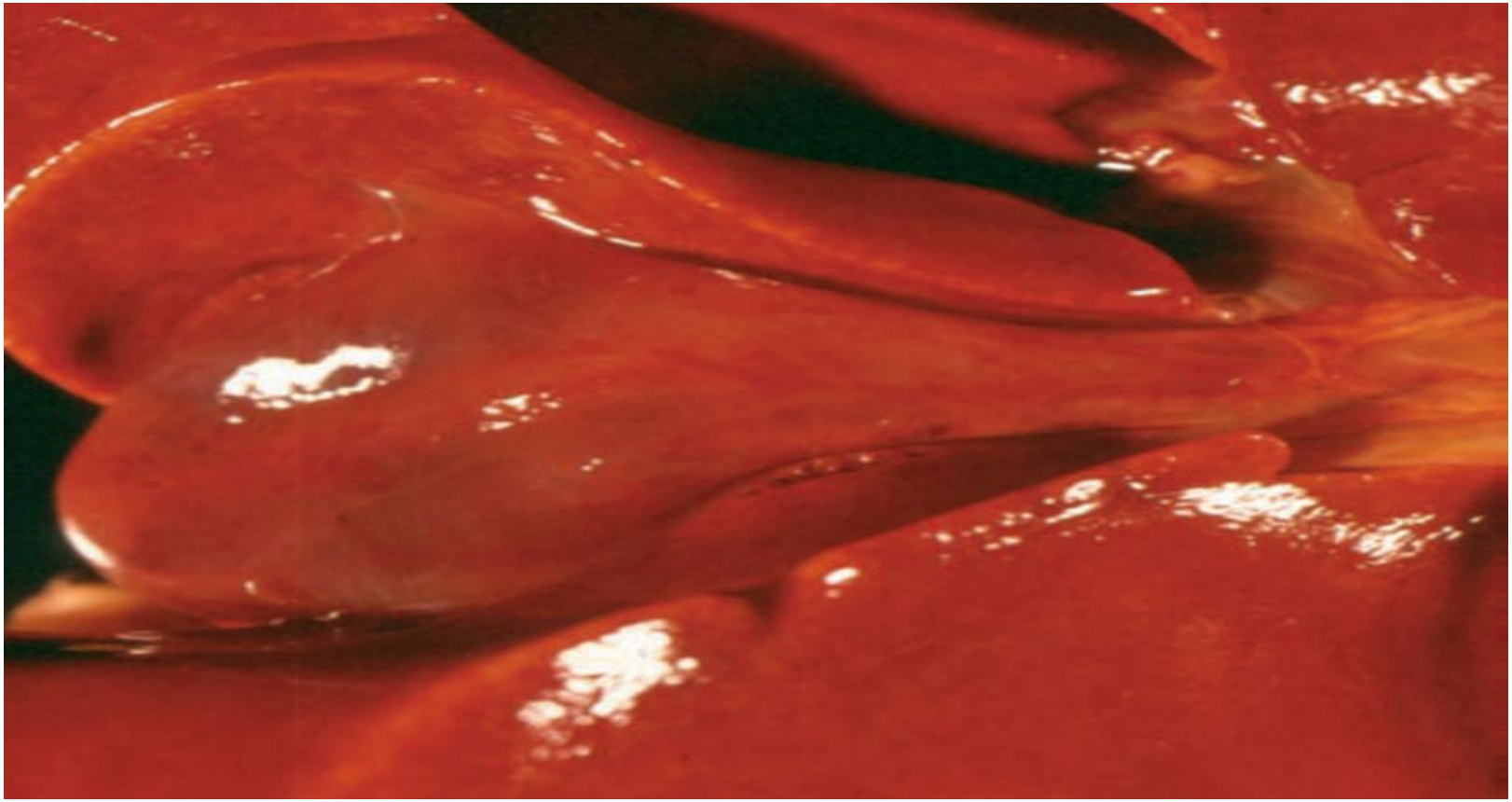
- Liver lesions:

  - Superposition of congestion and centro-lobular necrosis which gives it a gritty or orange peel appearance.
  - Biliary bladder involvement is constant and pathognomonic in acute forms with considerable thickening of the wall.

