Neoplasia and Tumor Biology-2

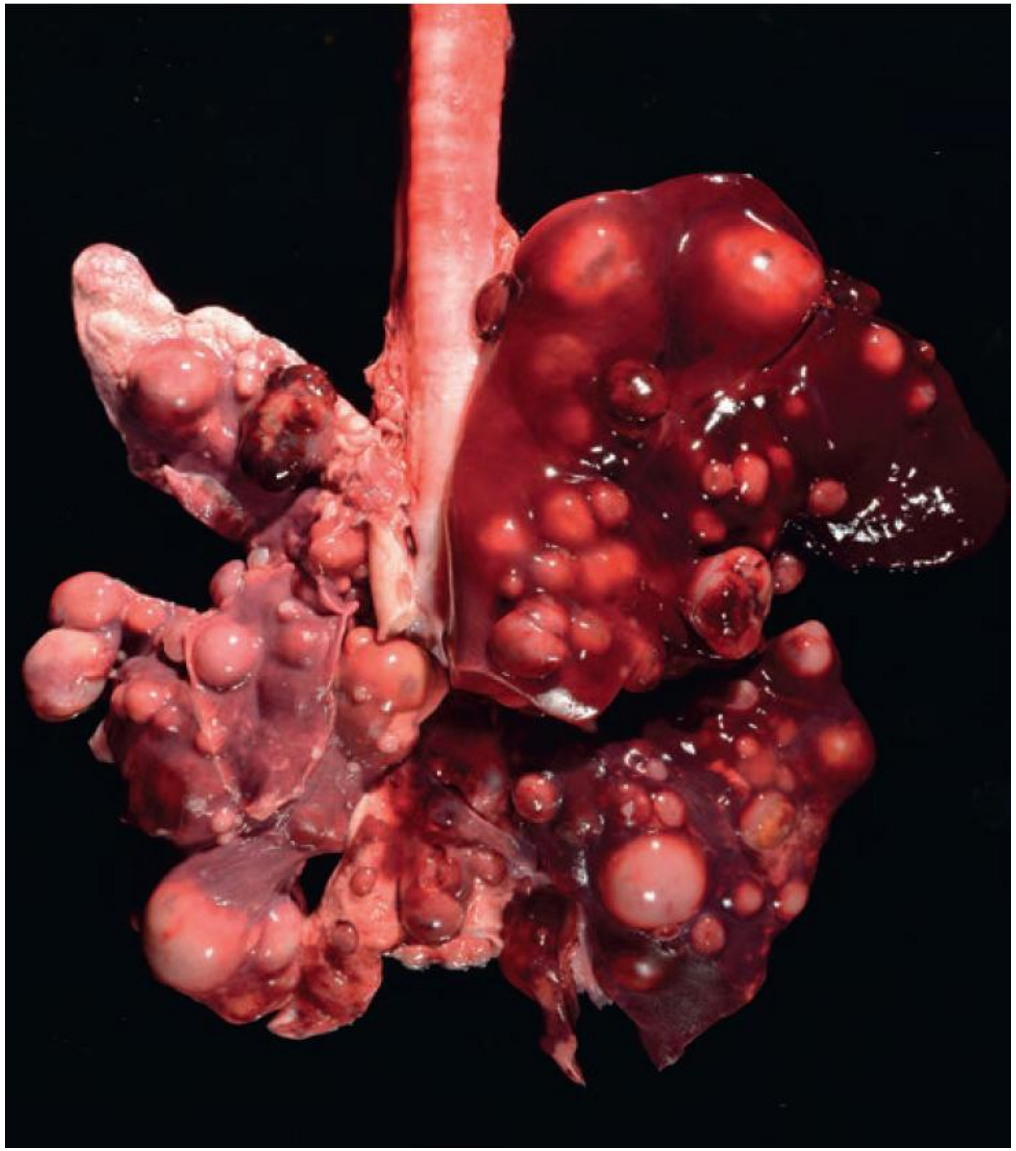
Veterinary Pathology-1
Su-Hyung Lee, DVM, PhD

Metastasis - The Spread of Cancer

Metastasis - The Spread of Cancer

The Significance of Metastasis

- Metastasis is the spread of a tumor to sites distant from the original tumor location.
- The primary tumor is not usually the cause of death for cancer patients.
- Death is usually due to metastases that interfere with critical bodily functions.
- In humans, tumor metastasis is responsible for approximately 90% of cancer mortality from solid tumors.
- Metastasis is a highly inefficient process; very few cells that leave the primary tumor successfully establish a metastatic colony.



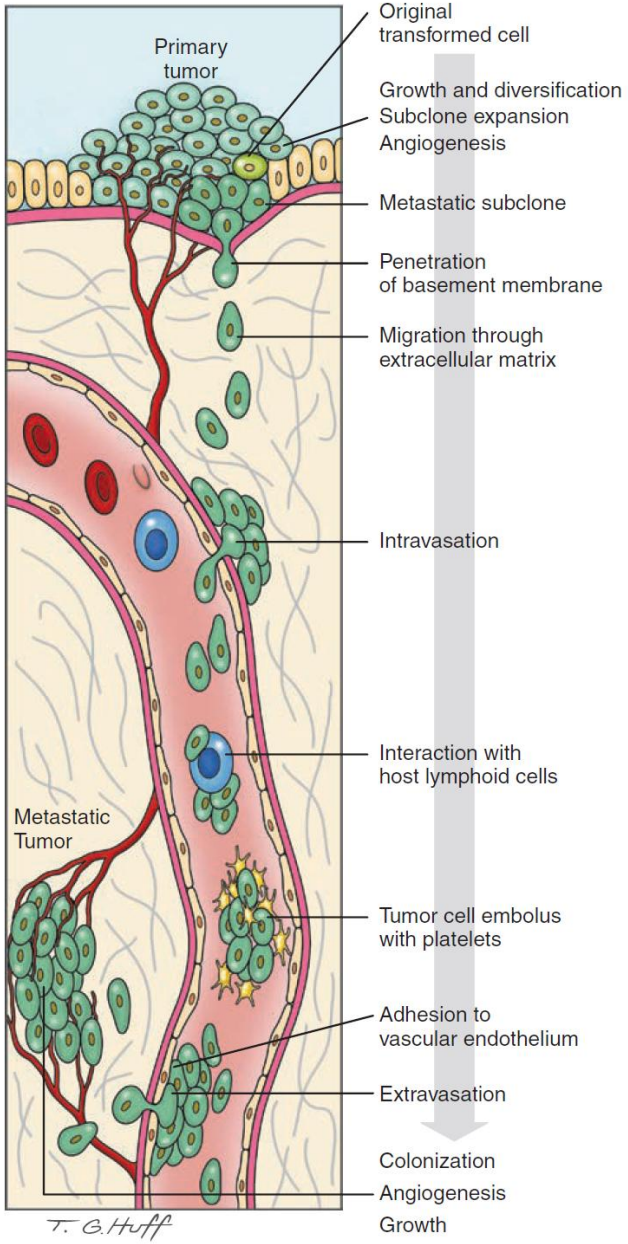
Metastatic Sarcoma, Lung, Dog.

Metastasis - The Spread of Cancer

The Metastatic Cascade: An Overview

❖ For a tumor cell to metastasize, it must complete a sequence of steps:

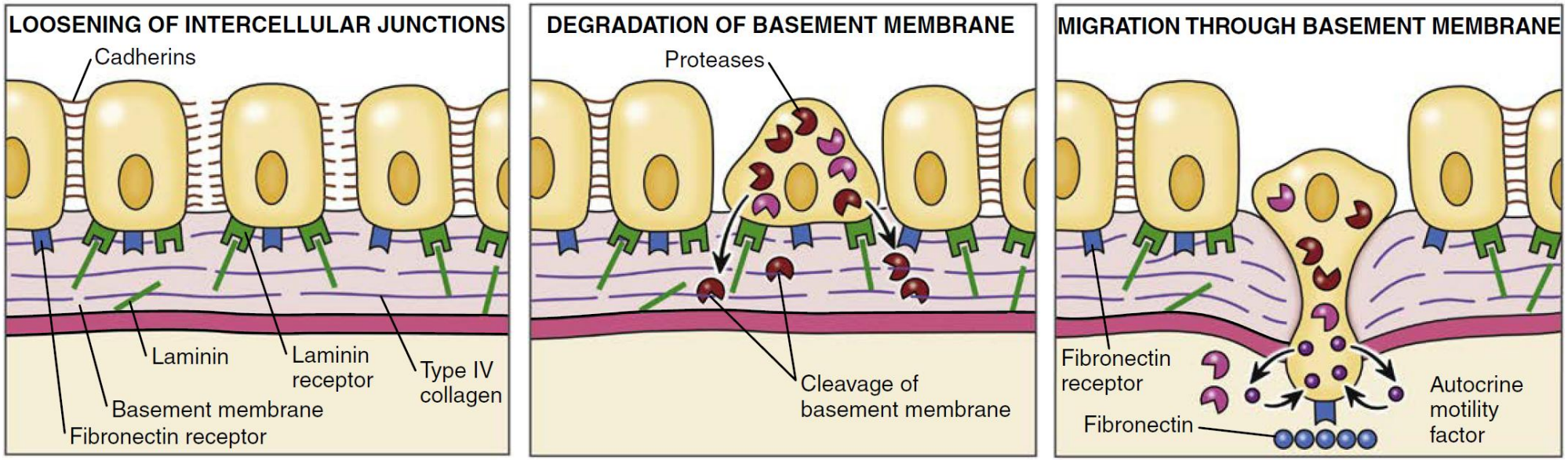
1. Local Invasion: Detach from the primary tumor and invade the surrounding stroma.
2. Intravasation: Enter a blood or lymphatic vessel.
3. Survival in Circulation: Evade host immune cells while traveling as a tumor embolus.
4. Arrest and Extravasation: Adhere to the endothelium at a distant site and exit the vessel.
5. Colonization: Survive and proliferate in the new microenvironment, forming a micrometastasis.
6. Angiogenesis: Induce new blood vessel formation to grow into a macroscopic tumor.



Metastasis - The Spread of Cancer

Local Invasion

- Loosening of Intercellular Junctions: Tumor cells must first detach from the main tumor mass. This often involves the downregulation of cell-to-cell adhesion molecules like E-cadherin.
- Degradation of Basement Membrane and ECM: To invade surrounding tissue, malignant epithelial cells actively degrade the basement membrane and ECM components.
- Protease Production: This degradation is accomplished by increasing net protease activity. Key enzymes include matrix metalloproteinases (MMPs), such as type IV collagenase, and urokinase.



Metastasis - The Spread of Cancer

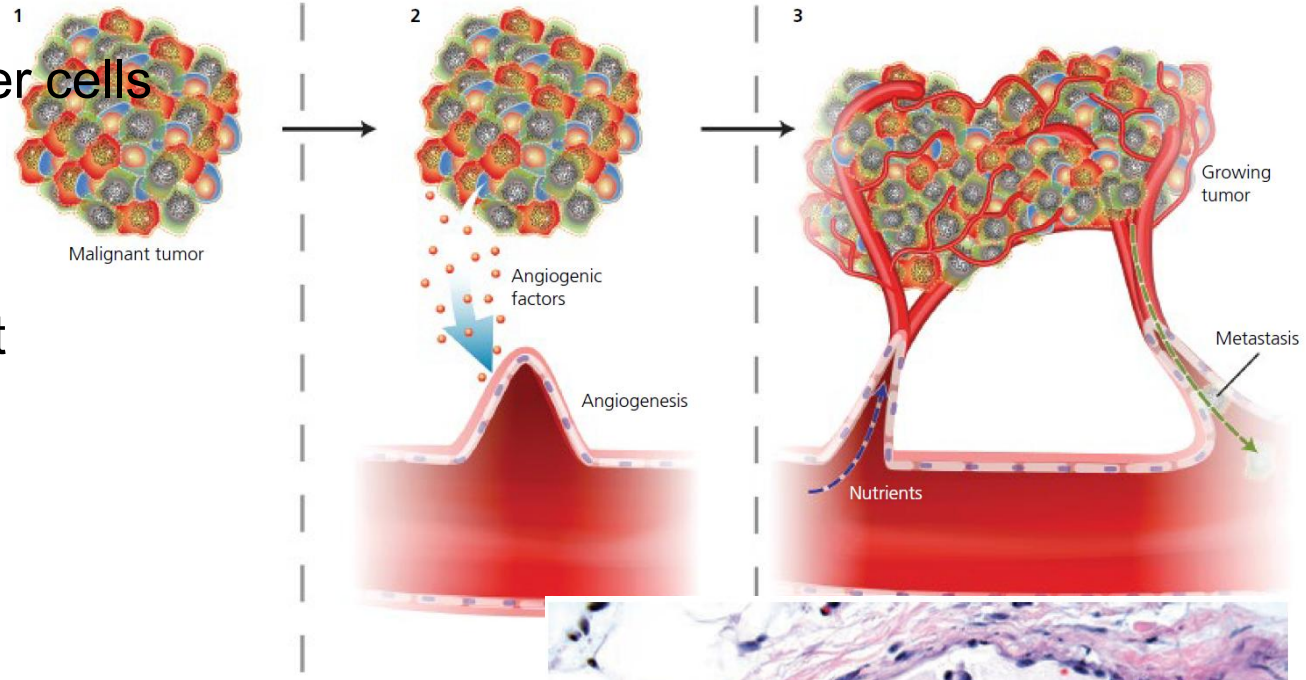
Epithelial-Mesenchymal Transition (EMT)

- Definition: A process where sessile, polarized epithelial cells are transformed into motile, fibroblast-like mesenchymal cells.
- Characteristics:
  - Loss of intercellular adhesion (e.g., decreased E-cadherin).
  - Enhanced expression of proteases.
  - Acquisition of migratory capabilities.
  - Change in shape from polygonal to spindle-shaped.
- Role in Cancer: EMT allows neoplastic epithelial cells to dissociate and migrate, thus fostering local invasion and distant metastasis.

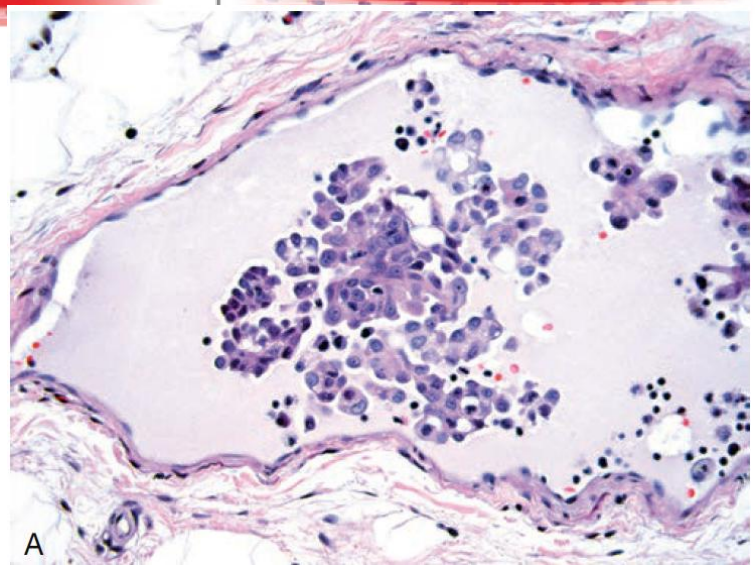
Metastasis - The Spread of Cancer

Intravasation and Transport

❖ Intravasation: The process by which cancer cells invade blood or lymphatic vessels.
- Tumor cells are attracted to vessels by chemotactic factors.
- They penetrate the endothelial basement membrane and pass between or through endothelial cells into the lumen.
- The process is facilitated by the inherent leakiness of tumor-associated vessels.



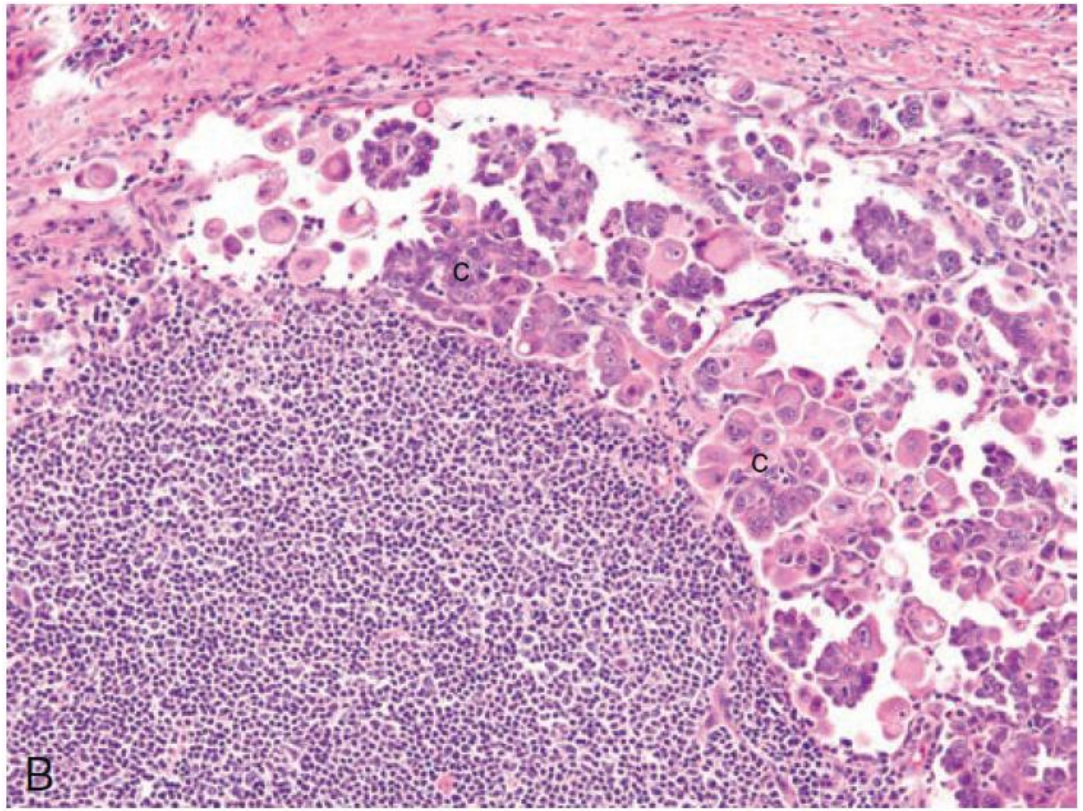
❖ Survival in Circulation:
- Once in a vessel, tumor cells tend to form small emboli.
- They may be attacked by host lymphocytes.
- They often become coated with platelets, which may actually protect the tumor embolus from immune-mediated destruction.



Metastasis - The Spread of Cancer

Extravasation and Colonization

- Extravasation: The process by which intravascular tumor cells leave the vessels at a distant site.
  - The site of extravasation is largely determined by the ability of tumor cells to interact with specific adhesion molecules on the endothelium of the target organ.
  - Once attached, they penetrate the vessel wall to enter the new tissue.
- Colonization:
  - The metastatic site must provide a suitable microenvironment ("soil") for the tumor cell ("seed") to grow.
  - Many metastatic cells may fail to grow or may enter a state of dormancy, where they survive for long periods without proliferating.



Metastasis - The Spread of Cancer

Pathways of Tumor Spread

❖ Lymphatic Spread:
- The most common pathway for initial dissemination of carcinomas.
- Tumor cells travel to regional lymph nodes following the normal routes of lymphatic drainage. The subcapsular sinus is often the first site of involvement.

❖ Hematogenous Spread:
- Typical for sarcomas, but also used by carcinomas.
- Tumors generally invade veins rather than arteries due to their thinner walls.
- The most frequent sites of hematogenous metastasis are the lungs and the liver, as they receive venous drainage from most of the body.

❖ Transcoelomic Spread (Seeding):
- Occurs when neoplasms invade a natural body cavity (e.g., peritoneal, pleural).
- Examples include ovarian carcinomas and mesotheliomas, which can spread widely on the surfaces of abdominal or thoracic organs, a condition termed **carcinomatosis**.

Systemic Effects of Cancer on the Host

Systemic Effects of Cancer on the Host

Direct Effects of Tumors

❖ Tumors directly compromise organ function by:

- Replacing (effacing) normal tissue.
- Compressing surrounding normal tissue or blood vessels, resulting in pressure atrophy or necrosis. This is particularly critical in confined spaces like the cranium.
- Causing obstruction or rupture of hollow organs.
- Eroding into blood vessel walls, causing acute hemorrhage.

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: An Overview

- Definition: Systemic clinical signs that are indirect and remote effects of a tumor, caused by tumor cell products rather than the physical mass of the primary tumor or its metastases.
- Incidence: Occur in approximately 75% of human cancer patients; incidence in veterinary patients is unknown but they are well-described.
- Significance:
  - May facilitate early tumor diagnosis.
  - Metabolic abnormalities may require treatment for effective cancer management.
  - The severity of the syndrome may reflect the tumor burden and can be used to monitor response to therapy.

System	Syndrome	Associated neoplasms
Endocrine	Hypercalcemia of malignancy	Lymphoma Apocrine gland carcinoma of anal sac Mammary carcinoma Thymoma Others
	Hypoglycemia	Hepatocellular carcinoma Salivary gland carcinoma Leiomyoma/leiomyosarcoma Plasma cell tumor Lymphoma Others
	Ectopic ACTH	Pulmonary carcinoma
Cutaneous	Paraneoplastic pemphigus	Lymphoma
	Alopecia	Pancreatic carcinoma (cat) Others
	Necrolytic migratory erythema	Glucagonoma
Hematologic	Hypergammaglobulinemia	Multiple myeloma Lymphoma
	Anemia	Many neoplasms
	Erythrocytosis	Renal carcinoma
Neurologic	Myasthenia gravis	Thymoma Others
	Peripheral neuropathy	Insulinoma Others
Renal	Glomerulonephritis	Multiple myeloma Polycythemia vera Others
Gastrointestinal	Gastroduodenal ulceration	Mast cell tumors Gastrinoma
Miscellaneous	Hypertrophic osteopathy	Pulmonary carcinoma Other thoracic masses Urinary bladder rhabdomyosarcoma

Tumors in Domestic Animals (2016)

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: Cachexia

- ❖ Definition: Significant weight loss and debility seen in many cancer patients.
- ❖ Characteristics:
  - Both muscle and fat are lost, in contrast to simple starvation where fat is lost preferentially.
  - The basal metabolic rate does not decrease as it does in starvation.
  - The condition cannot be reversed by simply increasing caloric intake.
- ❖ Etiology: Complex, but due in part to cytokines and hormones released by the tumor or host, particularly TNF-α (also known as cachectin), IL-1, and IL-6, which cause anorexia and debilitation.



https://onlinelibrary.wiley.com/doi/10.1111/jvim.16915

Systemic Effects of Cancer on the Host

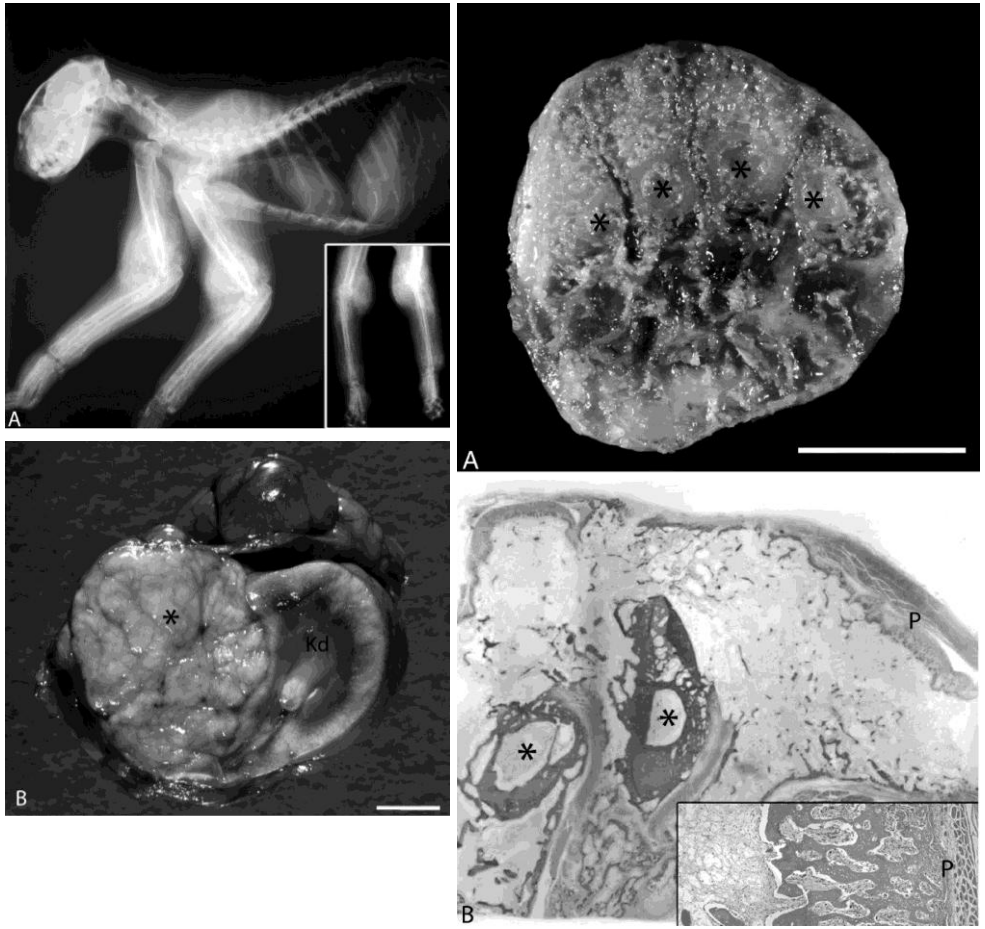
Paraneoplastic Syndromes: Endocrinopathies

- Functioning Endocrine Tumors: Tumors of endocrine glands may overproduce their normal hormonal products (e.g., thyroid adenomas causing hyperthyroidism).
- Ectopic Hormone Production: Non-endocrine tumors may produce hormonally active substances not normally found in their tissue of origin.
- **Humoral Hypercalcemia of Malignancy (HHM)**:
  - The most common example in veterinary medicine.
  - Caused by tumor secretion of parathyroid hormone-related peptide (PTHrP).
  - In dogs, it is most frequently seen with adenocarcinoma of the anal sac, lymphoma, and multiple myeloma.
  - PTHrP acts like parathyroid hormone, increasing serum calcium by releasing it from bones and enhancing its reabsorption in the kidneys.

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: Skeletal & Hematologic

- ❖ Hypertrophic Osteopathy:
  - A condition characterized by extensive periosteal new bone growth, particularly on the extremities.
  - It is strongly associated with space-occupying lesions in the thoracic cavity.
- ❖ Myelofibrosis:
  - Overgrowth of non-neoplastic fibroblasts in the bone marrow, which impairs normal hematopoiesis and can result in cytopenias.
- ❖ Anemia:
  - Commonly seen in cancer patients.
  - Causes are numerous, including anemia of inflammation, bone marrow effacement, blood loss, and hemolysis.
- ❖ Coagulopathies:
  - Disseminated intravascular coagulation (DIC) is frequently seen in dogs with hemangiosarcoma.



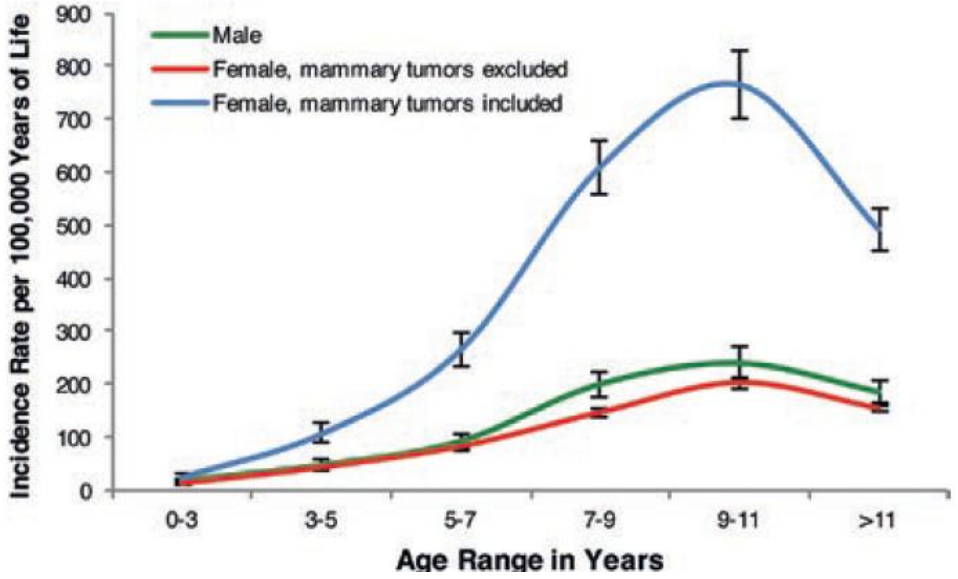
Hypertrophic Osteopathy Associated with a Renal Adenoma in a Cat, ***JVDI*** (2011)

The Molecular Basis of Cancer

The Molecular Basis of Cancer

Heritable Alterations in Cancer

- Cancer occurs as the result of the progressive accumulation of heritable genetic and epigenetic abnormalities in cells.
- Genetic Changes: Alterations in the DNA sequence itself, known as mutations. These are passed to all progeny of the cancer cell.
- Epigenetic Changes: Heritable changes in gene expression that are not due to a change in the DNA sequence. Examples include DNA methylation and histone modification.
- Driver Mutations: While tumor cells may have many mutations, only a few, termed driver mutations, are predominantly responsible for tumor development.



The Molecular Basis of Cancer

Types of Genetic Changes

- **Point Mutations**: Alteration of a single base in the DNA sequence.
- **Insertions** and **Deletions**: Addition or loss of DNA base pairs, ranging from a single base to an entire chromosome arm. Small insertions/deletions can cause a frameshift mutation.
- **Gene Amplification**: Results in the presence of multiple extra copies of a DNA sequence, often leading to overexpression of the encoded gene.
- **Aneuploidy**: An abnormal number of chromosomes in a cell, resulting from mistakes in chromosome segregation during mitosis.
- **Translocations**: Occur when pieces of two separate chromosomes break off and reattach inappropriately.

The Molecular Basis of Cancer

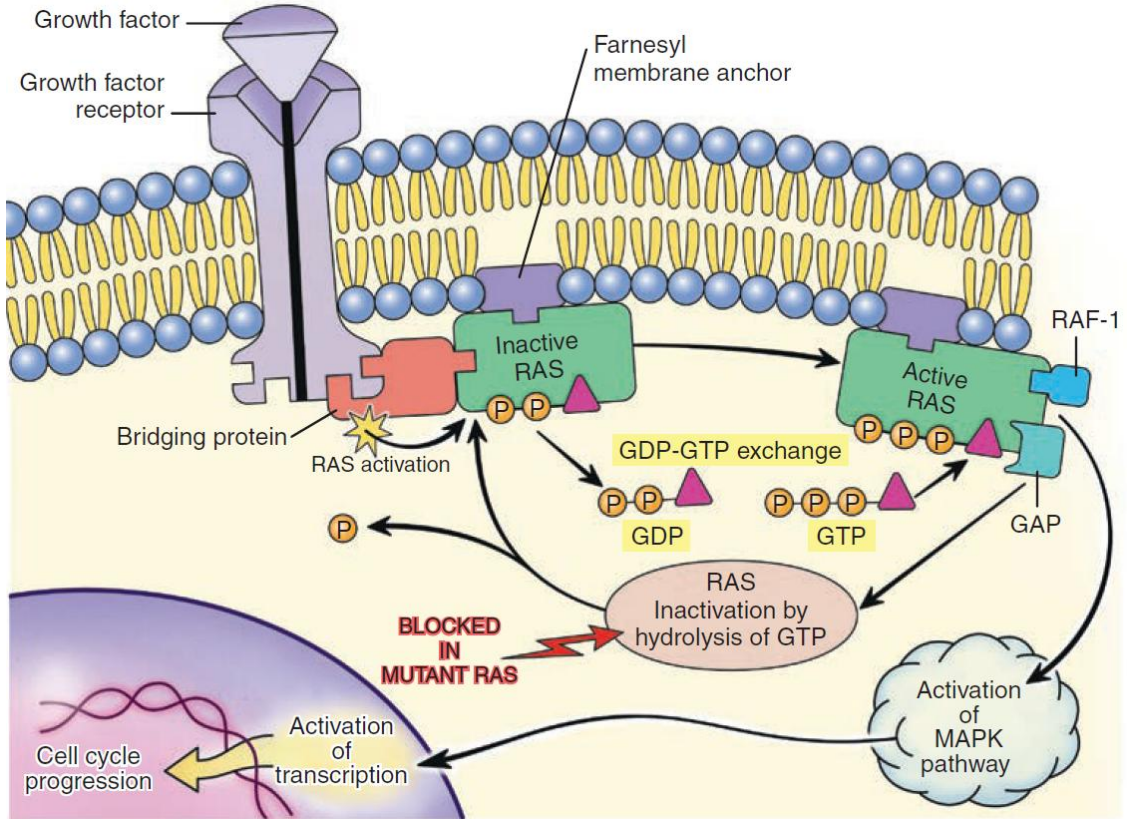
Epigenetic Changes

- **DNA Methylation**:
  - The addition of a methyl group to cytosine bases in DNA.
  - Hypermethylation of a gene's promoter region generally leads to gene silencing.
  - Cancer cells often exhibit global hypomethylation with paradoxical, gene-specific hypermethylation of tumor suppressor genes.
- **Histone Modification**:
  - Post-translational modifications of histone proteins (e.g., acetylation, methylation) alter the structure of chromatin.
  - Histone acetylation, for example, results in a more relaxed chromatin configuration (euchromatin), making DNA more accessible for transcription.
- **Non-coding RNAs** (e.g., microRNAs):
  - Small RNA molecules that do not encode proteins but regulate the expression of other genes, usually by blocking their translation.
  - Dysregulated miRNA expression contributes significantly to cancer development.

The Molecular Basis of Cancer

Oncogenes: The "Accelerators"

- Proto-oncogenes: Normal cellular genes that regulate cell growth and differentiation. They often encode products like growth factors, receptors, and signal transduction proteins.
- Oncogenes: When "activated" by overexpression or mutation, proto-oncogenes become oncogenes.
- Function: Oncogenes drive uncontrolled cell proliferation and render the cell unresponsive to normal growth inhibitory signals.
- Example: *RAS*
  - The *ras* genes encode proteins that transmit growth-stimulatory signals from receptors to the nucleus.
  - In many cancers, a mutation in a *RAS* gene leads to a constitutively active protein, resulting in continued signaling for proliferation even in the absence of growth factors.

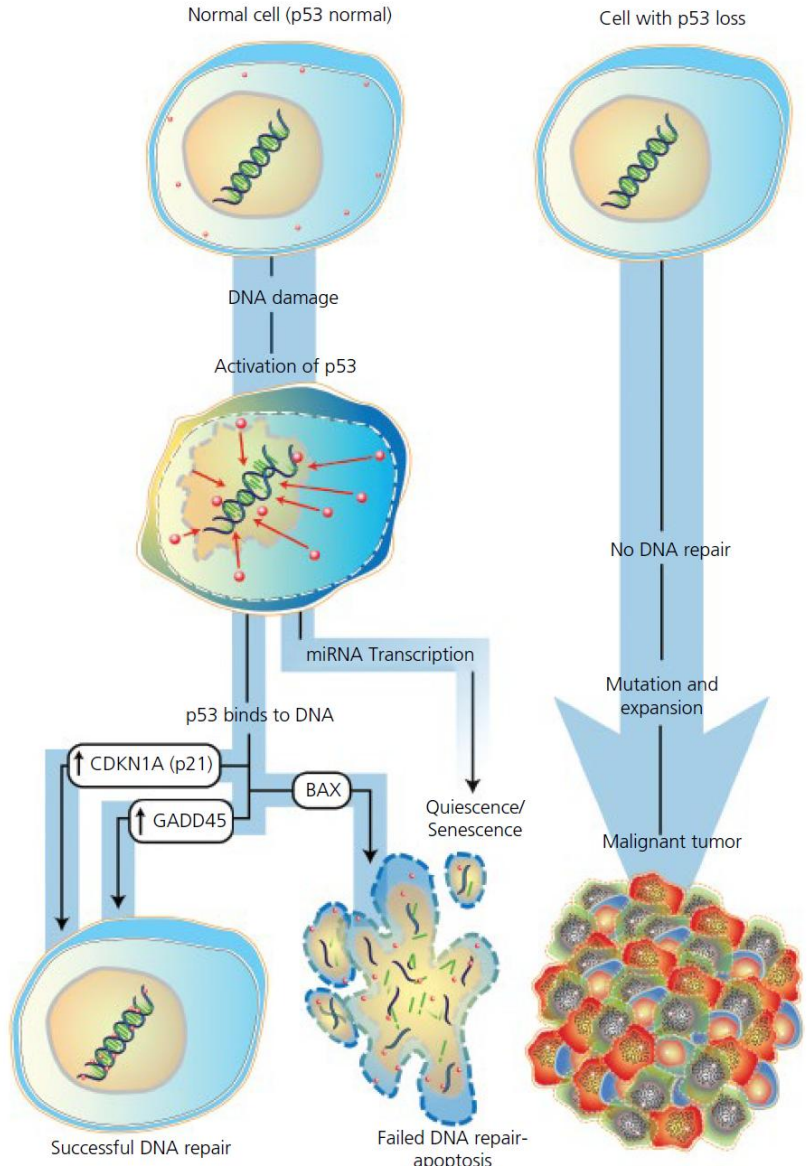


Tumors in Domestic Animals (2016)

The Molecular Basis of Cancer

Tumor Suppressor Genes: The "Brakes"

- ❖ Definition: Genes that normally inhibit cell proliferation and tumor growth. They include genes that control the cell cycle, apoptosis, and DNA repair.
- ❖ Inactivation: Unlike oncogenes which require activation, tumor suppressor genes contribute to cancer when they are inactivated.
- ❖ Example: TP53
  - The p53 protein is called the "guardian of the genome".
  - In response to DNA damage, p53 levels rise and it can either:
    - Stop the cell cycle to allow time for DNA repair.
    - Induce apoptosis if the damage is irreparable.
  - Loss of functional p53 is one of the most common events in human cancers, allowing genetically damaged cells to proliferate.

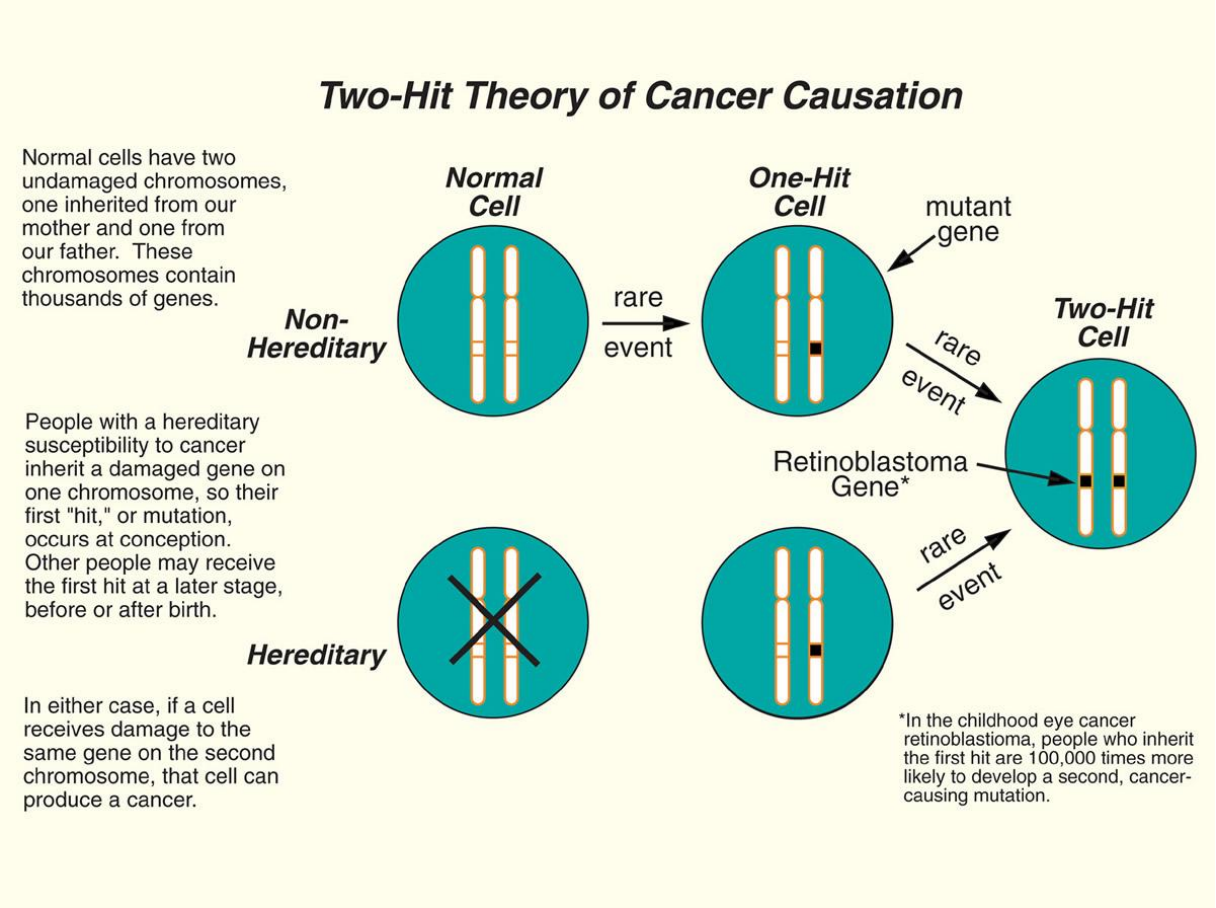


Tumors in Domestic Animals (2016)

The Molecular Basis of Cancer

Knudson's "Two-Hit" Hypothesis

- This hypothesis explains the mechanism of inactivation for many tumor suppressor genes.
- It states that both alleles of a tumor suppressor gene must be inactivated (suffer a "hit") for cancer to develop. Inactivation of only one allele is not sufficient, as the remaining normal allele can still produce a functional protein.
- **Sporadic Cancers**: An individual starts with two normal alleles. A single cell must undergo two independent, rare somatic mutations to inactivate both alleles, which is a much less likely event.
- **Familial Cancers**: Individuals inherit one mutated allele (the first hit) in every cell of their body. They then only need a single somatic mutation in the second allele (the second hit) in a given cell to initiate a tumor. This explains why these cancers appear at an earlier age and are often multifocal.



https://www.foxchase.org/about-us/history/discoveries-fox-chase-research/knudsons-two-hit-theory-cancer-causation

The Molecular Basis of Cancer

Defects in DNA Repair Genes

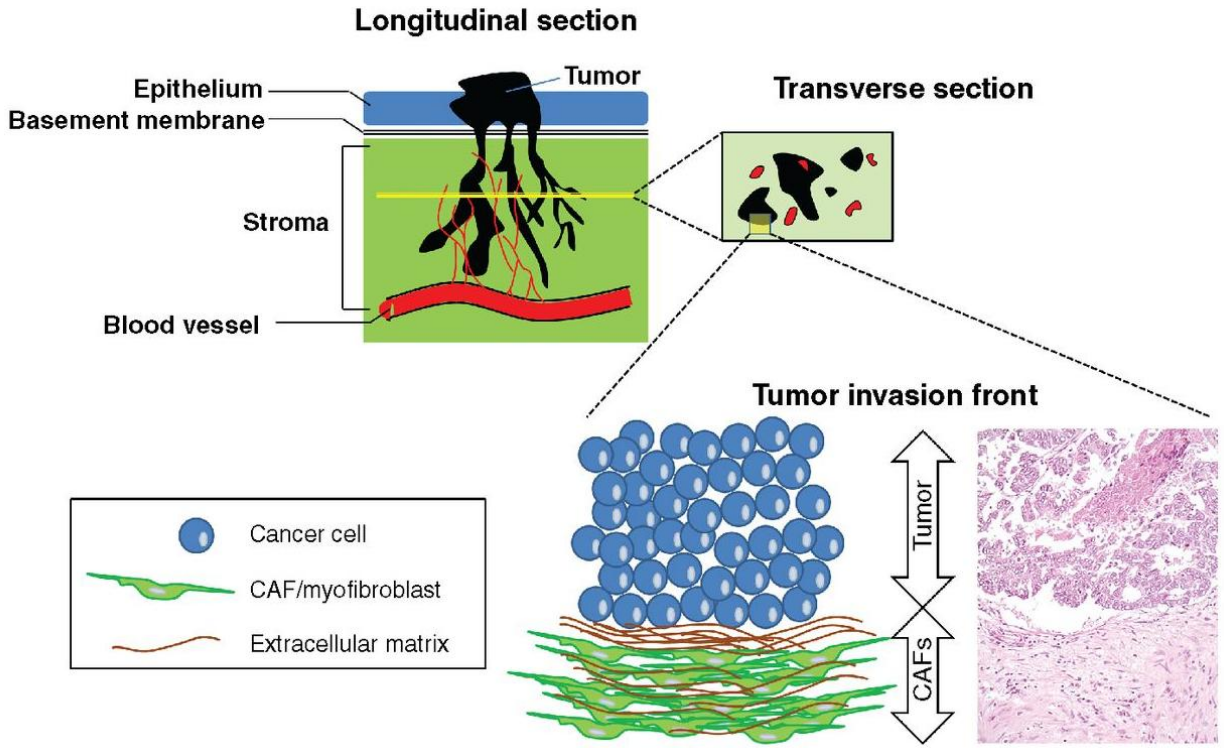
- The integrity of the genome is maintained by several DNA repair systems.
- Mismatch Repair: Enzymes like MLH1 and MSH2 "proofread" DNA to fix single nucleotide mismatches that occur during replication.
- Nucleotide Excision Repair: Repairs bulky DNA lesions, such as the pyrimidine dimers caused by UV radiation.
- Consequence of Defects: When a DNA repair gene itself is inactivated (e.g., through mutation), the cell can no longer fix DNA damage effectively. This leads to a dramatic increase in the rate of mutations throughout the genome (genomic instability), which exponentially increases cancer susceptibility.

The Tumor Microenvironment & Immunity

The Tumor Microenvironment & Immunity

Tumor Microenvironment: Parenchyma & Stroma

- ❖ A tumor consists of two main components:
  - Parenchyma: The neoplastic cells themselves.
  - Stroma: The non-neoplastic supporting structure.
- ❖ The stroma is composed of:
  - Extracellular Matrix (ECM): Collagen, glycoproteins, proteoglycans.
  - Blood vessels that supply nutrients.
  - Fibroblasts that synthesize the ECM.
  - A variety of inflammatory and immune cells.
- ❖ The amount of stroma varies considerably among tumors.