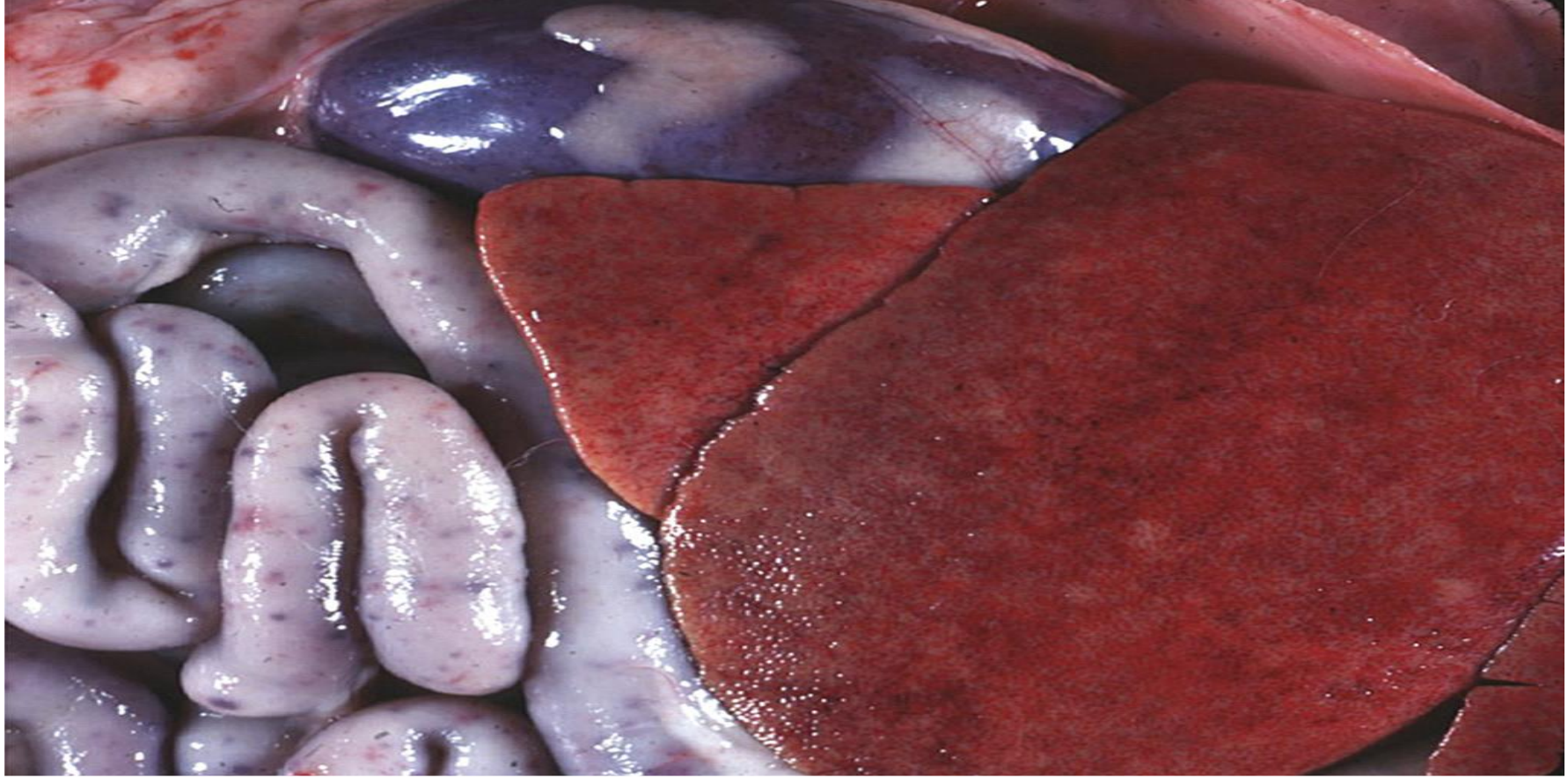


Dog: gall bladder edema, Infectious canine hepatitis (canine adenovirus I)

Viral hepatitis



Enlarged and speckled liver with rounded lobar edges + edema of the gallbladder characteristic of canine infectious hepatitis.