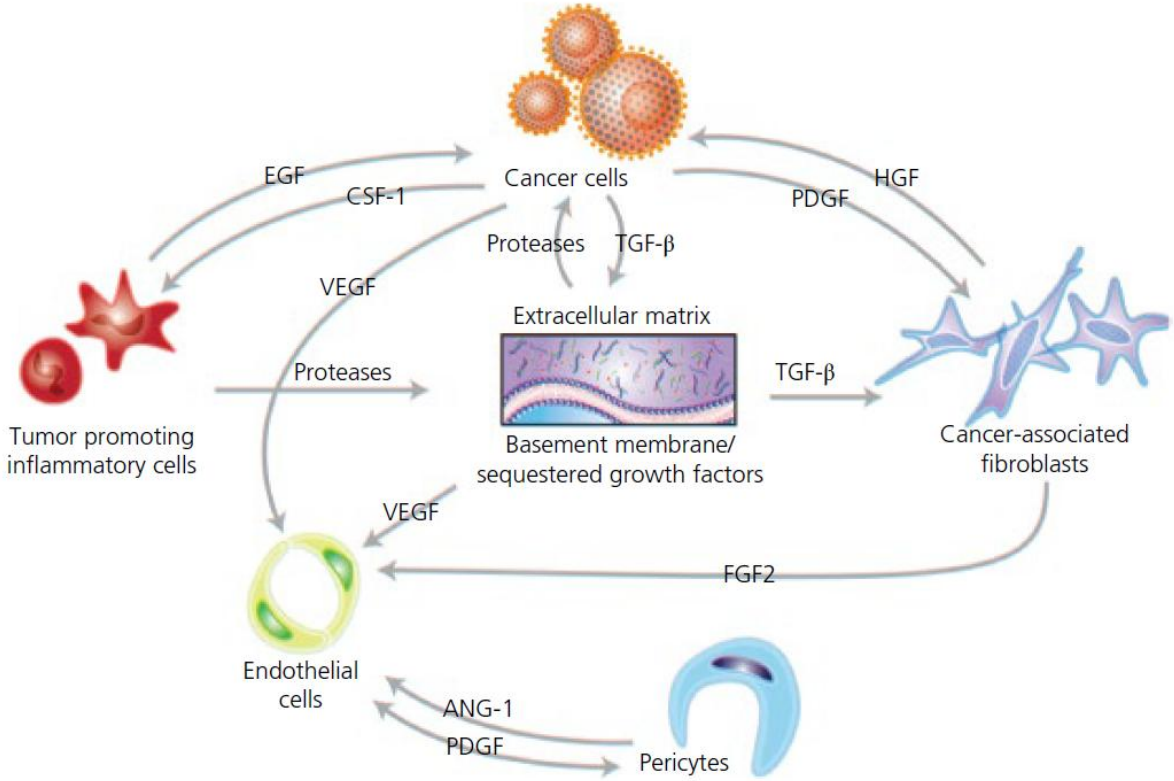


Mol Cancer Res. 2012;10(11):1403-1418

The Tumor Microenvironment & Immunity

Tumor-Stroma Interactions

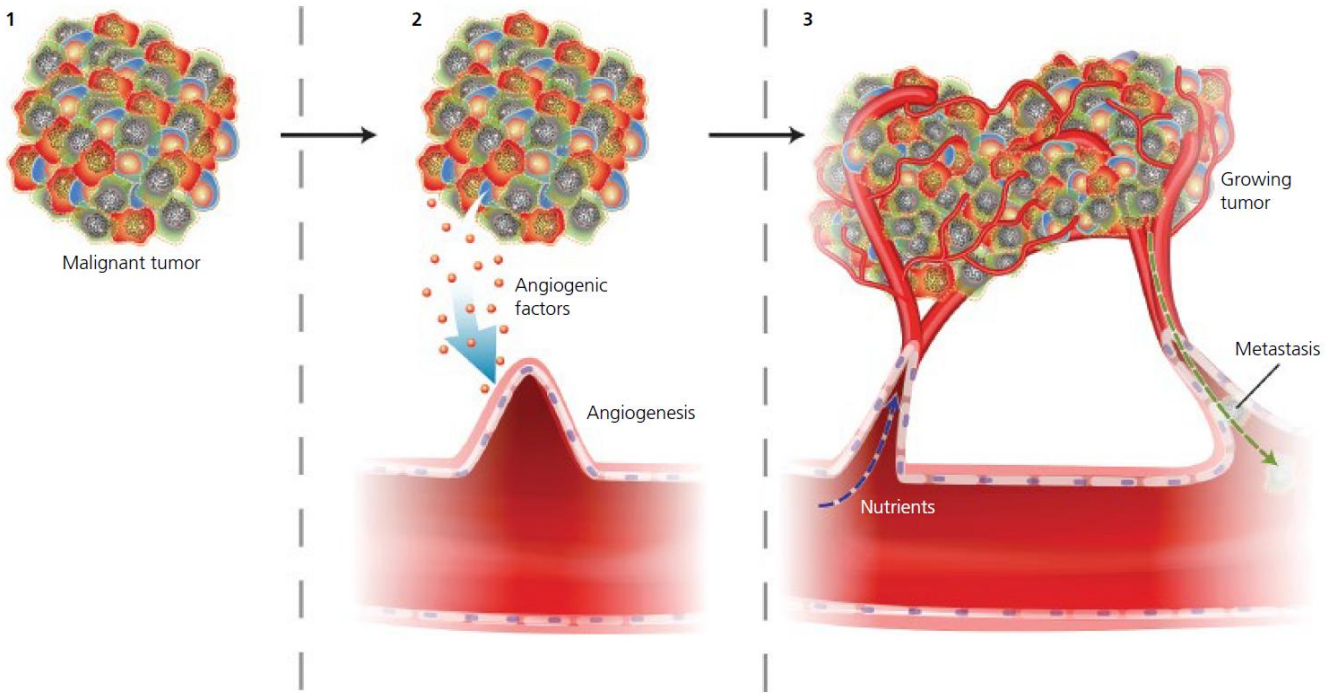
- ❖ Tumor cells and their stroma engage in complex, bidirectional signaling.
- ❖ Tumor cells influence the stroma:
  - They can stimulate the formation of new blood vessels (angiogenesis).
  - They can cause an extensive fibroblastic response with collagen deposition, termed a desmoplastic or scirrhous response.
- ❖ The stroma influences the tumor:
  - Proteases from stromal cells can release growth factors that are sequestered in the ECM, fostering tumor proliferation.
  - Inflammatory cells in the stroma can release mediators that may promote tumor growth



The Tumor Microenvironment & Immunity

Angiogenesis - The Tumor's Blood Supply

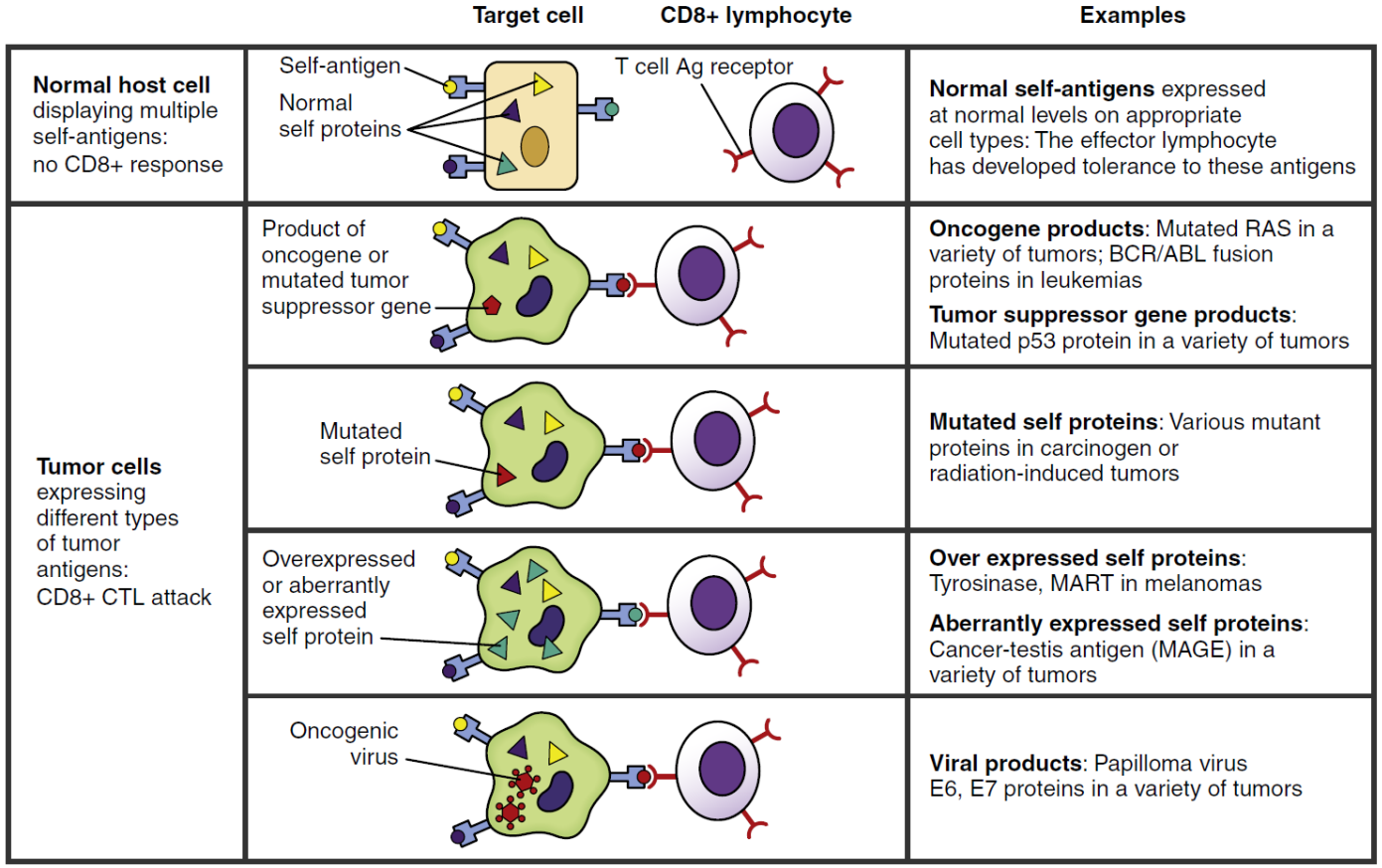
- Continued growth of solid tumors beyond 1-2 mm in diameter is dependent on an adequate blood supply.
- At some point, tumors undergo an angiogenic switch, allowing them to induce and sustain the formation of new blood vessels.
- Mechanism: Tumors initiate angiogenesis by producing angiogenic factors, most importantly Vascular Endothelial Growth Factor (VEGF), or by downregulating antiangiogenic factors.
- Tumor Vasculature: The resulting blood vessels are typically more dilated, tortuous, disorganized, and leaky than normal vessels, which can facilitate metastasis.



The Tumor Microenvironment & Immunity

Tumor Immunity and Immunosurveillance

- The immune system can recognize and destroy tumor cells, a process termed immunosurveillance.
- The hypothesis is that effective immunosurveillance suppresses tumor development, and a failure of this process allows tumors to emerge.
- Evidence for Immunosurveillance:
  - Immunosuppressed human transplant recipients have a dramatically increased susceptibility to tumors.
  - Many tumors are infiltrated by lymphocytes and macrophages, suggesting an ongoing immune response.



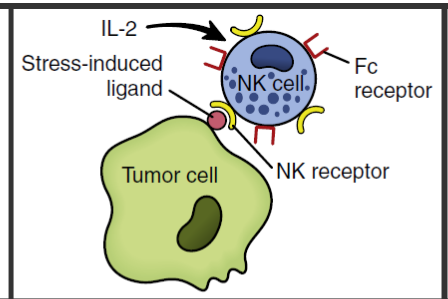
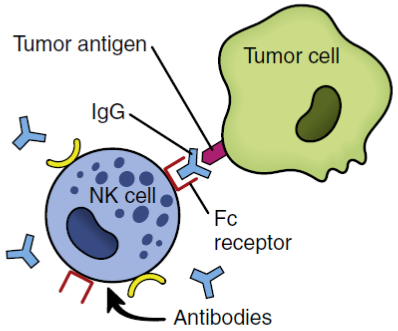
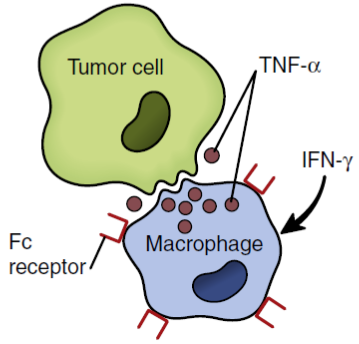
The Tumor Microenvironment & Immunity

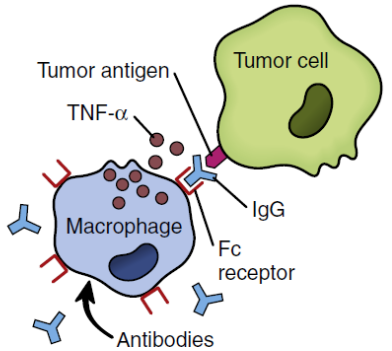
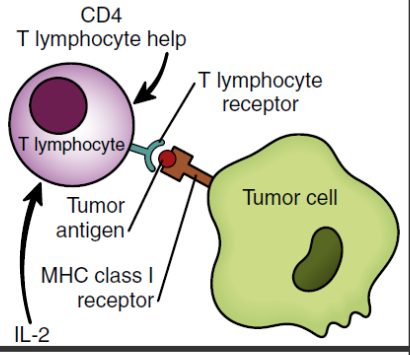
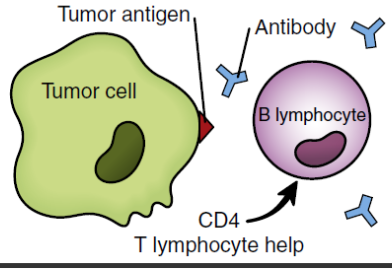
Tumor Antigens

- ❖ Tumor antigens are molecules expressed on the surface of tumor cells that can be recognized by the immune system.
- ❖ Tumor-Specific Antigens:
  - • Restricted to tumor cells.
  - • Examples
    - - Products of mutated oncogenes (e.g., mutated RAS)
    - - Mutated tumor suppressor genes (e.g., mutated p53)
    - - Proteins from oncogenic viruses (e.g., papillomavirus E6/E7 proteins).
- ❖ Tumor-Associated Antigens:
  - • Present on both tumor cells and some normal cells.
  - • Examples
    - - Oncofetal antigens (like CEA) that are expressed during embryonic development but re-expressed by tumors
    - - Differentiation antigens that are overexpressed on tumor cells compared to their normal counterparts.

The Tumor Microenvironment & Immunity

Cells Involved in Immunosurveillance against Tumors

Effector Cell		Activation/ Assistance	Target	Mode of Attack
NK cell		IL-2	Stress-induced ligand	Immunologic synapse (perforin/granzymes)
NK cell (ADCC)		Antibodies produced by B lymphocytes	Tumor antigen	Immunologic synapse (perforin/granzymes)
Macrophage		IFN-γ activation	Tumor cell membrane	TNF-α, reactive oxygen species, nitric oxide, lysosomal enzymes

Effector Cell		Activation/ Assistance	Target	Mode of Attack
Macrophage (ADCC)		Antibodies produced by B lymphocytes	Tumor antigen	TNF-α, reactive oxygen species, nitric oxide, lysosomal enzymes
T lymphocyte (CTL)		Help by CD4 T lymphocyte, IL-2 activation	Tumor antigen presented in MHC class I context	Immunologic synapse (perforin/granzymes)
B lymphocyte		Help by CD4 T lymphocyte	Tumor antigen	Membrane-attack complex (activated complement)

The Tumor Microenvironment & Immunity

Antitumor Mechanisms: Innate Immunity

- The innate immune system is the first line of defense and does not require prior sensitization.
- Natural Killer (NK) Cells:
  - A subset of lymphocytes that can kill tumor cells without previous encounter.
  - Preferentially target and kill cells that have lost or downregulated the expression of MHC class I molecules.
  - Killing is mediated by the release of perforin and granzymes, which induce apoptosis in the target cell.
- Macrophages:
  - Can kill tumor cells by releasing reactive oxygen species, lysosomal enzymes, nitric oxide, and TNF.
  - Their role is complex, as some tumor-associated macrophages can actually promote tumorigenesis by enhancing angiogenesis and suppressing other immune cells.

The Tumor Microenvironment & Immunity

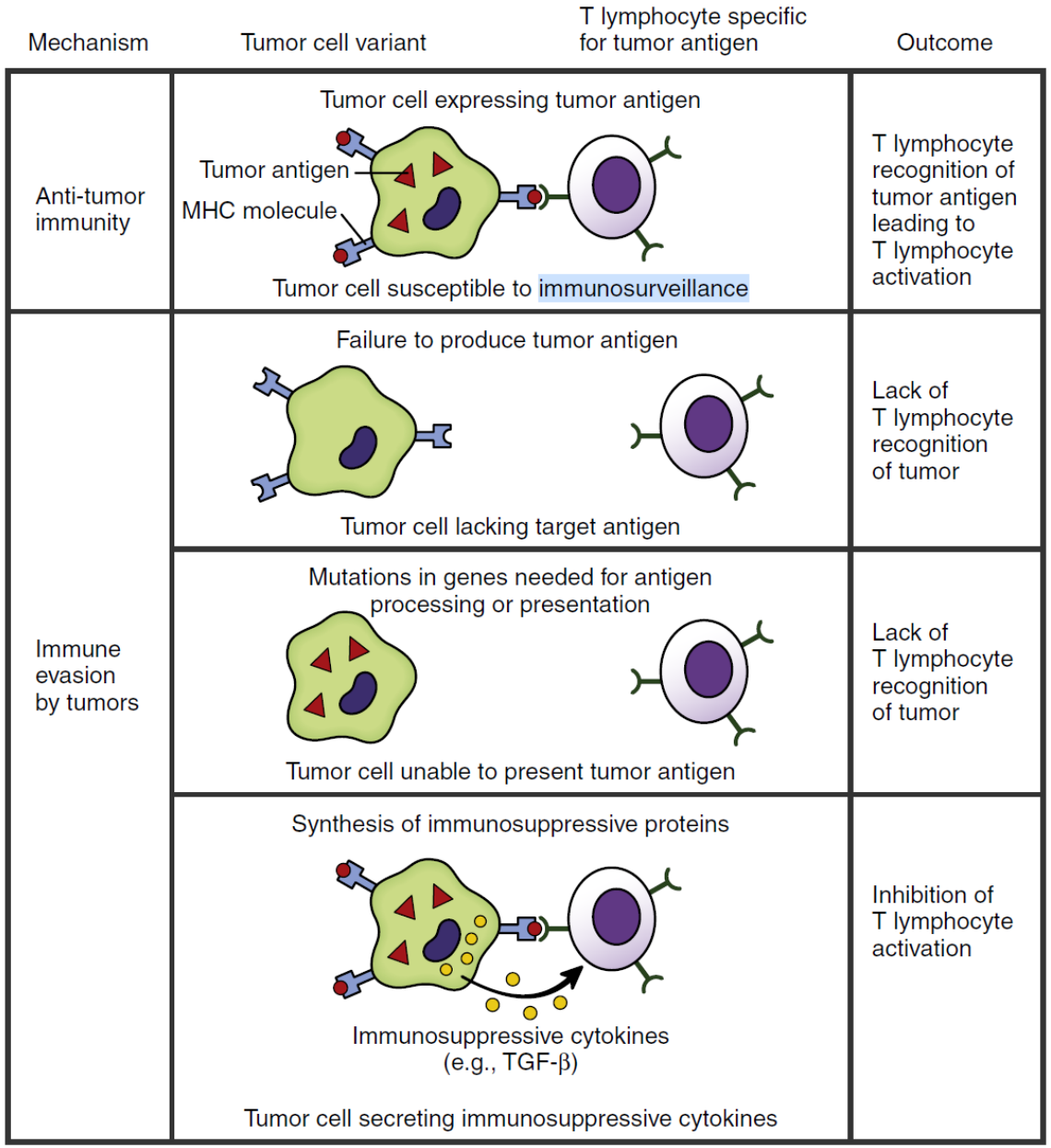
Antitumor Mechanisms: Adaptive Immunity

- The cell-mediated arm of the adaptive immune system is believed to mount the most effective antitumor defenses.
- Cytotoxic T Lymphocytes (CTLs):
  - The primary effector cells of the adaptive antitumor response.
  - They are typically CD8+ T cells that have been primed by dendritic cells to recognize a specific tumor antigen presented on MHC class I molecules.
  - They kill target tumor cells by the same perforin/granzyme mechanism as NK cells.
- B Lymphocytes (Humoral Immunity):
  - Differentiate into plasma cells that produce antibodies against tumor antigens.
  - Antibodies can kill tumor cells by activating the complement cascade or by arming NK cells and macrophages for antibody-dependent cell-mediated cytotoxicity (ADCC).

The Tumor Microenvironment & Immunity

How Tumors Evade the Immune Response

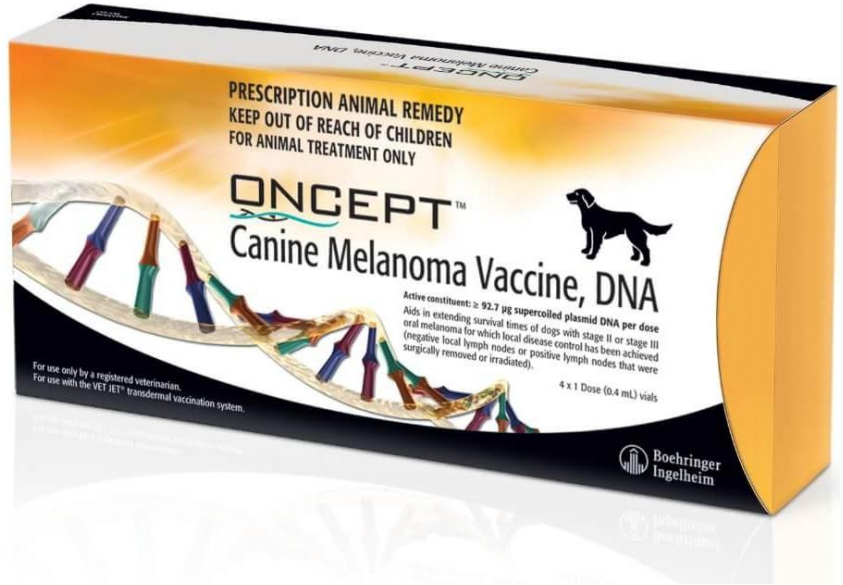
- Many tumors develop strategies to evade immunosurveillance:
  - **Altered MHC Expression**: They can lose or downregulate MHC class I expression to hide from CTLs.
  - **Antigen Masking**: They can stop expressing tumor antigens or hide them with a thick glycocalyx coat.
  - **Inducing Tolerance**: They can be perceived as "self" if antigens are presented without proper costimulatory signals, or through the action of regulatory T cells (Tregs), which actively suppress immune responses.
  - **Immunosuppression**: Tumors can produce immunosuppressive factors, like TGF-β, or express molecules (like Fas ligand) that trigger apoptosis in attacking T lymphocytes.