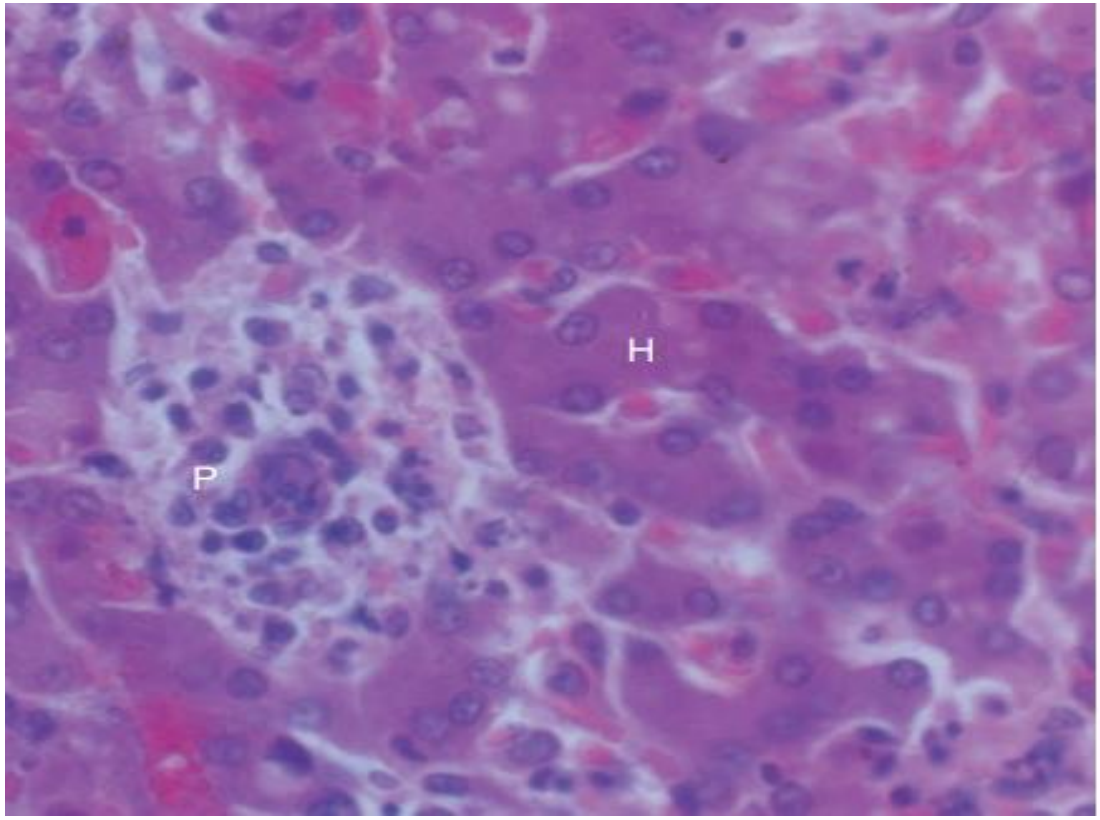


Liver of a dog affected by canine infectious hepatitis: Slightly enlarged, friable, yellow speckled discoloration (necrosis). Sometimes, fibrin is evident on the capsular surface.

Note the petechiae on the serosal surface of the intestines caused by vascular lesions.