The Tumor Microenvironment & Immunity

Tumor Immunotherapy

- ❖ Immunotherapeutic strategies aim to boost the host's immune response against the tumor.
- ❖ Passive Immunotherapy: Provides the patient with mature effector cells or antibodies.
  - • Example: Administration of monoclonal antibodies that are specific for a tumor antigen.
- ❖ Active Immunotherapy: Stimulates the patient's own immune system to attack the tumor.
  - • Example: Vaccination with tumor antigens to generate antitumor CTLs.
  - • A melanoma vaccine for dogs stimulates an immune response against tyrosinase.
- ❖ New Approaches: Blocking the activity of immunosuppressive cells like Tregs or tumor-associated macrophages is a promising new strategy.



Causes of Cancer & Animal Models

Causes of Cancer & Animal Models

Mechanisms of Carcinogenesis

- ❖ Carcinogens are agents that cause cancer.
- ❖ Chemical Carcinogens:
  - Direct-acting: Effective in the form they enter the body.
  - Indirect-acting (Procarcinogens): Require metabolic activation (often by cytochrome P450 enzymes in the liver) to become carcinogenic.
  - Most chemical carcinogens are mutagens that bind covalently to DNA to form DNA adducts.
- ❖ Radiation Carcinogenesis:
  - UV radiation (from sunlight) causes the formation of pyrimidine dimers, and is a major cause of skin cancer in sparsely haired areas.
  - Ionizing radiation causes chromosome breakage, translocations, and point mutations.
  - All forms of radiation are complete carcinogens, meaning they can both initiate and promote tumorigenesis.

Causes of Cancer & Animal Models

Oncogenic Viruses

❖ Viruses that cause cancer employ a variety of mechanisms:

- Dominant Oncogene Mechanism: Some retroviruses carry a viral oncogene (often a captured and mutated host proto-oncogene) in their genome. Uncontrolled expression of this oncoprotein drives cell proliferation.
- Insertional Mutagenesis: Viruses without their own oncogene can insert their DNA into the host genome in a way that activates a nearby cellular proto-oncogene, leading to its unregulated expression.
- Inhibition of Tumor Suppressors: Some viruses (e.g., papillomaviruses) produce proteins (like E6 and E7) that bind to and inactivate host tumor suppressor proteins like p53 and pRb.
- Indirect Mechanisms: Some viruses cause cancer by stimulating chronic inflammation or by suppressing the immune system, reducing immunosurveillance.

Causes of Cancer & Animal Models

Oncogenic Viruses

E-Table 6.2 Oncogenic Viruses of Animals

Classification	Virus	Species Affected	Associated Tumors
Retrovirus	Mouse mammary tumor virus	Mouse	Mammary adenocarcinomas
	Avian sarcoma-leukosis virus complex	Fowl	Various sarcomas, carcinomas, lymphomas, leukemias
	Avian reticuloendotheliosis virus complex	Fowl	Lymphomas, leukemias
	Mouse leukemia and sarcoma viruses	Mouse	Various sarcomas, carcinomas, lymphomas, leukemias
	Feline leukemia virus	Cat	Leukemias, lymphomas
	Bovine leukosis virus	Cattle	Leukemias, lymphomas
	Primate leukemia and sarcoma viruses	Primate	Fibrosarcomas, leukemias
	Mason-Pfizer monkey virus	Primate	Fibrosarcomas
	Feline immunodeficiency viruses	Cat	Lymphomas
	Maedi-visna virus	Sheep	Pulmonary carcinomas
Hepadnavirus	Hepatitis B group	Primate, rodent, duck	Hepatocellular carcinomas
Papovavirus	Polyoma	Mouse, raccoon	Various carcinomas, sarcomas
	Simian virus 40 (SV40)	Primate	Sarcomas (in rodents)
	Papilloma	Many species	Papillomas, carcinomas
Adenovirus	Types 2, 5, 12	Human	Sarcomas (in hamsters)
Herpesvirus	Frog herpesvirus	Frog	Adenocarcinomas
	Marek's disease	Fowl	Lymphoproliferative disease/ lymphomas
	Herpesvirus ateles and saimiri	Primate	Lymphomas, leukemias
Poxvirus	Various	Various	Fibromas, papillomas

Modified from Wyke J: Viruses and cancer. In Franks LM, Reich NM, editors: *Cellular and molecular biology of cancer*, New York, 2003, Oxford University Press.

Causes of Cancer & Animal Models

Naturally Occurring Tumors in Animals

- Many naturally occurring cancers in animals serve as important models for human cancer.
- The Dog as a Cancer Model:
  - Dogs have a comparable cancer incidence rate to humans.
  - They are outbred and share a common environment with humans, including exposure to carcinogens.
  - Many canine tumors, such as osteosarcoma and lymphoma, are biologically very similar to their human counterparts.
  - The more rapid progression of tumors in dogs allows clinical trials to be completed in a reasonable timeframe.
- Biobanking: The collection and storage of animal tumor tissues and related clinical information is becoming increasingly important for cancer research.

Diagnosis and Prognosis

Diagnosis and Prognosis

Cytologic Diagnosis

- Purpose: A useful and quick screening test for assessing masses. Can sometimes provide a definitive diagnosis.
- Techniques:
  - Fine-Needle Aspirate/Non-aspirate: A needle is used to collect cells from a mass, which are then expelled onto a slide.
  - Impression Smear: The freshly cut surface of an excised mass is blotted and then gently pressed onto a slide.
- Advantages: Quick, easy, minimally invasive, and allows for excellent evaluation of fine cellular detail.
- Limitations: Does not allow for evaluation of tissue architecture, making it difficult to assess for invasion or distinguish hyperplasia from benign neoplasia. The sample may not be representative of the entire lesion.

Diagnosis and Prognosis

Cytologic Criteria of Malignancy

❖ These are features of cellular atypia that suggest a potential for malignant behavior:

- Anisocytosis: Variation in cell size.
- Anisokaryosis: Variation in nuclear size.
- Macrocytosis / Macrokaryosis: Abnormally large cells or nuclei.
- High Nuclear-to-Cytoplasmic Ratio: Nuclei are disproportionately large relative to the cell size.
- Multiple/Prominent Nucleoli: Suggests high metabolic and synthetic activity.
- Coarse or "Stippled" Chromatin: Instead of smooth, evenly dispersed chromatin.
- Multinucleation or Bizarre Mitotic Figures.

❖ Caution: These criteria are only suggestive. Some reactive non-neoplastic cells can show atypia, and some malignant tumors (e.g., neuroendocrine) show very little atypia.

Diagnosis and Prognosis

Histopathologic Diagnosis

- The Golden Standard: A definitive diagnosis is frequently obtained by histologic evaluation of a biopsy specimen.
- Biopsy Types:
  - Incisional Biopsy: A portion of the lesion is removed to establish a diagnosis.
  - Excisional Biopsy: The entire mass is removed with the intent of both diagnosis and cure.
- Surgical Margin Evaluation: The margins of an excisional biopsy are evaluated to determine if the tumor has been completely removed. "Clean" margins are free of tumor cells, while "dirty" margins indicate incomplete excision and a risk of local recurrence.

Diagnosis and Prognosis

Tumor Grading

- Definition: A process performed by a pathologist to provide an indication of a tumor's biologic behavior and potential for malignancy.
- Basis: All grading schemes evaluate the degree of differentiation of the tumor cells (e.g., well-differentiated, moderately differentiated, poorly differentiated).
- Other Criteria: Schemes may also incorporate other histologic features:
  - Mitotic count (number of dividing cells).
  - The extent of tumor necrosis.
  - Evidence of invasiveness.
- Prognosis: The grade (e.g., Grade I, II, or III) is used to help predict the clinical outcome.

Diagnosis and Prognosis

Tumor Staging

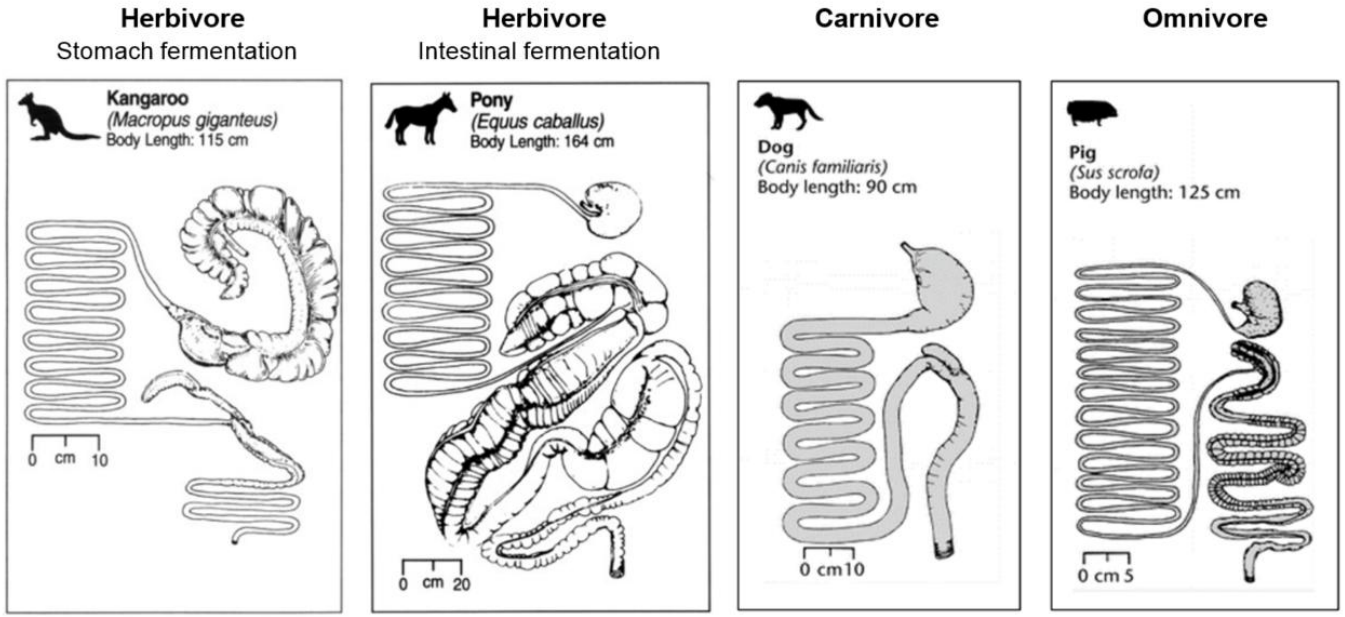
- Definition: A process, generally performed by the clinician, to determine the extent of tumor growth and spread in the animal.
- Purpose: Staging guides the therapeutic plan and provides crucial prognostic information.
- The TNM System: A widely used staging scheme based on:
  - T: The size of the primary tumor (T0 to T4).
  - N: The degree of regional lymph node involvement (N0 to N3).
  - M: The extent of distant metastasis (M0 to M2).

Conclusion

- Neoplasia is a complex, multistep process driven by the accumulation of genetic and epigenetic alterations.
- These alterations allow tumor cells to bypass normal controls on growth, evade cell death, and acquire malignant characteristics like invasion and metastasis.
- Understanding the fundamental biology of tumors—from their nomenclature and classification to their interactions with the host and their molecular drivers—is essential for accurate diagnosis, prognosis, and the development of effective therapies.

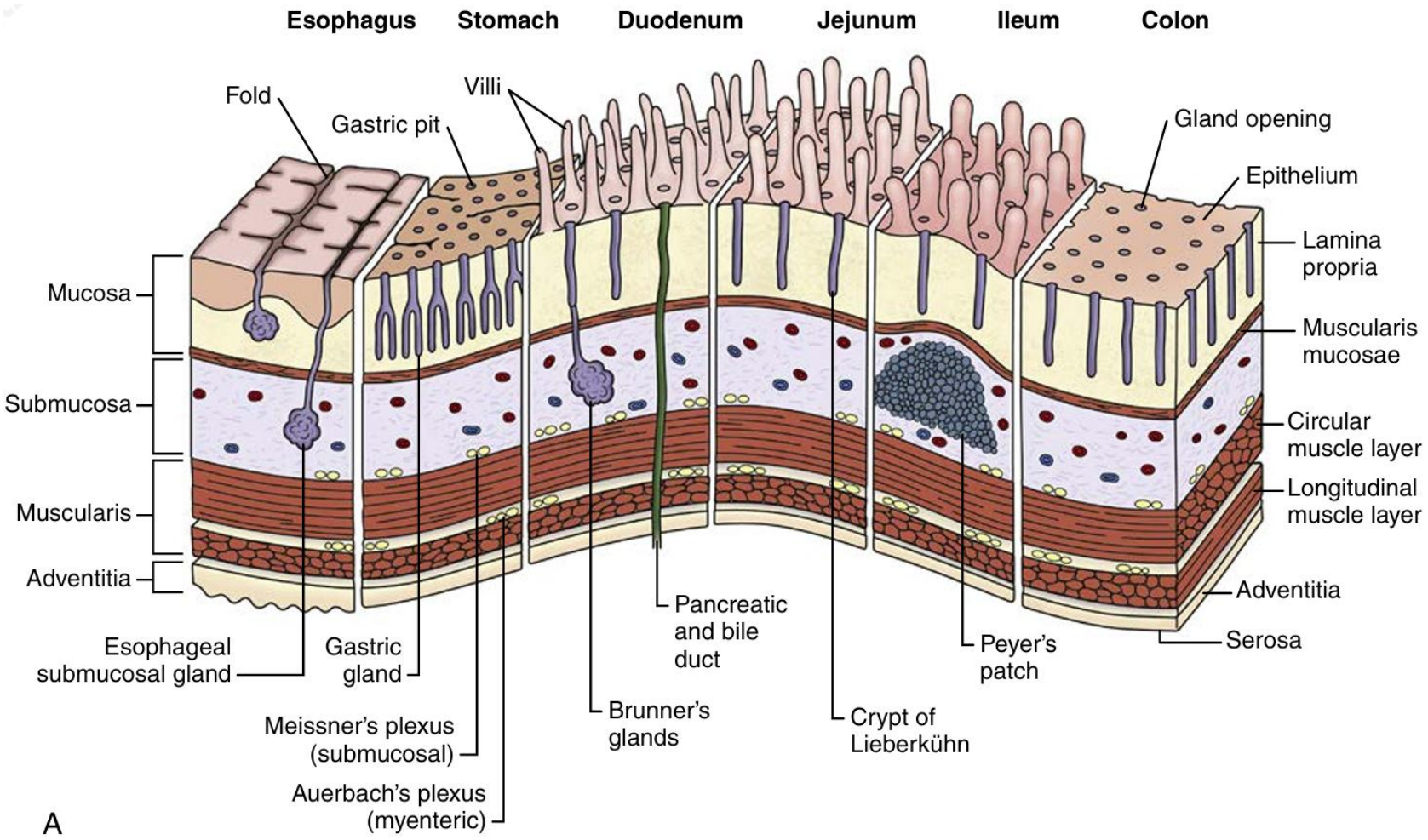
Digestive System Overview

- A complex **tubular system** specialized for digestion and absorption.
- Divided into **specialized organs** with unique structures and functions.
- **Variations across species** depending on diet and physiology:
  - Carnivores: Short, simple intestines.
  - Herbivores: Complex stomachs or large ceca for fermentation.



https://www.kiezebrink.eu/en/knowledge-base-pets/differences-in-digestive-system-between-herbivores-carnivores-and-omnivores

Digestive System Overview



Oral Cavity

• Structure:

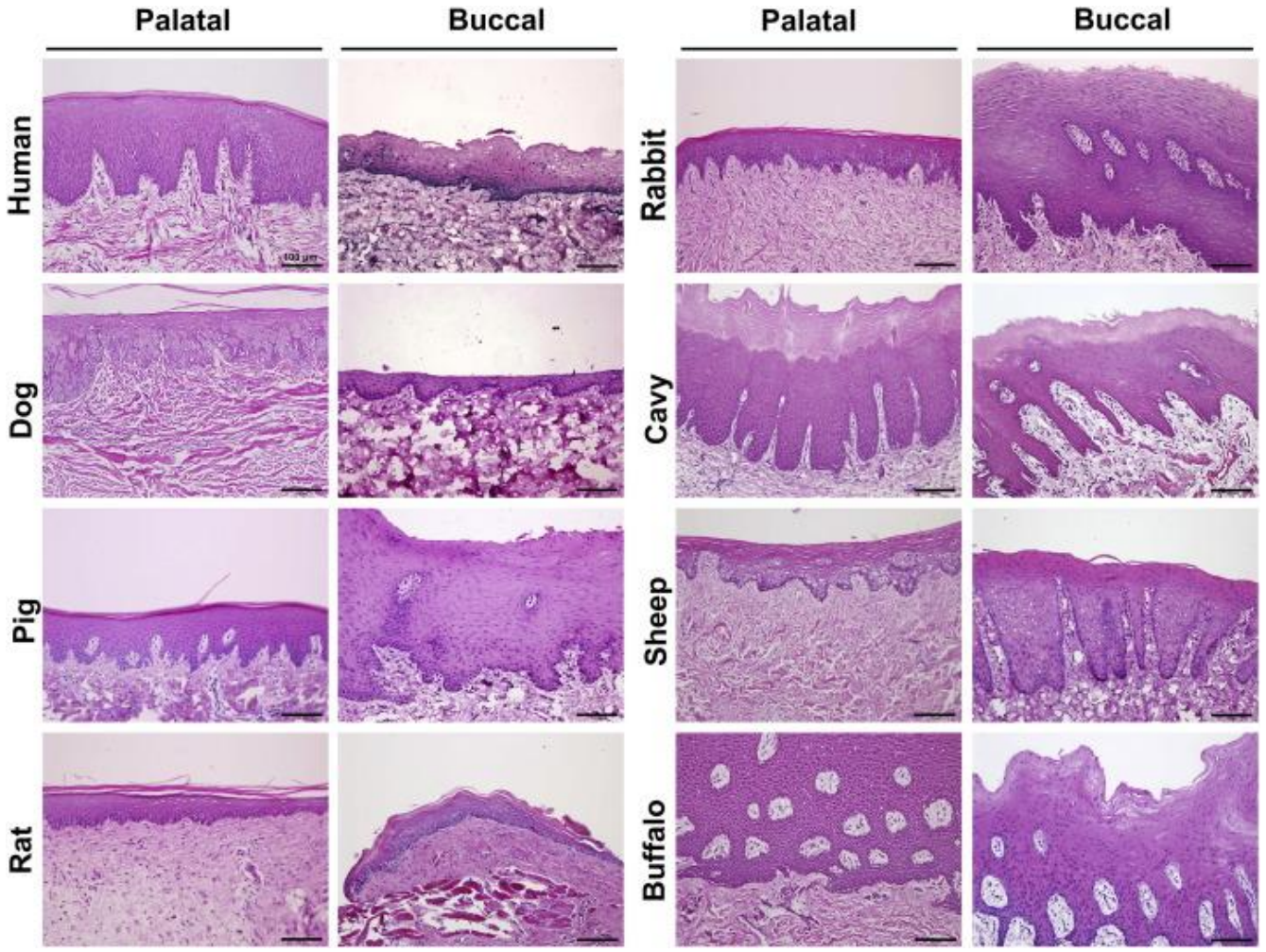
- Lined by **stratified squamous epithelium** (keratinized in some species).

- Contains teeth, tongue, and salivary glands.

• Function:

- Mechanical breakdown of food (**mastication**).

- Saliva aids in lubrication and contains digestive enzymes.



Histological features of oral epithelium in seven animal species: As a reference for selecting animal models

Esophagus

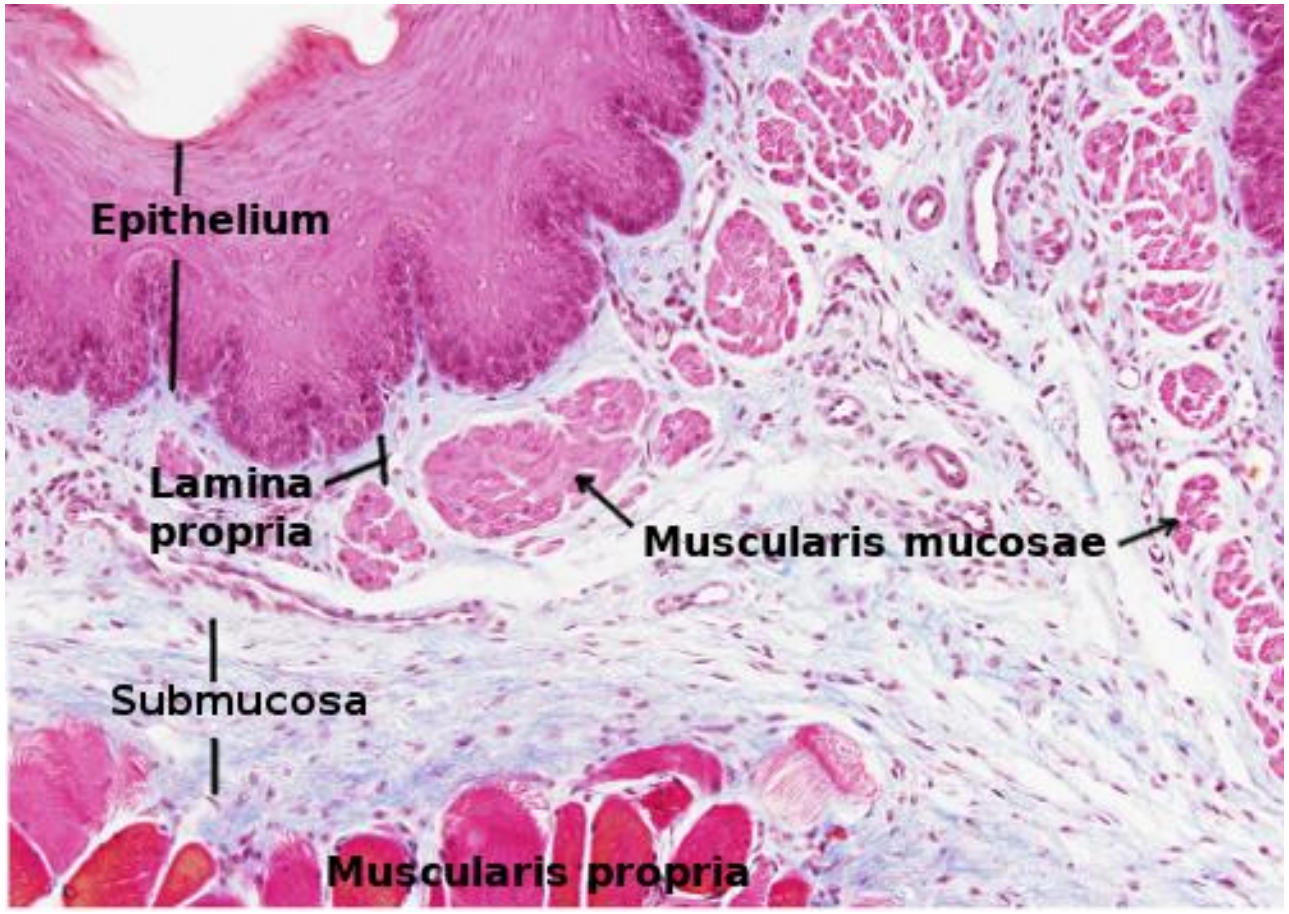
• Structure:

- Lined by **stratified squamous epithelium**.

- Muscular layers vary across species (striated vs. smooth muscle).

• Function:

- **Transports food** from oral cavity to stomach via peristalsis.

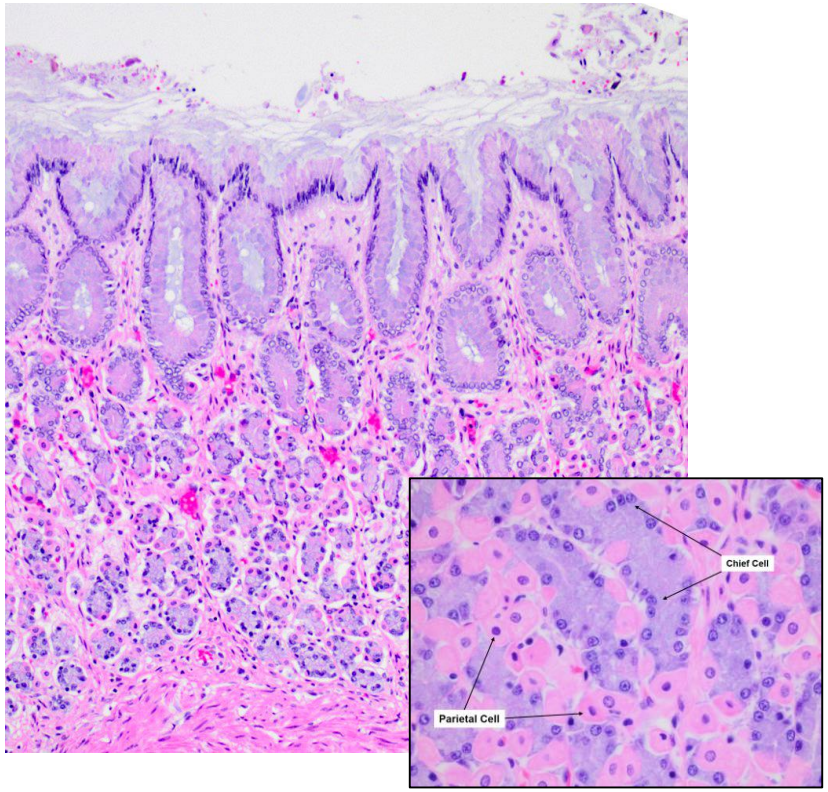


https://mmegias.webs.uvigo.es/02-english/2-organos-a/imagenes-grandes/digestivo-esofago.php#n

Stomach and Forestomach (Ruminants)

- **Monogastric Animals**:

 - Simple stomach with gastric glands secreting acid and enzymes.

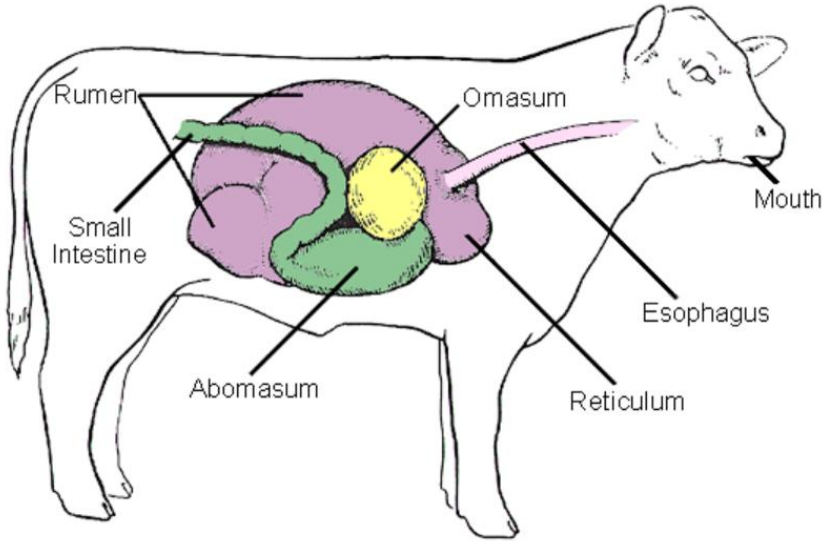


https://ohiostate.pressbooks.pub/vethisto/chapter/8-stomach/

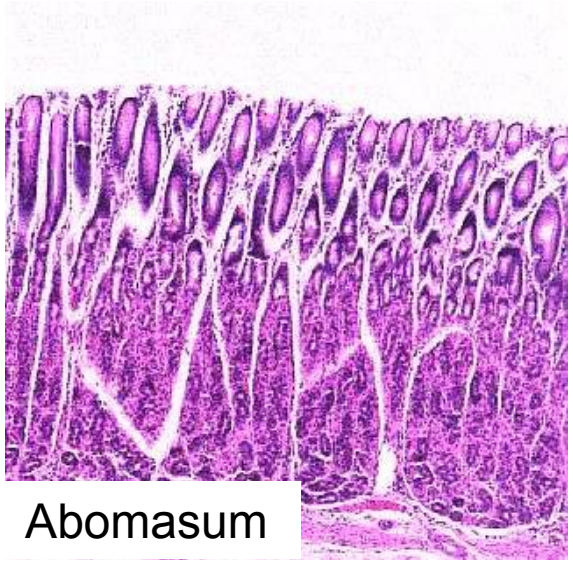
- **Ruminants**:

- Forestomachs (rumen, reticulum, omasum): **Fermentation** of cellulose.

- Abomasum: **Equivalent to monogastric stomach** for enzymatic digestion.



https://www.toppr.com/ask/content/concept/digestion-in-ruminants-200952/

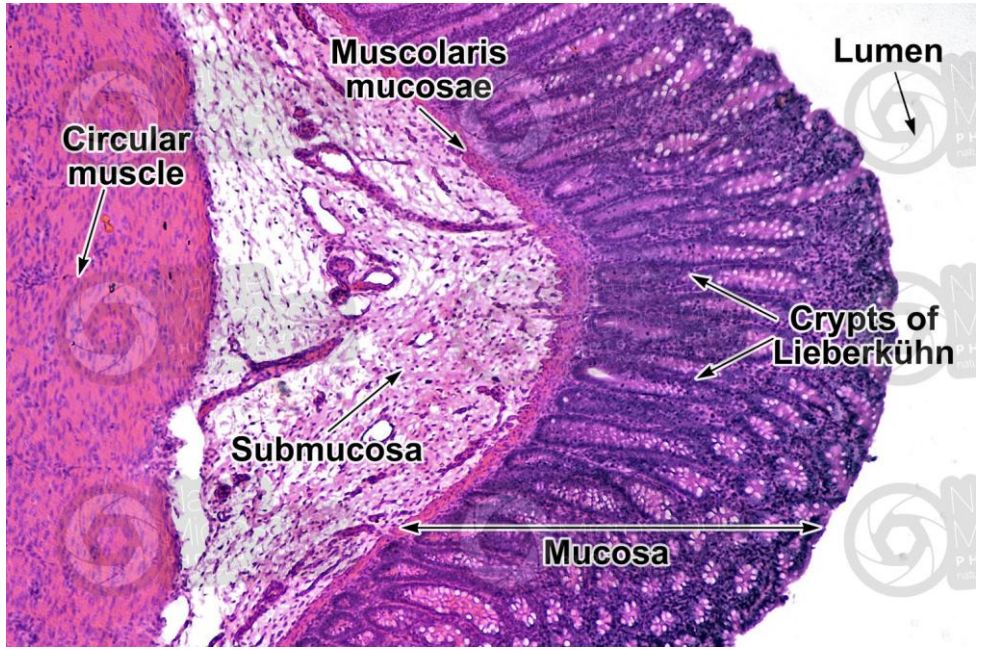


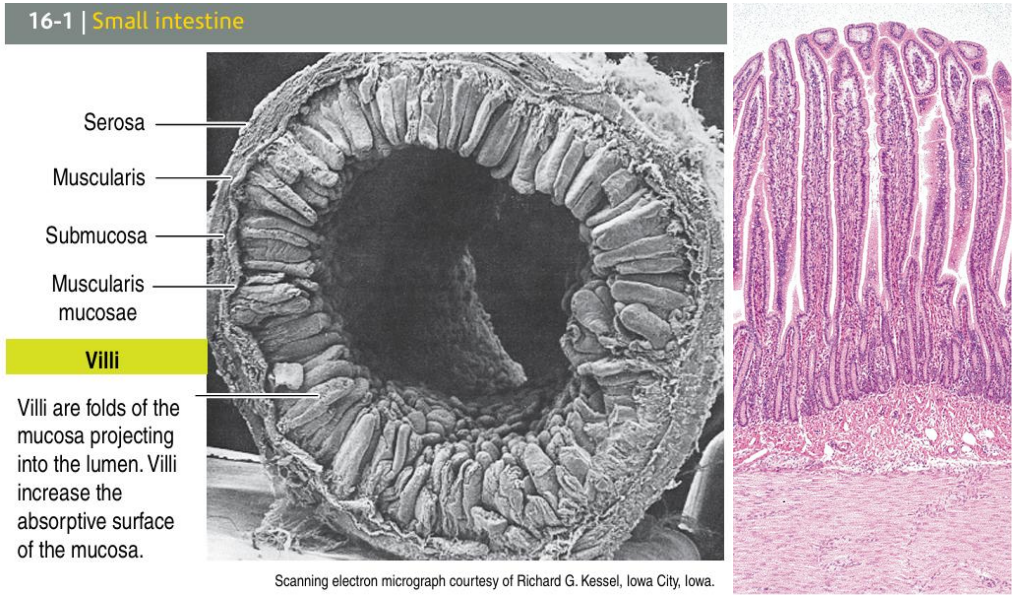
Abomasum

https://www.doctorc.net/Labs/Lab21/Examples/exabomas.htm

Small and Large Intestines

- Small Intestine:
- Villi and microvilli increase surface area for absorption.
- Functions: Digestion and nutrient absorption.
- Large Intestine:
- Absorbs water and electrolytes.
- Houses microbiota responsible for fermentation in herbivores.





Peritoneum, Omentum, and Mesentery

- Peritoneum:

- A serous membrane lining the abdominal cavity.

- Omentum:

- Fatty apron protecting abdominal organs.

- Mesentery:

- Supports intestines and contains blood vessels and lymphatics.

Disorder in the Digestive System

Gastrointestinal Aging

- Subtle changes, most recognized in dogs.

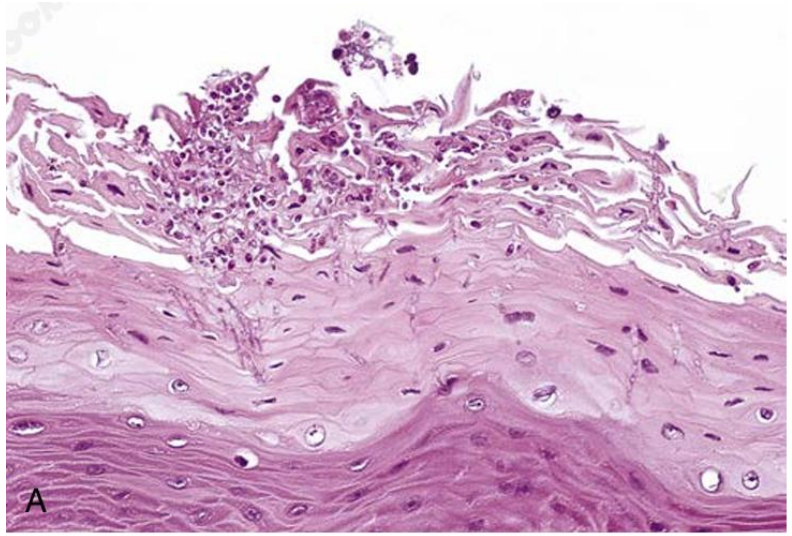
- Oral cavity:
- Plaque buildup leading to periodontitis.
- Dental crowding and malocclusions.

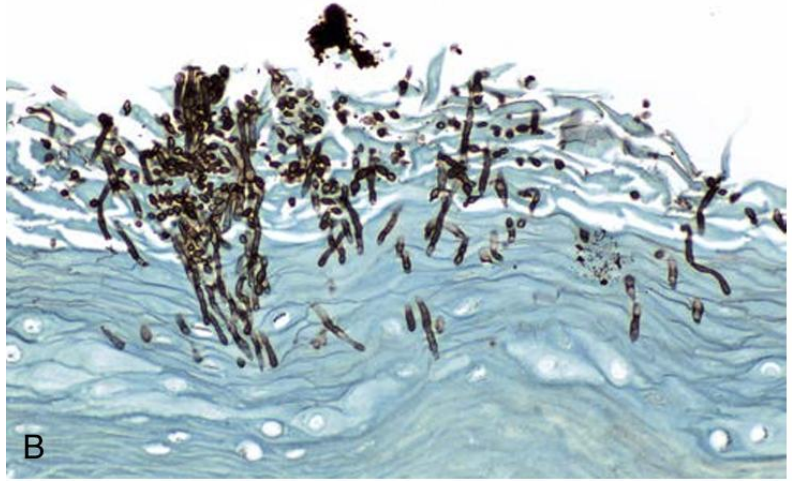
- Intestinal tract:
- Decreased saliva and gastric acid secretion.
- Villus size decreases, slowed gastric emptying.

Oral Cavity Disorders

- Protective functions:
- Prevents harmful xenobiotics through taste and feel.

- Disorders:
- Thrush (caused by *Candida spp.*) due to antibiotic use.
- Plaque formation and periodontitis in small breeds.





Esophageal and Forestomach Disorders

- Esophagus:
- **Rapid healing** (5-8 days turnover rate).
- Horses unable to vomit due to strong esophageal sphincter.

- Forestomach (ruminants):
- Digestion of cellulose via **microbial flora**.
- Reticulum and omasum aid in mechanical breakdown.

Stomach and Intestine Disorders

- Stomach:

- Parietal cells secrete HCl and intrinsic factor.
- Chief cells secrete pepsin.

- Intestinal disorders:

- Chronic injury causes inflammation.
- Examples: Boxer colitis, Johne’s disease, lymphoma.

Innervation Disorders

- Dysautonomia and Agangliosis:
- Affects intestinal motility.
- Causes: Botulinum toxin, idiopathic, hereditary.

- Gut-brain axis:
- Altered microbiota affects brain function.
- Associated with conditions like irritable bowel syndrome.

Diarrhea: Pathogenesis and Types

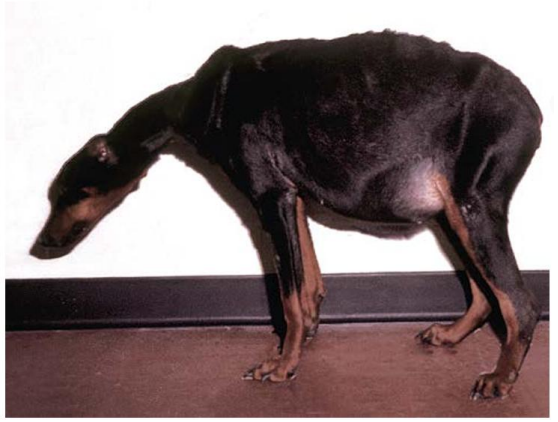
- Types:
- Noninflammatory (ETEC, *Cryptosporidium parvum*).
- Inflammatory (*Salmonella*, *Lawsonia*).

- Mechanisms:
- Malabsorption and fermentation.
- Hypersecretion via chloride ion channels.

Peritoneal Disorders: Ascites & Fat Necrosis

• Ascites:

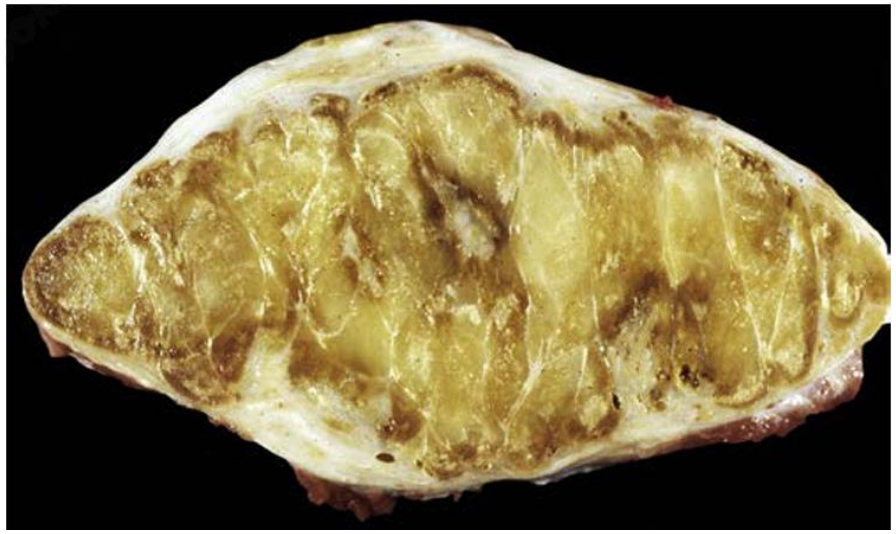
- Fluid accumulation due to hypoproteinemia, lymphatic blockage.



• Fat necrosis:

- Nutritional, pancreatic, traumatic, or idiopathic causes.

- Saponification forms chalky deposits.



Peritonitis and Pneumoperitoneum

• Peritonitis:

- Causes: Bacterial, **viral**, parasitic, or mechanical.

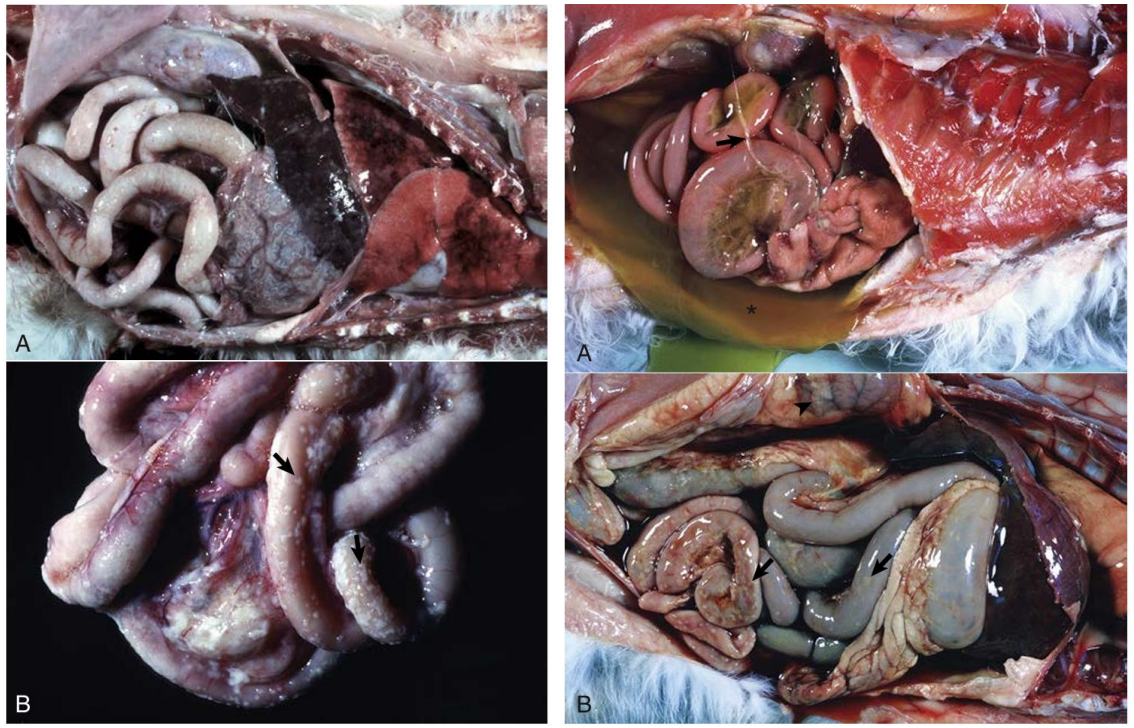
- Forms: Suppurative, fibrinous, granulomatous.

• Pneumoperitoneum:

- Perforation-induced (GI or reproductive tract).

- Traumatic causes (surgery, accidents).

FIP



Feline Infectious Peritonitis (FIP)

의뢰하신 2군데의 조직 각각 2단면에 대한 병리조직학적 검사를 진행한 결과, 맹장과 맹장 주변 **장간막 조직 및 장간막 림프절**에서는 유사한 양상으로 **화농성 육아종성 염증 소견이 관찰되었습니다**.

본 예에서 관찰된 화농성 육아종성 염증 소견에 대하여, 염증의 조직학적 소견과 분포 양상 상 감염성 원인체에 의해 발생하였을 가능성이 높다고 사료됩니다. 고양이에서는 feline infectious peritonitis virus (FIP) 등의 virus, toxoplasma 등의 원충, 곰팡이, 전신적인 mycobacterium 등의 세균 감염 등이 이와 같은 병변을 일으킬 수 있습니다. 본 예의 경우, H&E 염색상에서 감염성 원인체는 확인되지 않았으며, 일부 **염증성 결절들이 주로 혈관 주변으로 존재**하고, 본 **환축의 나이**, 임상적으로 관찰하신 육안 소견(**다발성**으로 분포된 병변) 등을 종합하였을 때, Feline infectious peritonitis (FIP)의 가능성에 대한 고찰이 우선적으로 필요할 것으로 사료됩니다. 다만, H&E 염색상에서는 감염성 원인체가 관찰되지 않을 수도 있어 다른 감염성 원인체의 가능성을 완전하게 배제할 수는 없었으며, 혈청검사 및 Giemsa stain, PAS, GMS(Grocott's methenamine silver) stain, Fite's stain (modified Acid-fast stain), Gram stain 등의 특수 염색 및 좀 더 민감한 방법인 병변부에서 원인체의 직접적인 분리 동정, 배양, PCR 등의 기법이 원인체 감별에 도움을 줄 수 있을 것으로 사료됩니다. 다른 부위/장기로의 염증 파급에 대한 예후 관찰이 필요할 것으로 사료됩니다.

의뢰하신 조직에서 종양성 병변은 관찰되지 않았습니다.

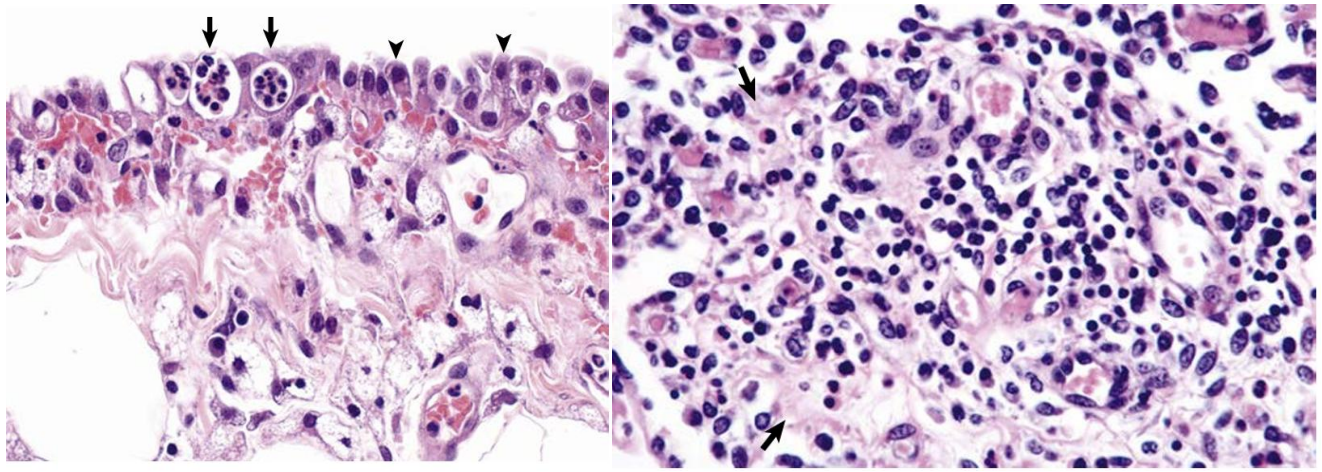
참고로, FIP virus는 분변이나 타액에 의해 구강, 비강을 통하여 감염되며, **전염성이 강한** 것으로 알려져 있으므로 만약 동거했던 다른 개체들이 있다면 이 개체들에 대해서도 임상적인 검토가 필요할 것으로 사료됩니다.