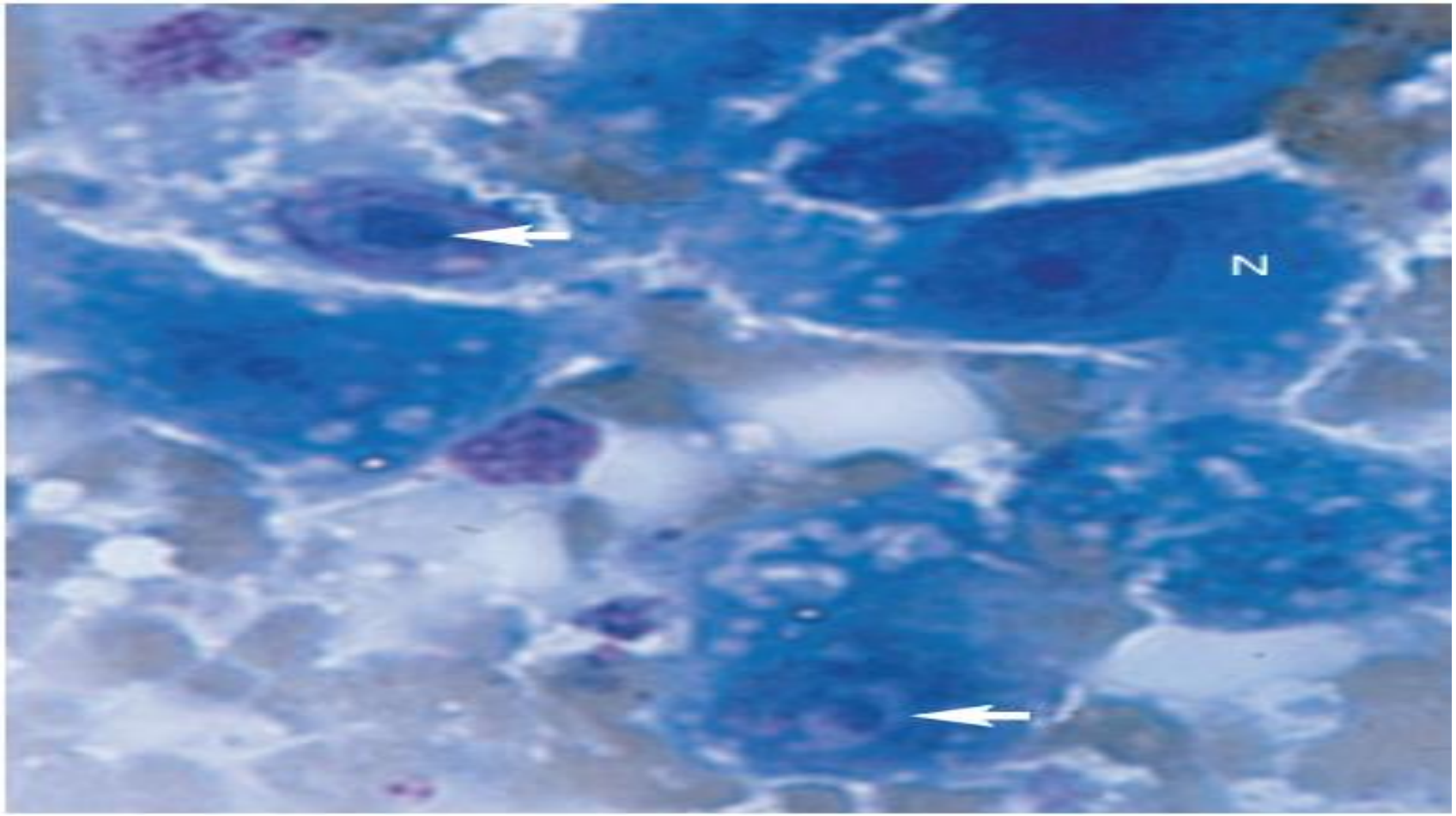
- **Microscopically**

- Congestive and necrotizing serum hepatitis (centrolobular necrosis).
- Presence of intranuclear inclusions = Bird-eye appearance specific to hepatocytes and Kupffer cells.



Histological appearance of massive centrolobular necrosis in a fatal case of contagious canine hepatitis = some remaining viable hepatocytes (H) around a portal vein (P) in the peripheral lobular region (H & E staining, × 250).

Cytological appearance of intranuclear inclusions in hepatocytes (arrows) in an impression smear of liver tissue at autopsy (Wright staining, × 400) from a puppy following infection with CAV-1. Compare to the nucleus of the hepatocytes (N).

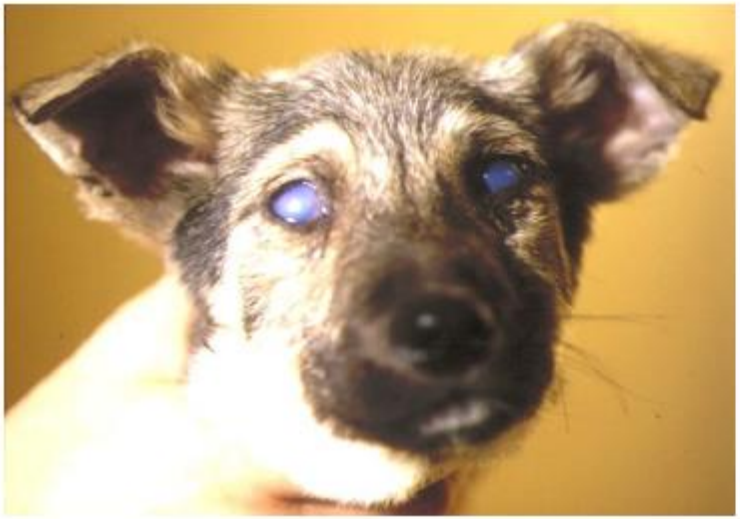


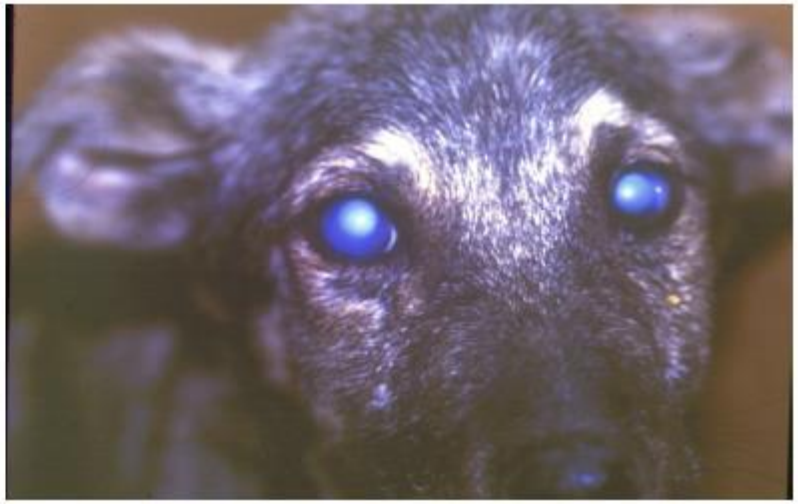
Diagnosis

Clinical signs

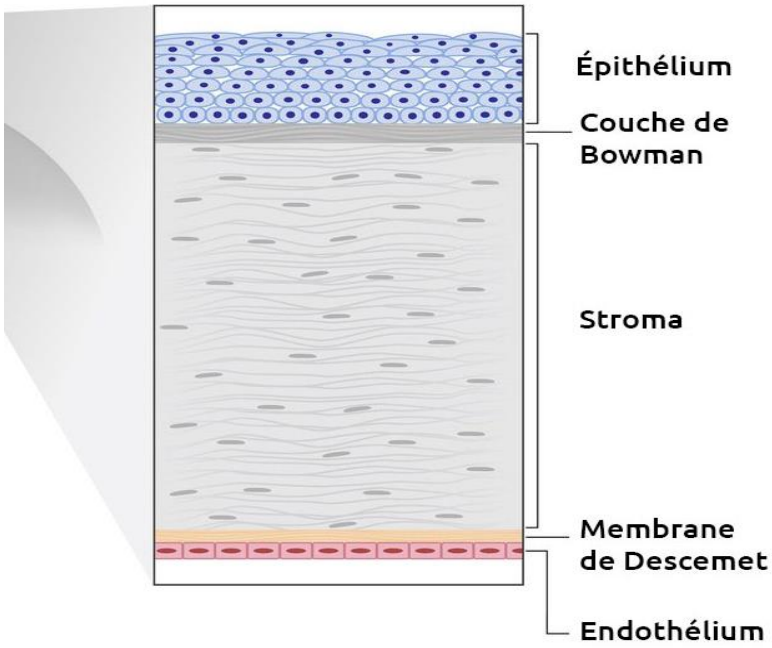
- Unvaccinated dog less than a year old.
- Sudden mortality.
- **Recognition of Symptoms:**

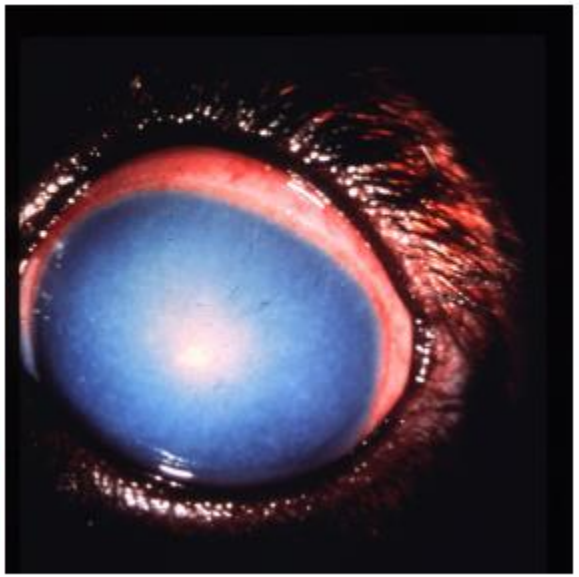
Thermal curves, Digestive signs: gastroenteritis, Abdominal palpation: Pain in the right hypochondrium, Hypertrophy of the submandibular lymph nodes, tonsillitis, Blue keratitis, uveitis.