Peritonitis and Pneumoperitoneum

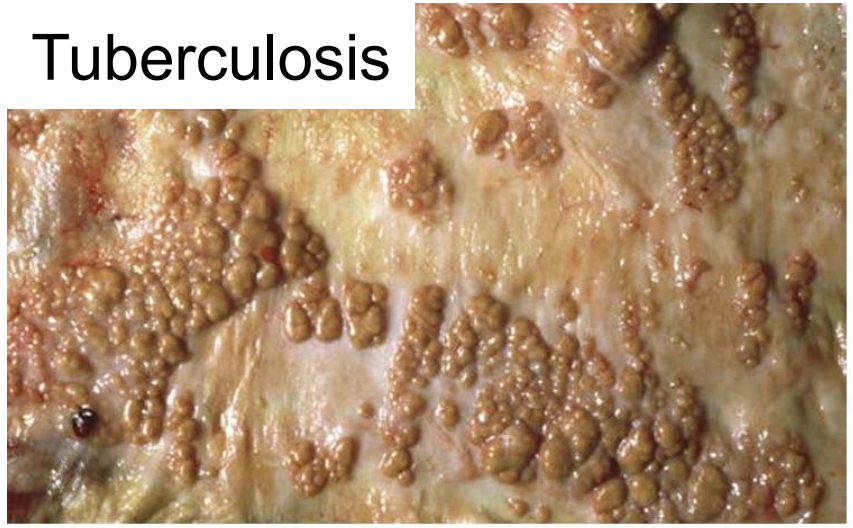
• Peritonitis:

- Causes: Bacterial, viral, **parasitic**, or mechanical.

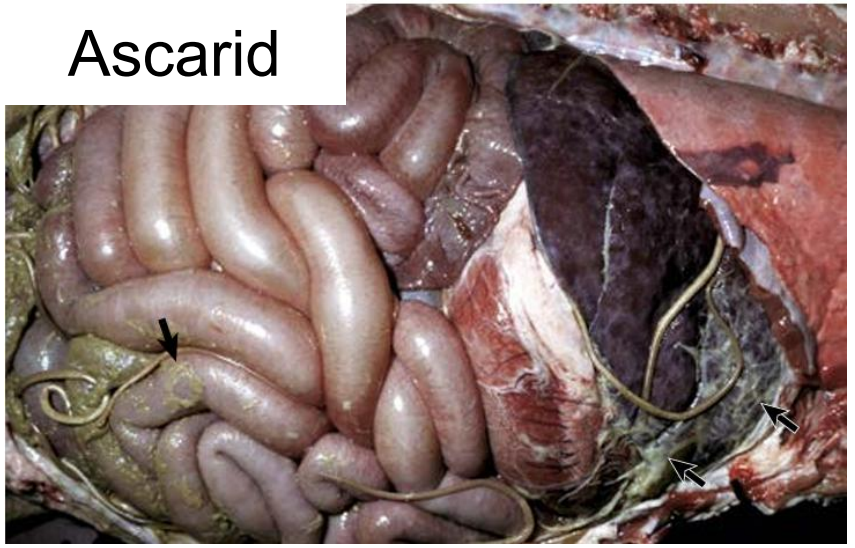
- Forms: Suppurative, fibrinous, granulomatous.



Tuberculosis



Ascarid



Clinical Consequences of Dysfunction

- Dehydration:
- Fluid loss >85% water in feces.

- Hypovolemia:
- Reduced tissue perfusion.

- Electrolyte imbalance:
- Hypokalemia, metabolic acidosis.

- Shock:
- Leads to hypovolemic shock and multi-organ failure.

Defense Mechanisms

Introduction to Defense Mechanisms

• The alimentary system has specialized barriers:

- Mechanical barriers (physical structures).

- Biochemical barriers (enzymes, pH).

- Immunologic barriers (GALT, immune cells).

• Protects against:

- Pathogenic bacteria, viruses, parasites, and toxins.

- Taste buds
- Vomiting
- Saliva
  - Flushing action so that potential pathogens are cleared from the oropharynx
  - Protective coating of the mucosa
  - Contains antimicrobial lysozyme, lactoferrin, lactoperoxidase, and immunoglobulins
- Gastric pH
- Microbiota/microbiome–lower GI tract (damaged by toxicants; carcinogen activation)
  - 100 trillion (anaerobic) bacteria (10 × host); 3.3 million genes (150 × host)
  - Bacteriocins
  - Compete for nutrients
  - Compete for attachment sites
  - Promote immune system maturation
  - Biotransformation
  - Enterotype
- Secreted immunoglobulins
- Extraintestinal secretions from the liver and pancreas
  - Lactoferrins
  - Peroxidase
- Intestinal proteolytic enzymes
- Intestinal biotransforming and metabolic enzymes
- Phagocytes and other effector cells within the submucosa
- High rate of epithelial turnover
- Shedding of receptor-laden ALP and catalase-containing vesicles from microvilli
- Large surface area
- Dilution with ingesta
- Increased peristalsis resulting in diarrhea
- Mucus–contains phages that destroy bacteria $> 1 \times 10^4$
- Paneth cells (antimicrobial peptides, lysozymes, phospholipase A2, defensins-cryptdins)
- Innate lymphoid cells
- Adaptive immune system
- Kupffer cells (liver)
- Genetic polymorphisms (HLA) and host gene expression.

Mechanical Barriers in the Alimentary System

- Epithelial barriers:

- Stratified squamous epithelium resists trauma.

- Mucus layer:

- Traps pathogens and prevents attachment.

- Peristalsis:

- Flushes pathogens through intestinal movement.

Biochemical Barriers

- Saliva:

- Contains lysozyme, thiocyanate, and lactoferrin.

- Gastric acid:

- Low pH destroys ingested pathogens.

- Antimicrobial peptides:

- Defensins and cryptdins secreted by Paneth cells.

Immunologic Barriers

• Gut-Associated Lymphoid Tissue (GALT):

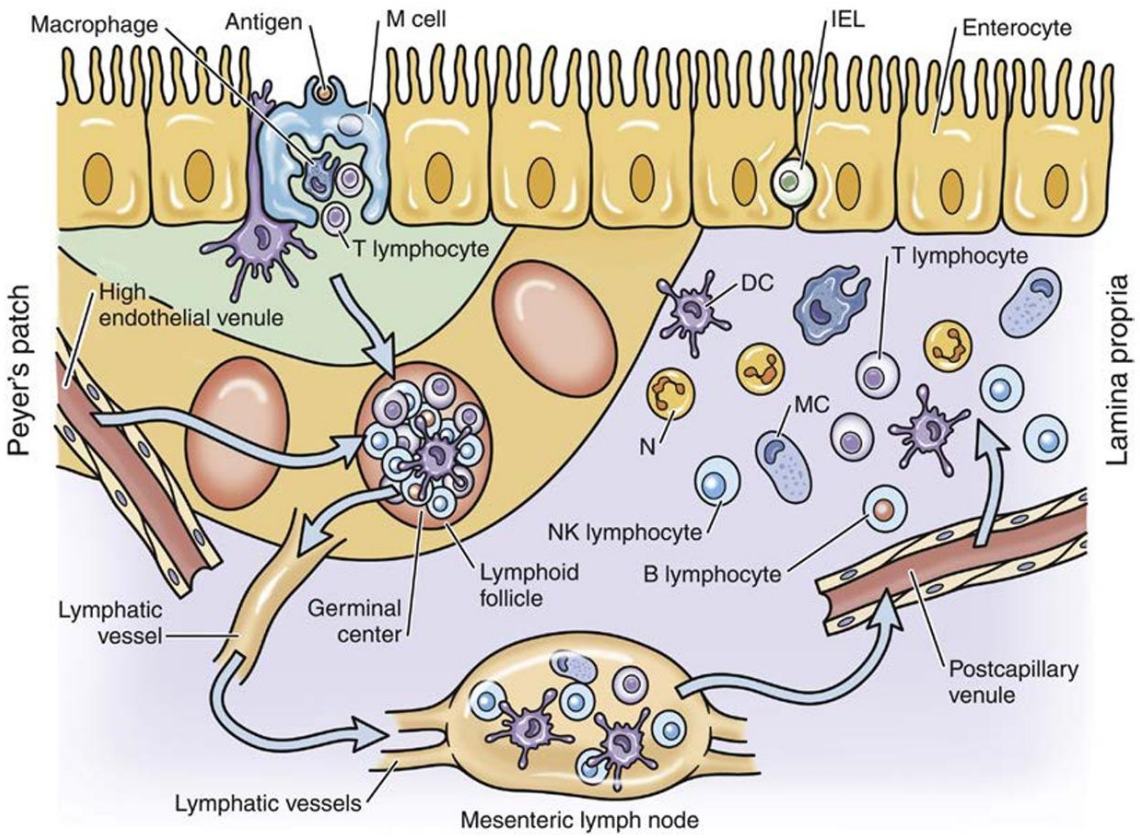
- Specialized immune tissue in the intestinal lining.

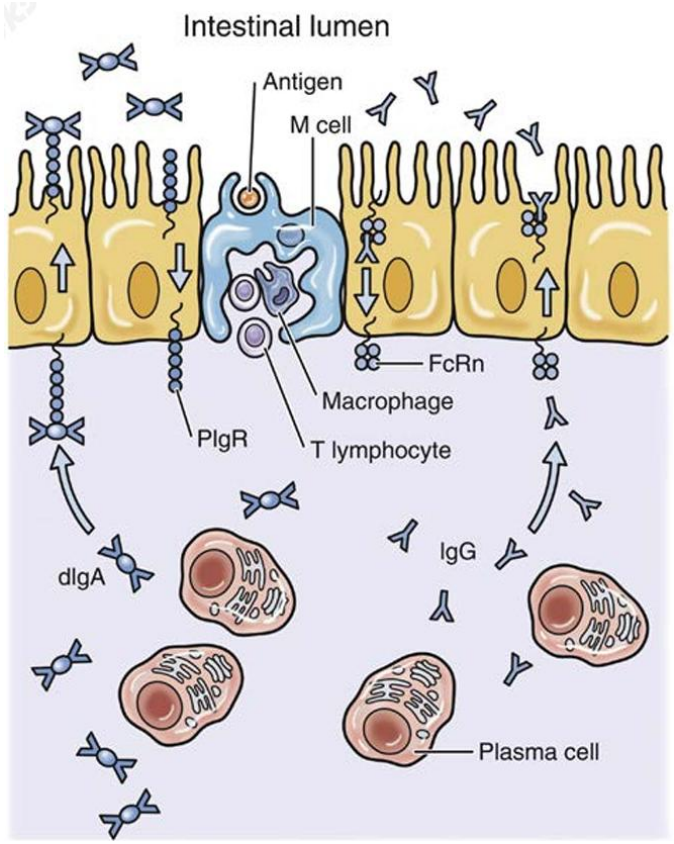
• Secretory IgA:

- Prevents pathogen adhesion to mucosal surfaces.

• Peyer's patches:

- Initiate immune responses against intestinal antigens.





Cellular Defense Mechanisms

- Enterocytes:

- Absorb nutrients and act as antigen-presenting cells.

- Paneth cells:

- Secrete antimicrobial peptides.

- M cells:

- Transport antigens from the intestinal lumen to GALT.

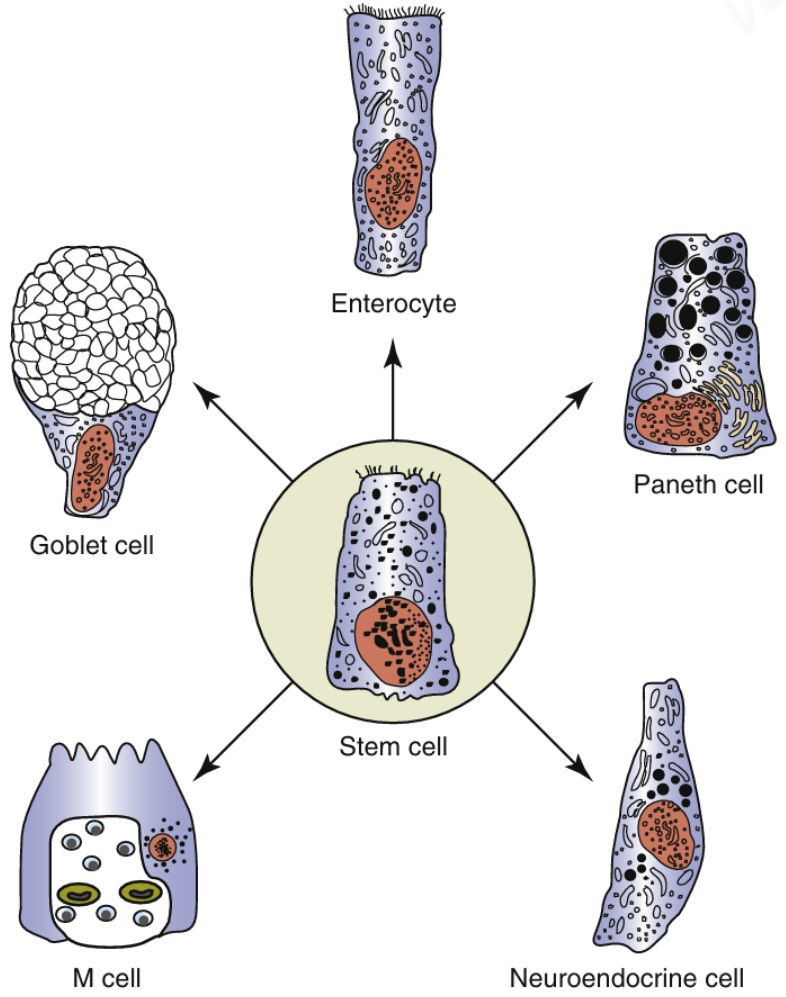


Figure 7.4 Epithelial Cell Types of the Small Intestine. Progenitor stem cells, located in the intestinal crypts, give rise to all other epithelial cell types lining the crypt and covering the villi.

Microbial Flora as Defense

• Commensal bacteria:

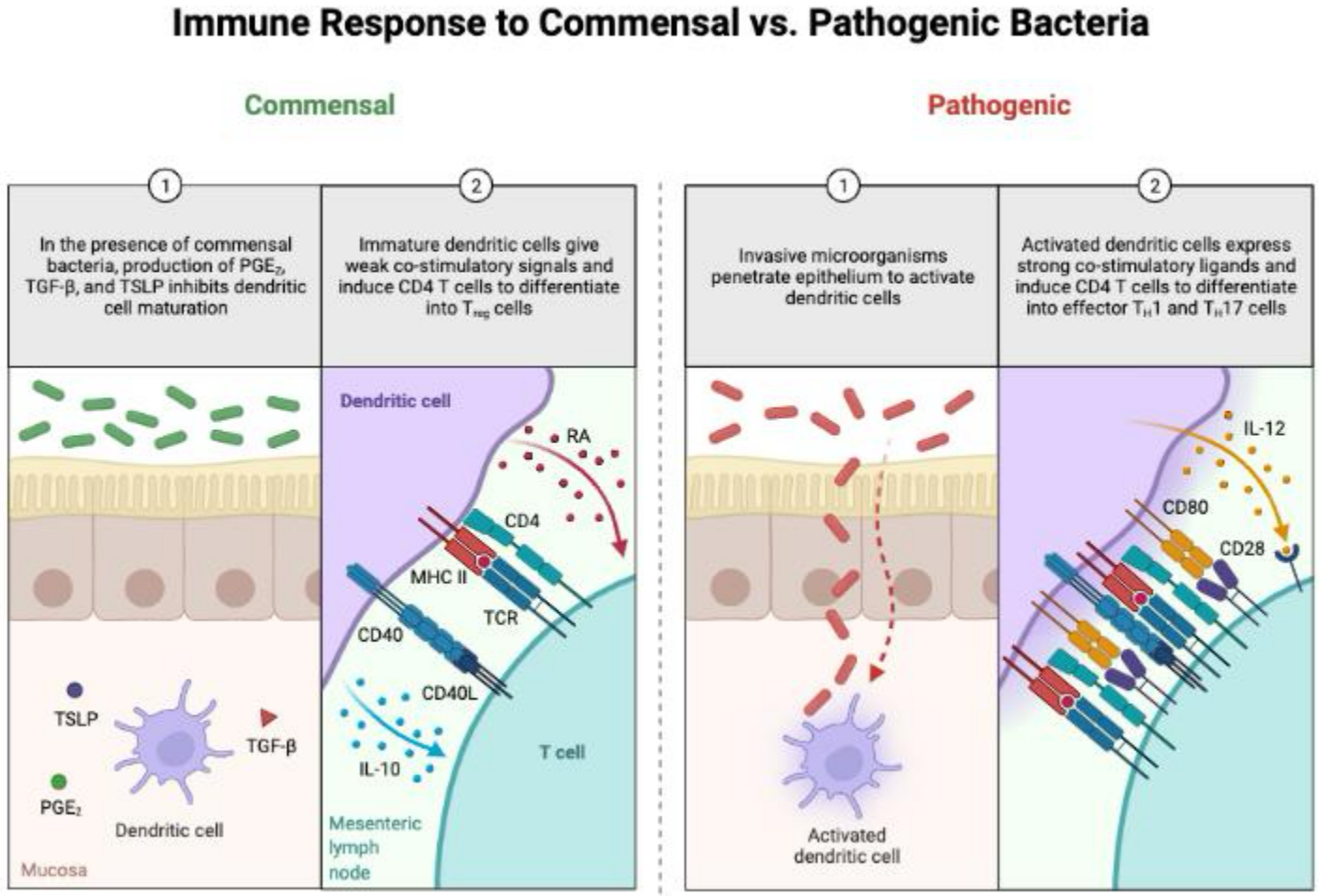
- Occupy ecological niches, limiting pathogen colonization.

• Competitive exclusion:

- Outcompetes harmful bacteria for nutrients and attachment sites.

• Microbiota:

- Supports immune system development and function.



Neuroimmune Interactions and TLRs

• Toll-like receptors (TLRs):

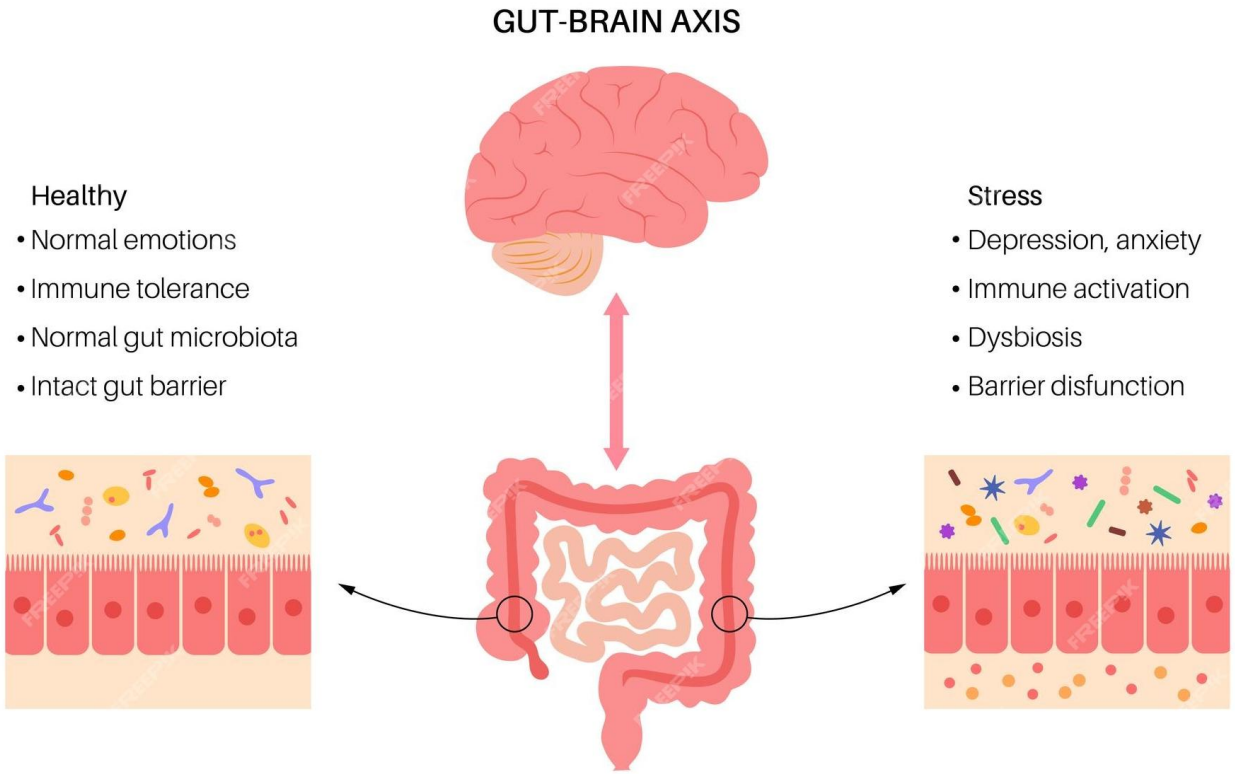
- Detect pathogens and activate immune responses.

• Gut-brain axis:

- Bidirectional communication between the gut and brain.

• Dysbiosis:

- Microbial imbalances can impact neurological health.