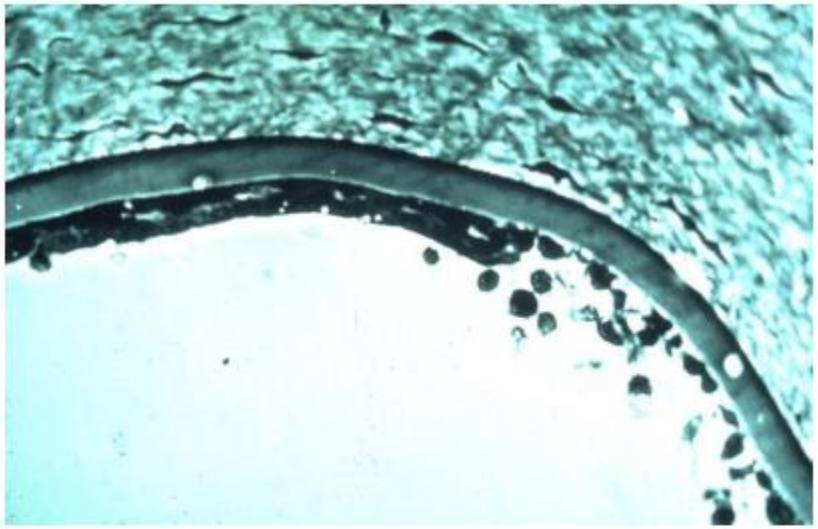




Œdème cornéen







Lésions de l'endothélium postérieur de la cornée

Paraclinical

- Constant hepatic dysfunction indicating hepatitis.

Enzymatic dosage

Example: Very high increase of ALAT>400UI/l

(Normal value in dogs: 20-70UI/l).

- Leukopenia = Marked neutropenia (<2000 neutrophils/mm3) followed by a reactive leukocytosis.
- Rarely, proteinuria, indicating immunological origin nephritis.

- ***Virus search: By PCR***

❖Rarely used in practice.

❖Samples: Urine from the living animal; liver, spleen from the carcass.

- ***Serological***

❖Not used in clinical settings.

❖The presence of AC is not significant: High frequency of inconspicuous forms.