Pathogen Evasion of Barriers

- ***Salmonella spp.*:**

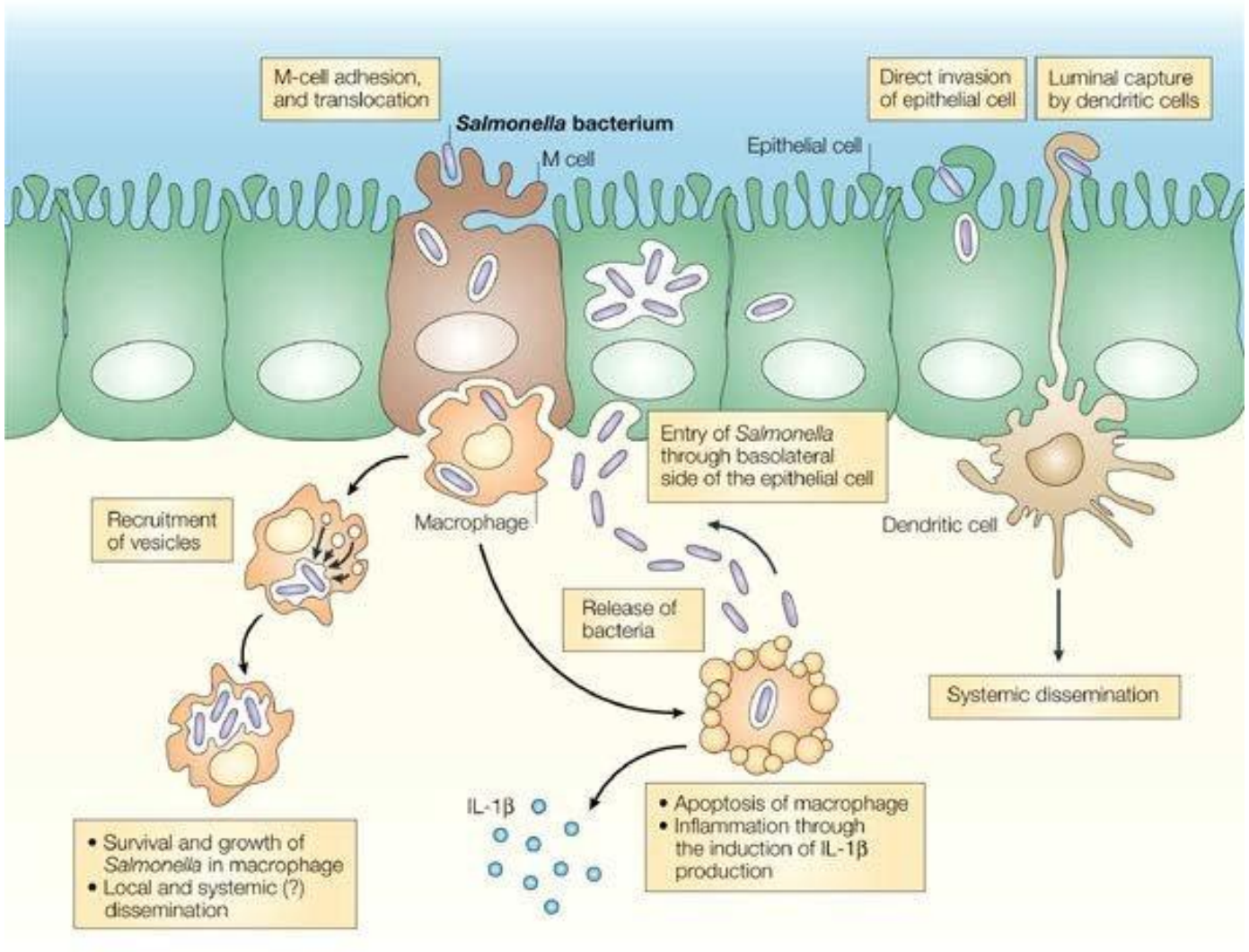
- Invades epithelial cells and avoids immune detection.

- *Escherichia coli*:

- Uses fimbriae for strong mucosal adhesion.

- *Bovine Viral Diarrhea Virus (BVDV)*:

- Disrupts lymphoid tissue, compromising immune responses.



Epigenetic control of O-antigen chain length in Salmonella enterica. 2016

Pathogen Evasion of Barriers

• *Salmonella spp.*:

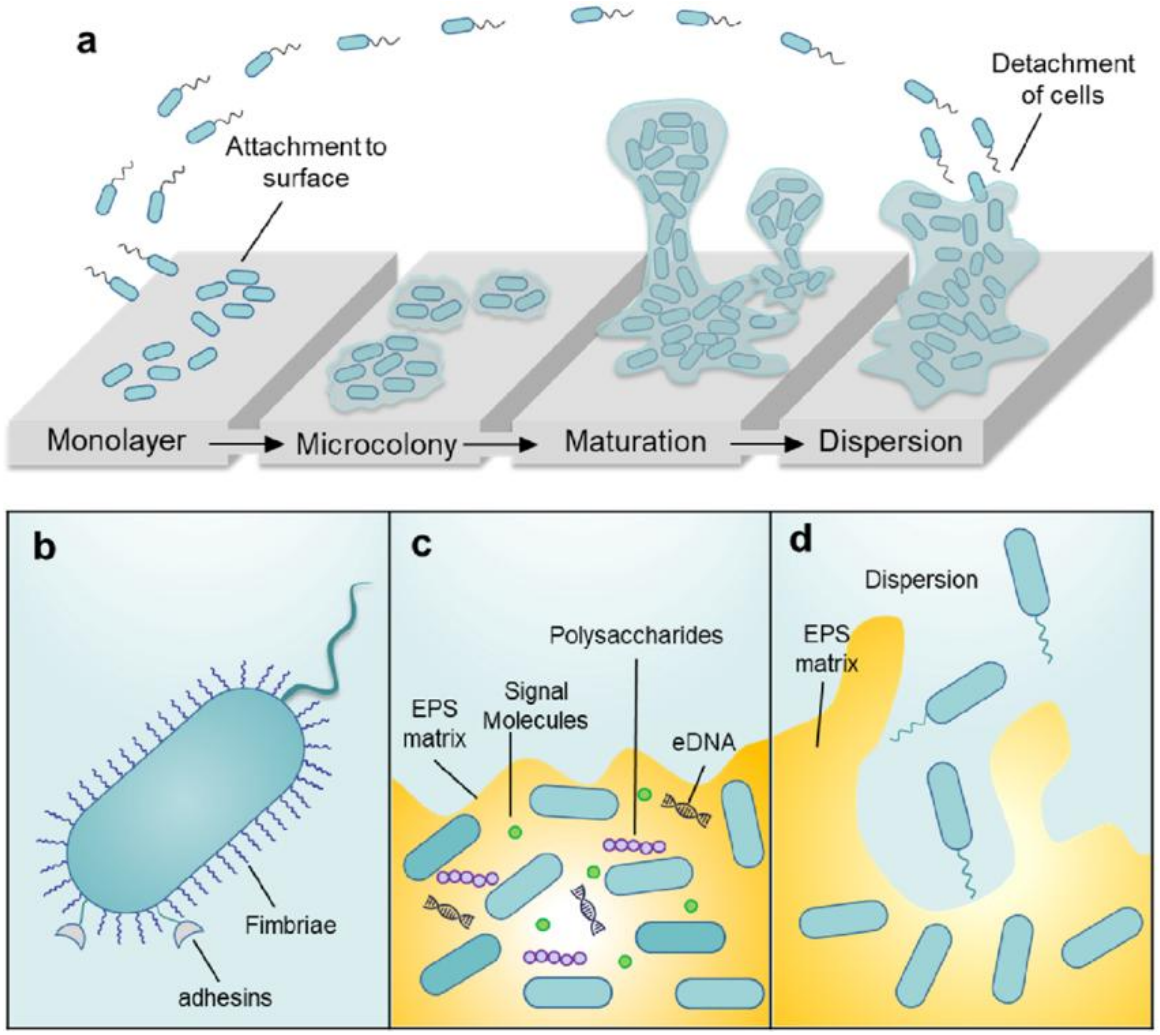
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• *Bovine Viral Diarrhea Virus (BVDV)*:

- Disrupts lymphoid tissue, compromising immune responses.



Advances in Nanotechnology for Biofilm Inhibition. 2023

Pathogen Evasion of Barriers

• *Salmonella spp.*:

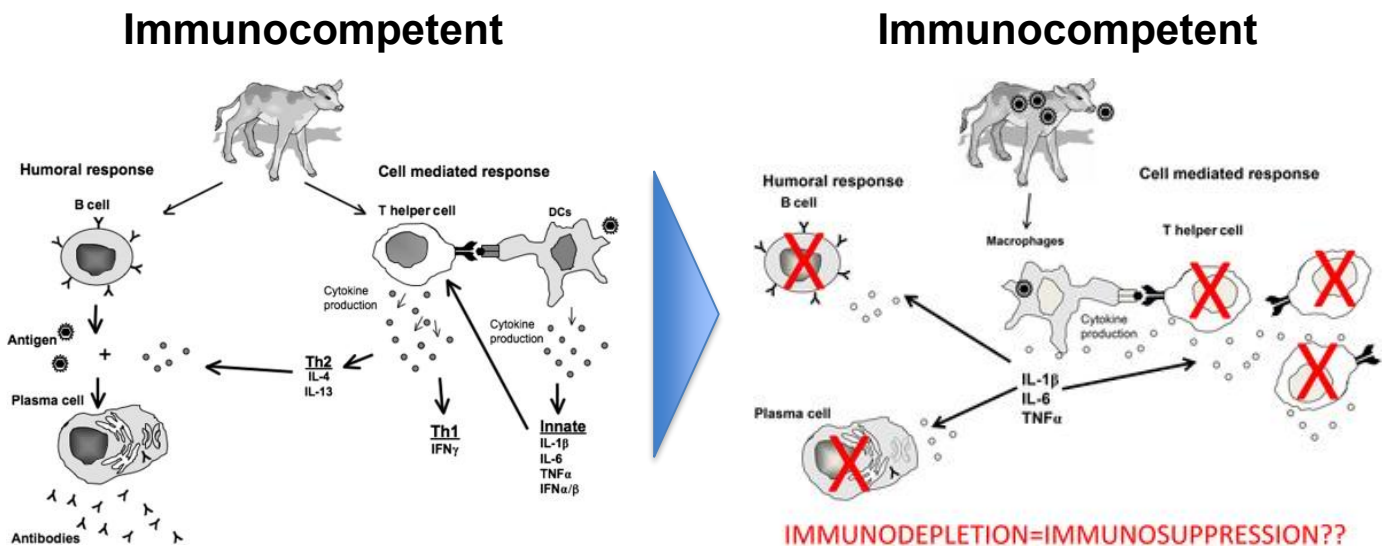
- Invades epithelial cells and avoids immune detection.

• *Escherichia coli*:

- Uses fimbriae for strong mucosal adhesion.

• ***Bovine Viral Diarrhea Virus (BVDV)*:**

- Disrupts lymphoid tissue, compromising immune responses.



Immune response to bovine viral diarrhea virus—looking at newly defined targets. 2015

Clinical Implications of Barrier Failures

- Barrier failure can lead to:
- Chronic diarrhea and inflammation.
- Opportunistic infections due to weakened defenses.

- Clinical examples:
- Inflammatory bowel disease (IBD).
- Johne’s disease in ruminants.

Conclusion and Therapeutic Strategies

- Enhancing barrier defenses:
- Probiotics to support microbiota.
- Anti-inflammatory medications.

- Immunotherapy:
- Targeting TLRs to modulate immune responses.

- Early diagnosis and treatment improve outcomes.

Portals of Entry

Introduction to Portals of Entry

- The alimentary system is exposed to various pathogens.

- Major portals of entry:
  - Ingestion (oral cavity, food, water).
  - Cough-induced ingestion from the respiratory system.
  - Systemic spread via bloodstream (viremia, bacteremia).

- Entry points vary by species and pathogen type.

Box 7.2 Portals of Entry

ALIMENTARY SYSTEM

- Coughed up from the lungs and swallowed
- Hematogenous: Systemic bloodborne infection
- Ingestion
- Parasite migration

PERITONEUM, OMENTUM, MESENTERY, AND PERITONEAL CAVITY

- Alimentary tract: Stomach ulcer, ruptured segment of intestine, reticulum foreign body
- Biliary system
- Common bile duct
- Hematogenous: Systemic bloodborne infection
- Liver rupture or abscess
- Ovary: Ruptured cyst
- Pancreas: Acute pancreatitis, neoplasms
- Parasite migration
- Penetration through the abdominal wall
- Penetration through the diaphragm
- Perforation from rectal examination
- Rupture of uterus with infection (pyometra/metritis)
- Spleen: Rupture, neoplasm seeding, abscess rupture
- Umbilicus: Neonatal
- Urinary bladder rupture

Ingestion as a Primary Route

- Most common portal of entry for pathogens.

- Contaminated food and water are primary sources.

- Examples:
- *Escherichia coli*: Causes diarrhea via toxin production.
- *Salmonella spp.*: Invades intestinal mucosa and triggers inflammation.

- Protective mechanisms:
- Gastric acid barrier.
- Salivary enzymes (lysozyme, lactoferrin).

Cough-Induced Ingestion

- Respiratory-to-digestive spread of pathogens.

- Mechanism:
- Pathogens from the respiratory tract coughed up and swallowed.
- Enter the digestive tract and establish infections.

- Example:
 - *Rhodococcus equi* in horses: Causes enteritis following respiratory infection.

Systemic Spread: Blood-Borne Infections

• Viremia:
- Viruses in the bloodstream spread to the alimentary system.
- Example: *Bovine Viral Diarrhea Virus (BVDV)* targets lymphoid tissues.

• Bacteremia:
- Bacteria spread systemically and cause enteric infections.
- Example: *Salmonella spp.* causes systemic bacteremia.

• Toxemia:
- Toxins produced by bacteria spread through blood.
- Example: *Clostridium perfringens*.

Mucosal Breach and Pathogen Spread

- Pathogens enter through mucosal damage or trauma.

- Lymphatic spread:
- Pathogens enter lymph nodes and disseminate systemically.

- Vascular spread:
- Pathogens spread through blood vessels after penetrating mucosa.

- Common causes:
- Mechanical trauma, dental issues, oral ulcers.

Oral Cavity as a Pathogen Entry Point

• Mechanical trauma enables pathogen entry:
- Poor dental hygiene leads to plaque buildup.
- Periodontitis allows deeper bacterial invasion.

• Pathogens:
- *Escherichia coli* and *Streptococcus spp.* colonize oral lesions.

• Clinical impact:
- Leads to systemic infections and tooth loss.

Tonsils' Role in Pathogen Spread

• Tonsils lack afferent lymphatic vessels:

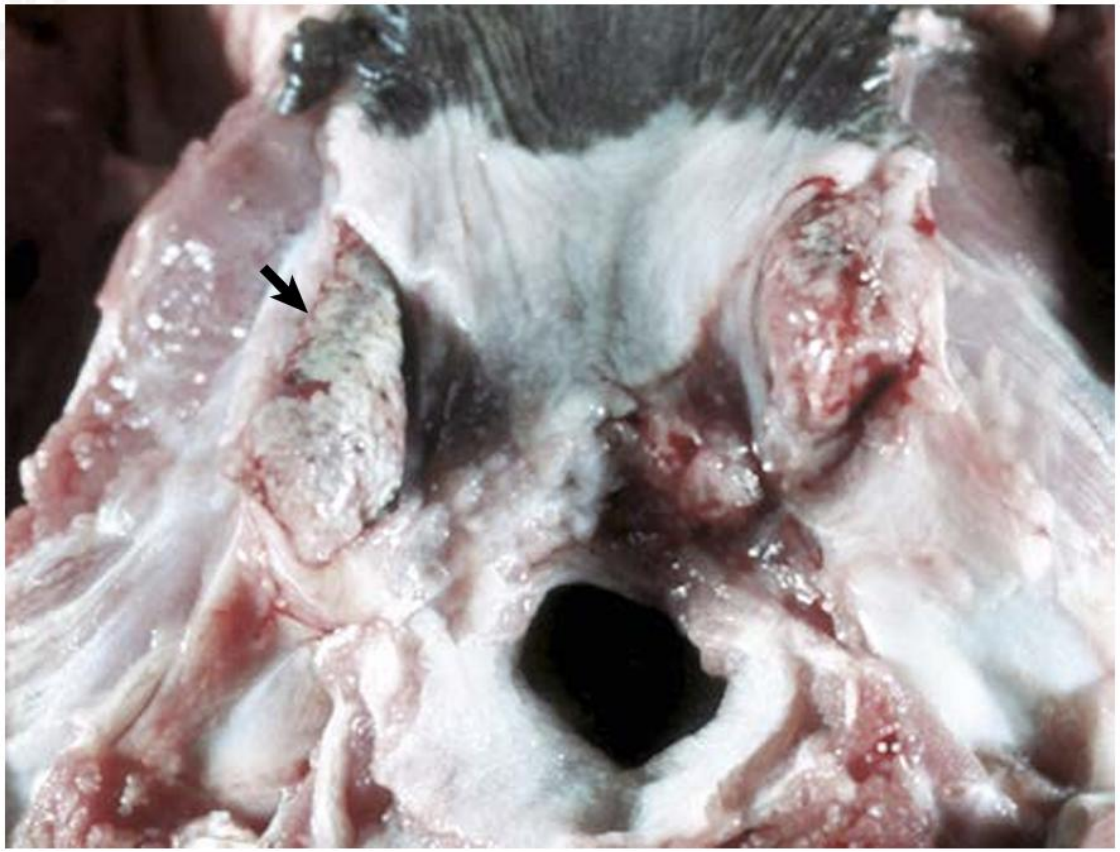
- Pathogens can directly infect tonsillar tissue.

- Blood-borne infections target tonsils.

• Pathogen examples:

- *Feline Parvovirus*: Multiplies within tonsils.

- *BVDV*: Spreads to tonsils via bloodstream.



Pathogen-Specific Entry Mechanisms

- *Salmonella spp.*:
- Invades intestinal mucosa and spreads systemically.

- *Escherichia coli (ETEC)*:
- Releases toxins causing fluid secretion and diarrhea.

- *Bovine Viral Diarrhea Virus*:
- Targets lymphoid tissues and causes mucosal necrosis.

Clinical Implications of Pathogen Entry

- Early invasion can lead to:
- Severe inflammation.
- Diarrhea and dehydration.

- Systemic spread:
- Causes septicemia and multi-organ failure.

- Diagnosis:
- Blood cultures, biopsies, and PCR-based tests.

- Early intervention improves outcomes.

Conclusion and Preventative Strategies

• Proper hygiene and veterinary care are essential.

• Vaccinations:
- Prevent infections from *Salmonella*, *E. coli*, and *BVDV*.

• Oral hygiene:
- Reduces dental infections and systemic spread.

• Early diagnosis and treatment:
- Reduces complications from systemic infections.

Response to Injury

Dysfunction and Response to Injury

- Injury responses in the alimentary system vary by tissue and species.
- Includes inflammation, necrosis, lymphangiectasia, innervation disorders, and **diarrhea**.
- Infectious agents play a major role in pathogenesis and disease severity.

Inflammation: Pathology and Mechanisms

• Acute inflammation:

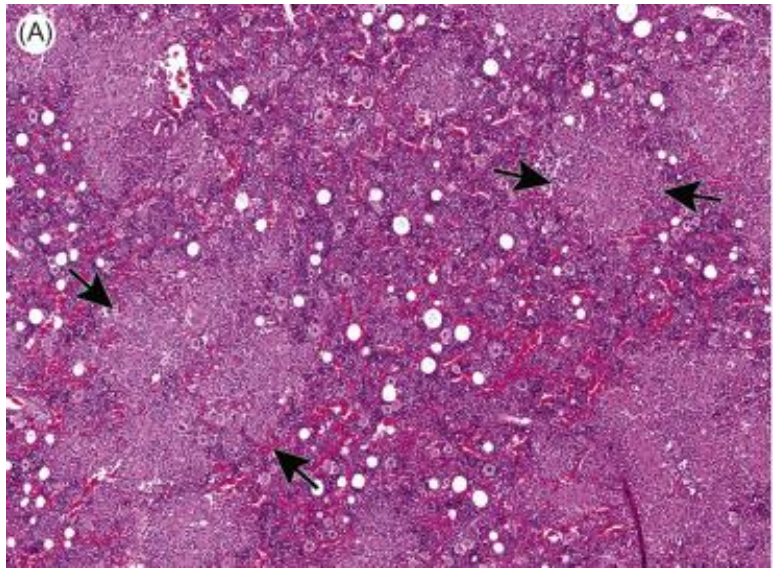
- Caused by infections like *Salmonella spp.*, *E. coli*.

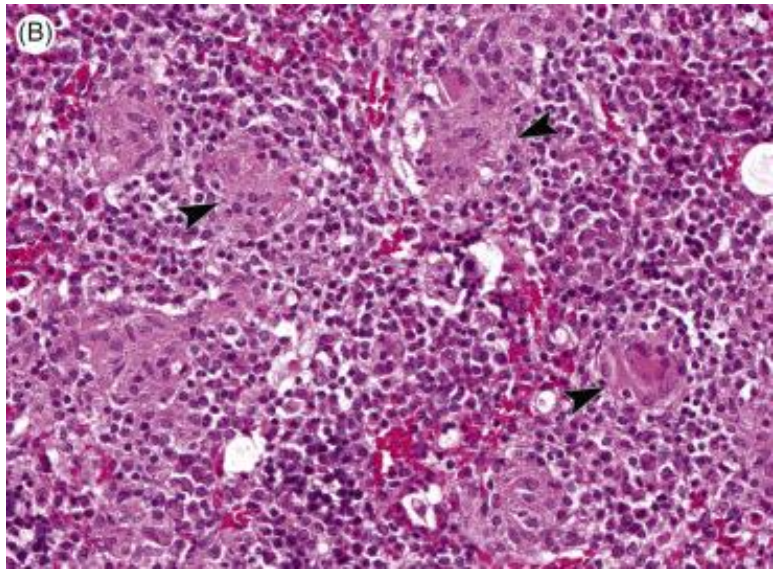
- Leads to edema, hyperemia, and tissue damage.

• Chronic inflammation:

- Persistent injury (e.g., Johne's disease in ruminants).

- Granuloma formation and fibrosis.





https://www.sciencedirect.com/topics/medicine-and-dentistry/granulomatous-inflammation

Necrosis and Cellular Death

• Pathogenesis:

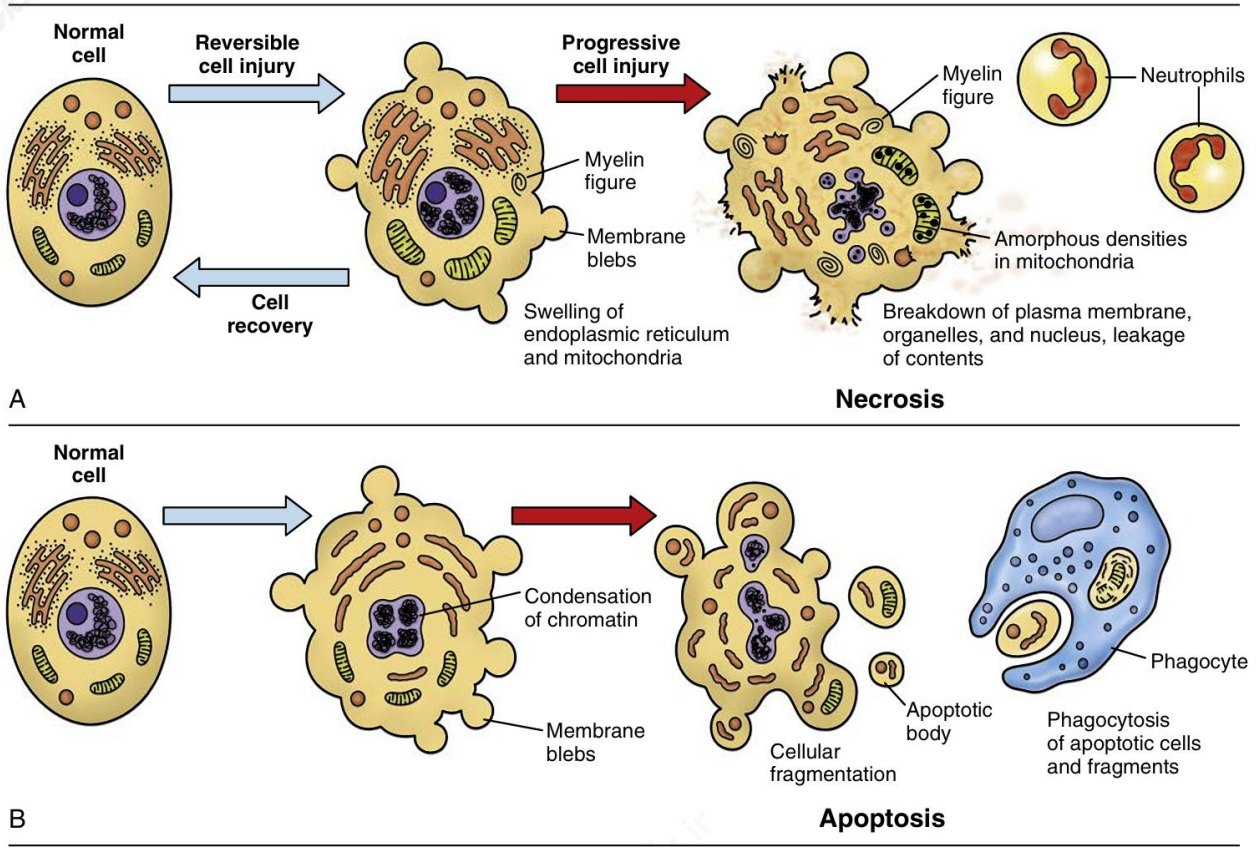
- Toxins (e.g., *Clostridium perfringens* enterotoxin) induce cell death.