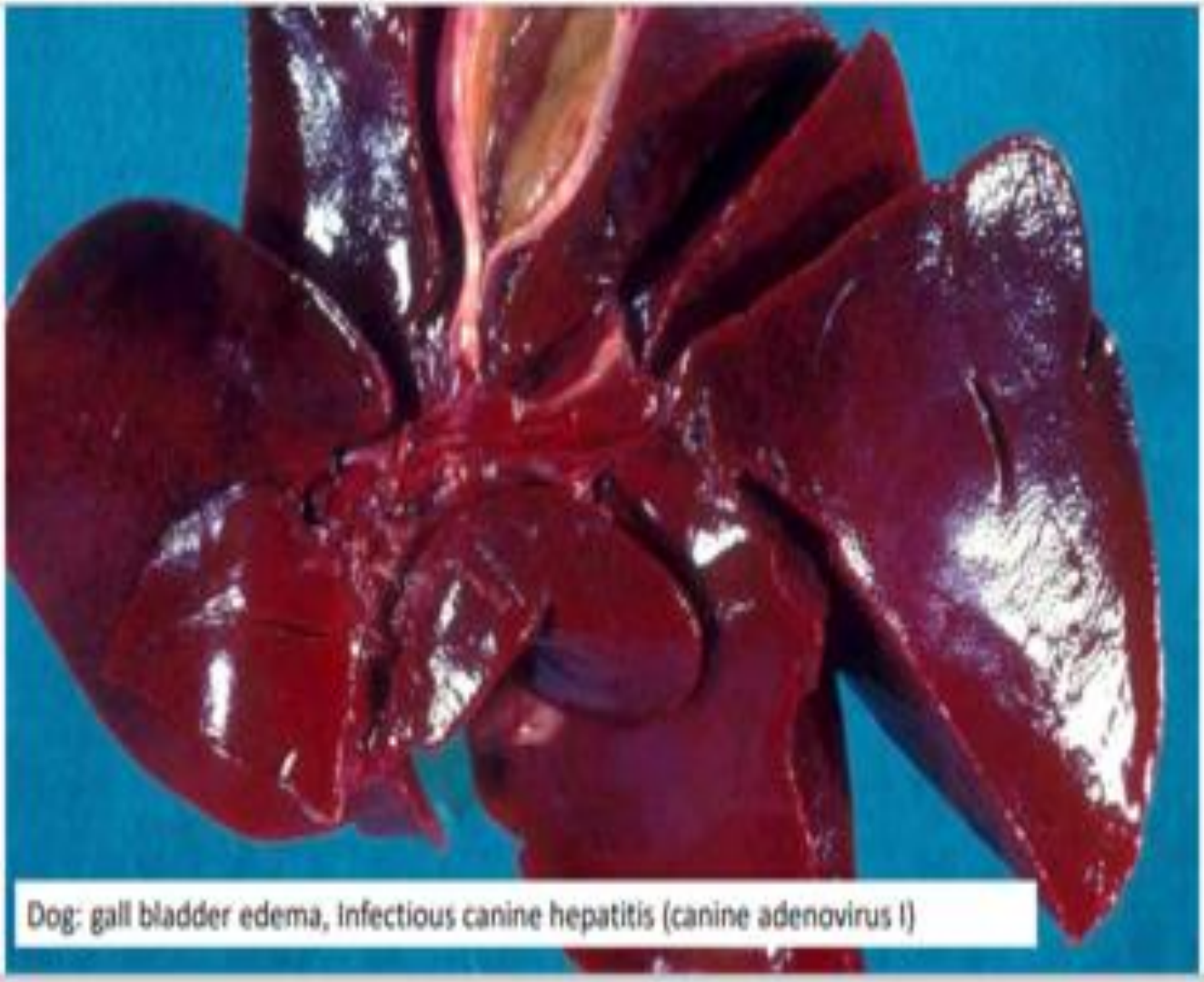
- **Virus isolation**

- All bodily secretions and tissues.
- Sensitive and specific, but generally only available as a research tool.

- **Necropsy**

Recognition of characteristic lesions

- Hepatitis.
- Swelling of the gallbladder.
- Hemorrhagic effusions in serous membranes.

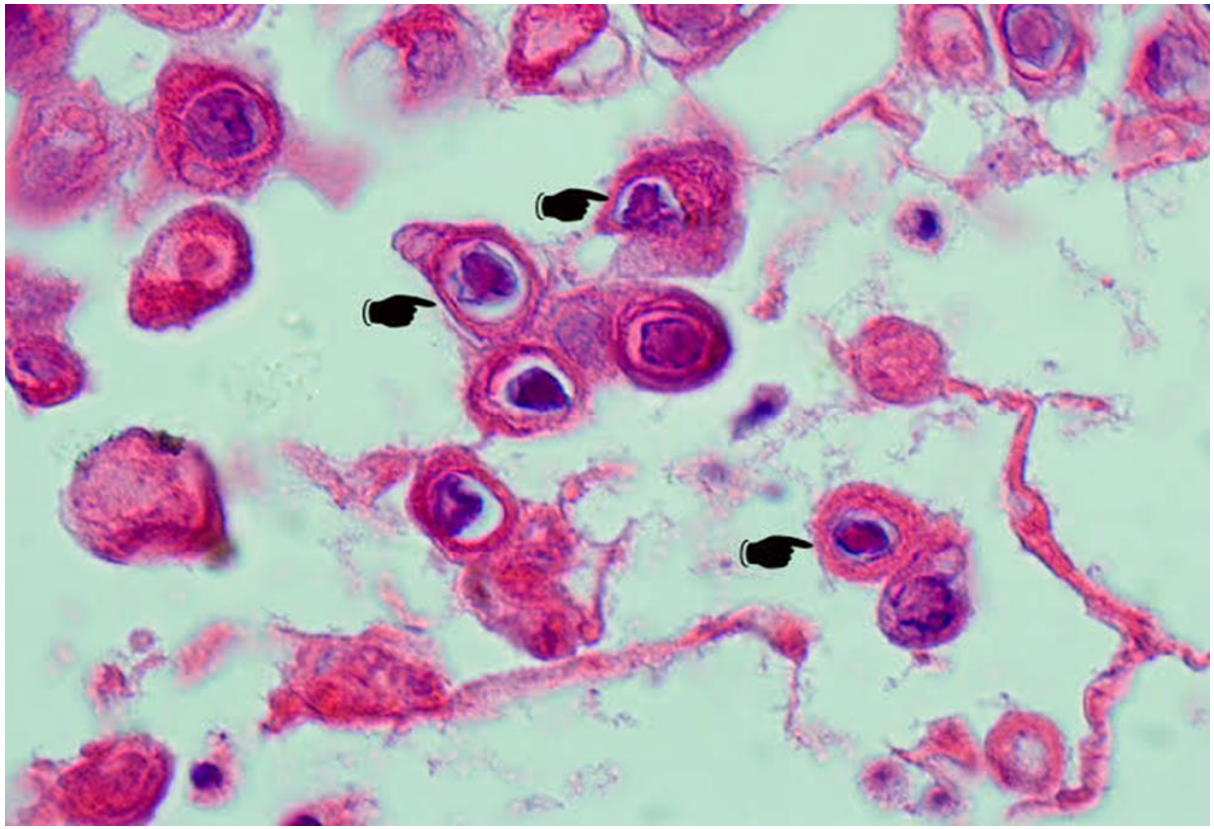


Dog: gall bladder edema, Infectious canine hepatitis (canine adenovirus I)

Viral hepatitis

➢Histology

Intraneuclear inclusions in hepatocytes.



Prognosis

- Depends on the severity of the disease = reflects:
  - Immune status of the dog.
  - Viral strain.
- It is possible that recovered dogs develop chronic hepatitis or chronic glomerulonephritis, but the extent to which this actually occurs is unknown.

Treatment

- **Symptomatic**

- Gastroenteritis:

Fluid therapy (crystalloid = NaCl), electrolytes, colloid, dextrose or transfusion = As needed.

- Antiemetics, antacids, sucralfate, partial or total parenteral nutrition = As needed.

- Hepatic encephalopathy: Lactulose enemas, oral lactulose (in the absence of vomiting).
- The use of broad-spectrum parenteral antimicrobials (ampicillin, aminoglycosides, etc.) should be considered in dogs with hemorrhagic gastroenteritis who may develop bacteremia as a result of bacterial translocation.
- DIC: Heparin.
- Severe corneal edema and uveitis: Topical glucocorticoids (negative fluorescein test) and atropine may be used to prevent glaucoma.

- **Specific**

Limited efficacy.

Effective only in the first few hours.

Homologous serum:

Homo-serum: 5mg/kg IV or SC to be repeated after 3 days.

Prophylaxis

Prophylaxis is based on medical prophylaxis.

- **Sanitary**

Rarely practiced; because sick animals should remain isolated for several months due to prolonged urinary excretion of the virus.

- **Medical**

- **Passive immunization**

Abandoned

➢ Active

❖ Two types of vaccines from CAV-1:

1- Live attenuated vaccine: protection for several years can cause blue keratitis, uveitis, and interstitial nephritis with excretion of the vaccine strain in urine.

2- The inactivated vaccine is effective, does not cause lesions but its duration of protection is limited.

❖Live attenuated CAV-2 vaccine provides protection against both serotypes (CAV-1/ CAV-2).

Does not cause renal or ocular lesions.

However, the vaccine may trigger a mild respiratory condition.

Example

A dose of 1 mL contains:

- Live attenuated virus of canine distemper (CDV), Lederle strain
- Live attenuated canine adenovirus type 2 (CAV-2), Manhattan strain
- Canine parvovirus (CPV), CPV780916 strain
- Live attenuated canine parainfluenza virus (CPIV), Manhattan strain

Chiens de compagnies vivants seuls				
Vaccins	**Primo-vaccination**		**Recommandations des rappels**	**Commentaires**
	Âge ≤ 16 semaines	**Âge > 16 semaines**		
CAV-2 (Vaccin à virus vivant atténué, sous-cutané)	6-8 semaines d'âge, puis toutes les 3-4 semaines jusqu'au plus tôt 14-16 semaines	Deux doses recommandées à 3-4 semaines d'intervalle, toutefois, une dose unique étant considérée comme protectrice	1 an, puis tous les 3 ans	**Fortement recommandé.** Administrer avec les vaccins anti-CPV-2 et anti-CDV
CAV-2 (Vaccin à virus vivant atténué, Intranasal)	Une dose dès l'âge de 3 semaines	Une seule dose	Annuel	Les vaccins parentéraux par le CAV-2 sont préférés pour la protection contre le CAV-1. Administré avec les Virus parainfluenza canin type 2 et B. bronchiseptica (intranasal)
CAV-1(Vaccin à virus vivant atténué, sous-cutané)				Non recommandé lorsque CAV2 est disponible en raison des effets indésirables
Chiens vivants en collectivités (refuges, élevages, etc.)				
Vaccins	**Primo-vaccination**		**Recommandations des rappels**	**Commentaires**
	Âge ≤ 16 semaines	**Âge > 16 semaines**		
CAV-2 (Vaccin à virus vivant atténué, sous-cutané)	1ière administration, au plus tôt, à l'âge de 6 semaines*, puis toutes les 2 à 3 semaines jusqu'à 16 semaines au plus tôt	Deux doses recommandées à 2-3 semaines d'intervalle, toutefois, une dose unique étant considérée comme protectrice.	1 an, puis tous les 3 ans	**Fortement recommandé.** Le vaccin fournit une forte protection Ne pas utiliser pendant la gestation. Administrer avec les vaccins anti-CPV-2 et anti-CDV

**/ Vaccination can be done from the 4th - 5th week of age in response to epizootics.*

Public health

- CAV-1 does not infect humans.