- Viral infections (e.g., *BVDV*) destroy lymphoid tissue.

• Clinical significance:

- Mucosal ulceration

- Impaired nutrient absorption



Lymphangiectasia and Protein-Losing Enteropathy

• Cause:

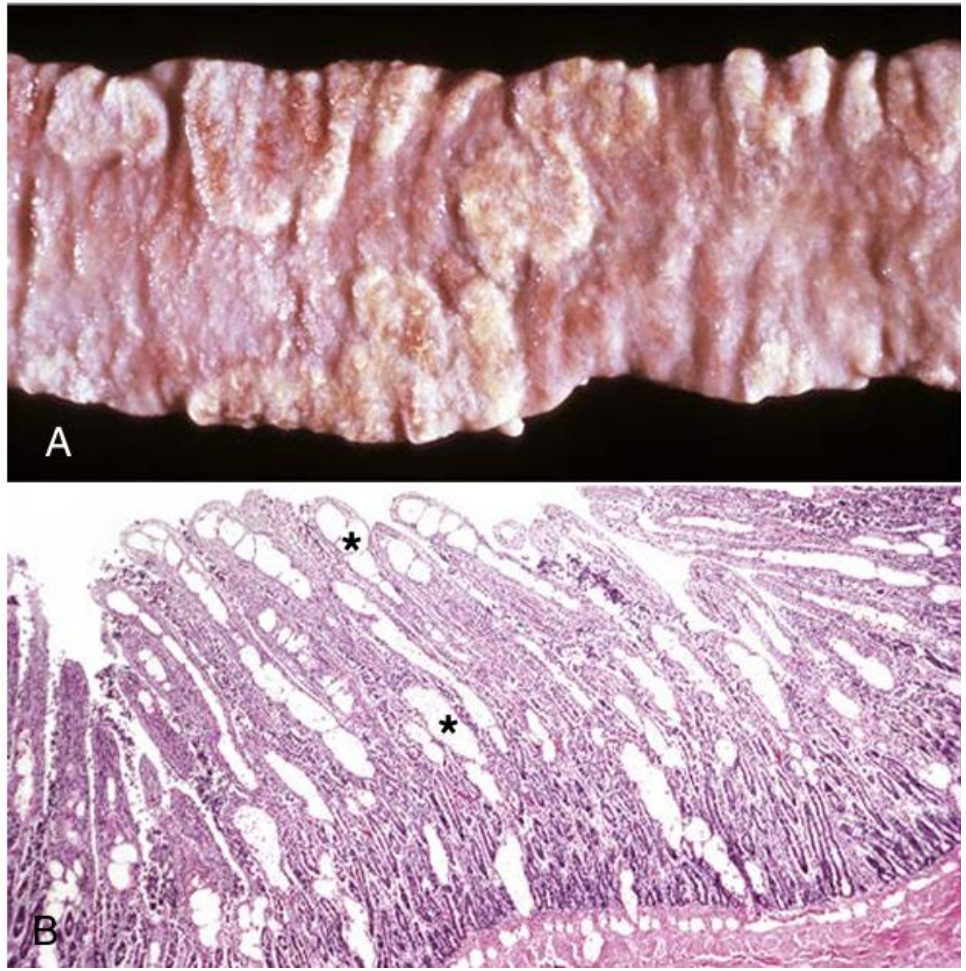
- Obstruction of lymphatic vessels due to lymphoma or chronic inflammation.

• Pathogenesis:

- Dilation of lymph vessels.
- Leakage of lymph into the intestinal lumen.

• Clinical outcomes:

- Hypoproteinemia
- Diarrhea and weight loss



Disorders of Innervation

- Dysautonomia:
- Loss of autonomic innervation in dogs and cats.

- Causes:
- Infectious agents (e.g., botulinum toxin)
- Idiopathic degeneration

- Symptoms:
- Megaoesophagus
- Constipation or incontinence





Diarrhea: Etiology and Clinical Implications

• Types:
- Noninflammatory: Caused by *E. coli*, rotavirus.
- Inflammatory: Caused by *Salmonella spp.*, *Clostridium difficile*.

• Pathogenesis:
- Damage to enterocytes → Malabsorption
- Hypersecretion from toxin-producing bacteria

Diarrhea

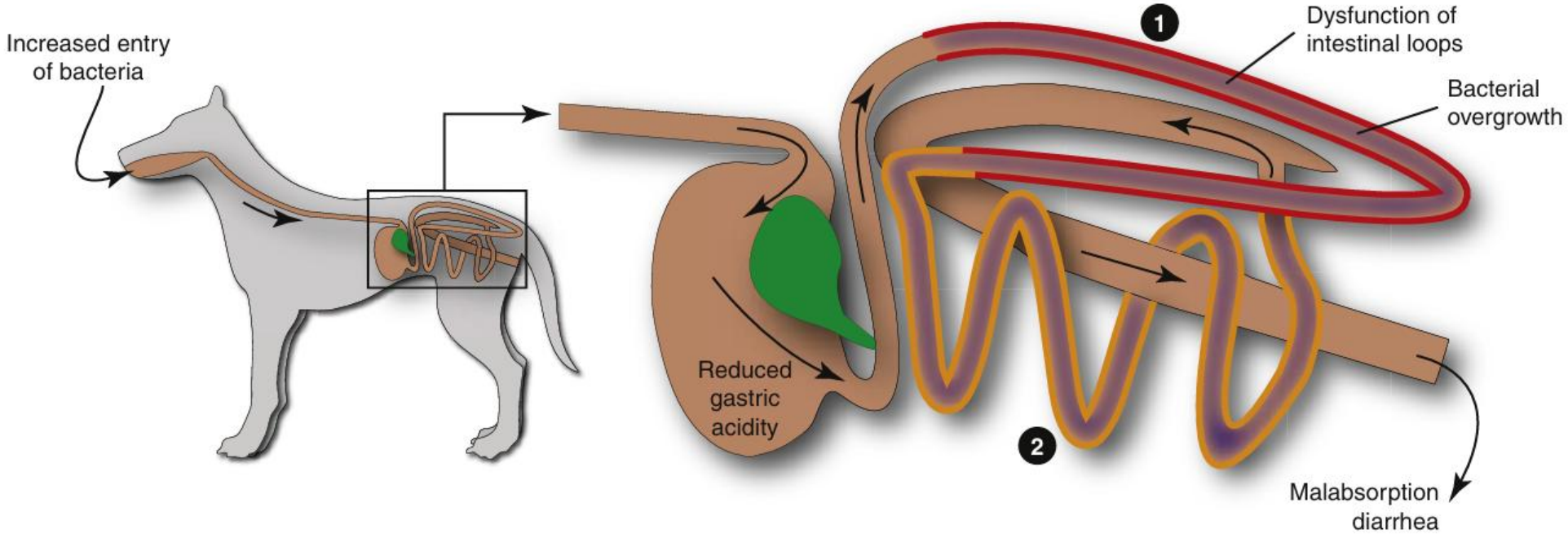
Definition of Diarrhea

• Abnormally fluid feces accompanied by increased volume and frequency.

• Two mechanistic types:

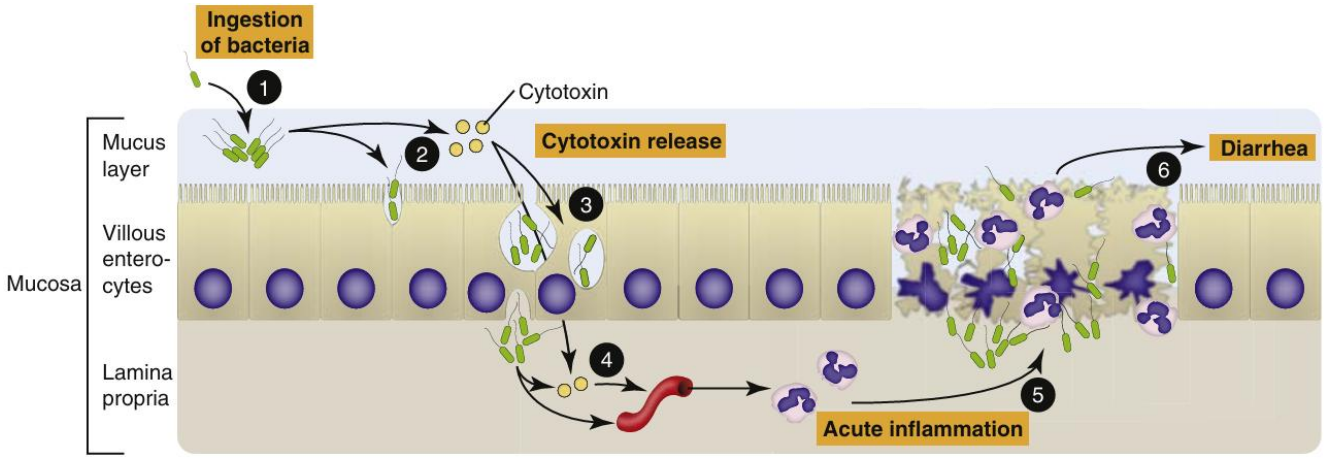
- Noninflammatory: Disrupts absorption without destroying cells (e.g., ETEC, rotavirus).

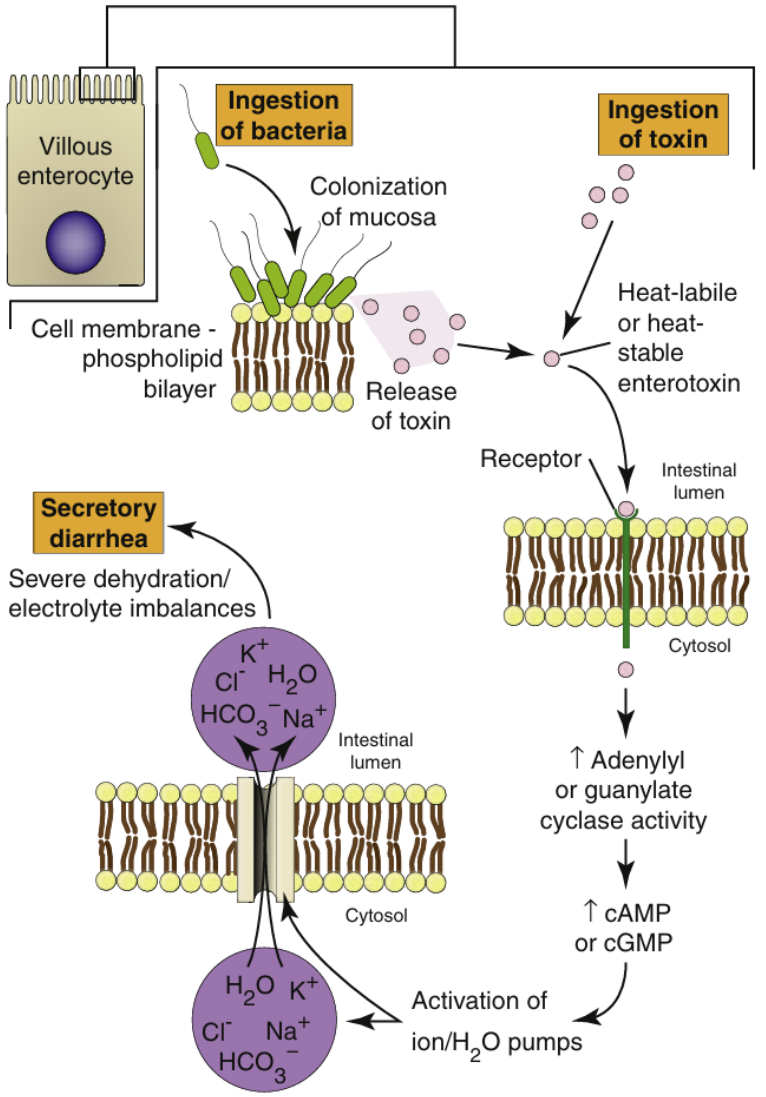
- Inflammatory: Invades tissues, triggers cytokine cascades (e.g., *Salmonella*, *Lawsonia*).



Pathogenesis of Diarrhea

- Mechanisms involved:
- Malabsorption → Osmotic diarrhea.
- Chloride hypersecretion via CFTR → Secretory diarrhea.
- Exudation → Leakage due to increased capillary permeability.
- Hypermotility → Reduced nutrient absorption.

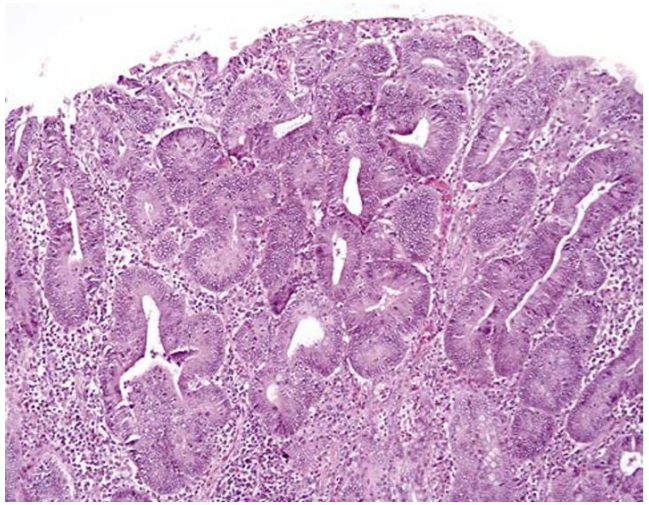


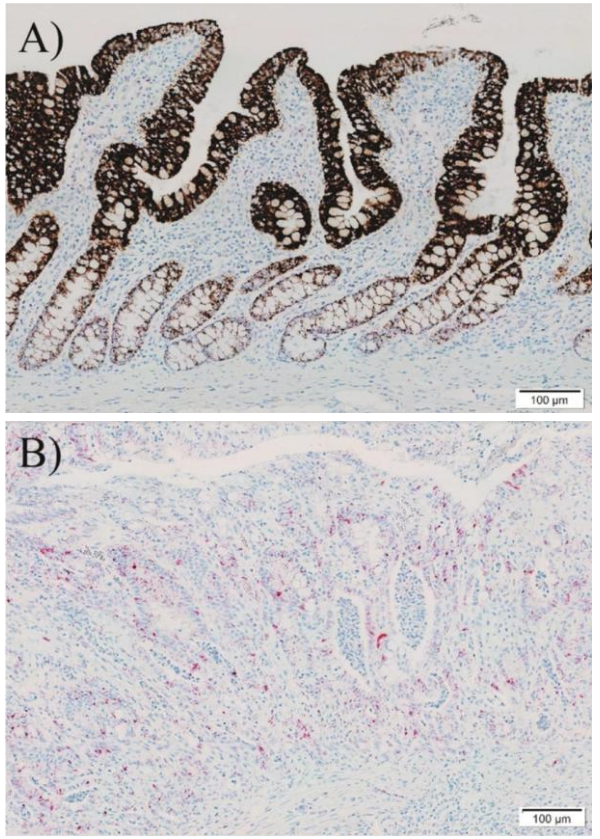


Infectious Agents Causing Diarrhea

- Bacteria:
- *Escherichia coli* (ETEC): Enterotoxins induce noninflammatory diarrhea.
- *Salmonella spp.*: Invasive, triggers inflammation.
- ***Lawsonia intracellularis***: Induces hyperplasia of enterocytes.
- Parasites:
- *Cryptosporidium parvum*: Affects proximal intestine.







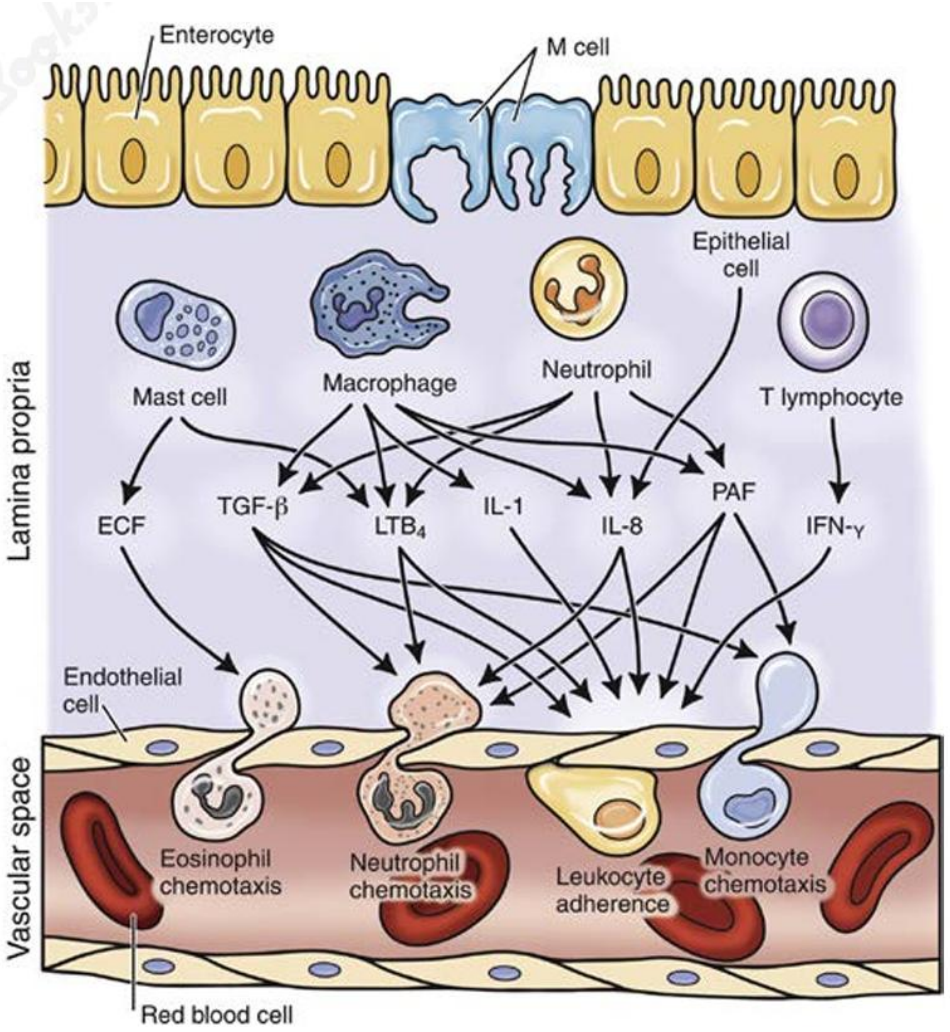
https://open.lib.umn.edu/swinedisease/chapter/proliferative-enteritis-or-ileitis/

Lawsonia intracellularis infected enterocytes lack sucrase-isomaltase which contributes to reduced pig digestive capacity. 2021

Immune Response and Inflammation

- Cytokine release:
- IL-8 recruits macrophages.
- Mast cells release histamine, prostaglandins.

- T Lymphocyte Action:
- Induces villus atrophy.
- Causes crypt hyperplasia.



Nonintestinal Causes of Diarrhea

- Endocrine disorders:

- Hyperthyroidism (particularly in feline), Addison's disease.

- Pancreatic dysfunction:

- Pancreatic insufficiency, pancreatitis.

- Renal causes:

- Chronic renal failure.

Consequences of Severe Diarrhea

• Fluid and electrolyte loss:
- Dehydration and hypovolemia.
- Electrolyte imbalance (↓ potassium, ↑ hydrogen ions).

• Systemic effects:
- Hypoglycemia → Ketoacidosis → Acidosis.
- Leads to hypovolemic shock.

Conclusion: Clinical Significance

• Monitoring fluid loss and electrolyte levels is critical.
• Prompt treatment of infectious causes reduces complications.
• Supportive care is essential to prevent hypovolemic shock.

Stomatitis and Gingivitis

Introduction: Stomatitis and Gingivitis

- Inflammation of **oral mucosa (stomatitis)** and **gums (gingivitis)**.

- Common causes:

- Infectious agents (bacterial, viral, fungal).
- Trauma, foreign bodies, or dental plaque.

Pathogenesis of Stomatitis and Gingivitis

• Bacterial biofilms initiate gingival inflammation.

• Progression:
- Inflammatory infiltrates damage periodontal ligaments.
- Leads to tooth loss if untreated.

• **Gross Findings**:
- Red, swollen gums, ulceration of oral mucosa.
- Pus formation in severe cases.

• **Microscopic Findings:**
- Inflammatory cell infiltration.
- Degeneration of connective tissue.

Infectious Causes of Stomatitis

- Bacterial agents:
  - *Fusobacterium spp.*, *Porphyromonas spp.*
- Fungal infections:
  - *Candida spp.* (oral thrush).
- Viral agents:
  - *Feline Calicivirus* (cats), *Herpesvirus*.

Feline chronic gingivostomatitis (FCGS)는 구강 내 어디서든 발생할 수 있으나, 주로 oropharynx 와 oral cavity의 경계 부분이나, 잇몸의 rostral part 에서 호발하며, 육안적으로는 독립된 결절 양상이 아닌 구강 내 전반적인 비후로 관찰되는 경우가 많습니다. 병변의 정도에 따라 통증, 연하곤란, 식욕부진, 체중감소, 구취, 타액분비과다 등의 임상증상 뿐 만 아니라 병변이 심해질 경우 골 융해를 일으킬 수도 있습니다. 염증을 일으키는 원인은 아직 정확하게 밝혀진 바는 없으나, 다양한 원인들 중 feline calicivirus infection 등 virus 감염과 Pasteurellosis 등 bacterial 감염, 환축의 면역반응이상과의 연관성이 주목받고 있습니다.
한편, 지속적인 물리적/화학적 자극에 의해 위와 같은 조직학적 소견이 국소적으로 관찰될 수도 있으므로 병변의 진행 양상이나 치료에 대한 반응 등을 참고한 임상적인 고찰이 본 염증에 대한 파악에 도움이 될 것으로 사료됩니다.
다수의 염증세포 침윤으로 인해 육안적으로 종양처럼 돌출된 결절형태로 관찰될 수도 있지만 의뢰하신 조직에서 종양성 병변은 관찰되지 않았습니다.

Vesicular Stomatitides: Overview

• Viral diseases causing vesicle formation in the oral cavity.

• Major viral pathogens:
- *Foot-and-Mouth Disease Virus* (FMDV).
- *Vesicular Stomatitis Virus* (VSV).
- *Swine Vesicular Disease Virus*.

Table 7.1 Vesicular Stomatitides

Disease	Cause	Ruminant	Pigs	Horses
Foot-and-mouth disease	Picornavirus	+	+	–
Vesicular stomatitis	Rhabdovirus	++	+	+
Vesicular exanthema of swine	Calicivirus (vesivirus)	–	++	–
Swine vesicular disease	Enterovirus	–	++	–

Vesicular Stomatitides: Overview

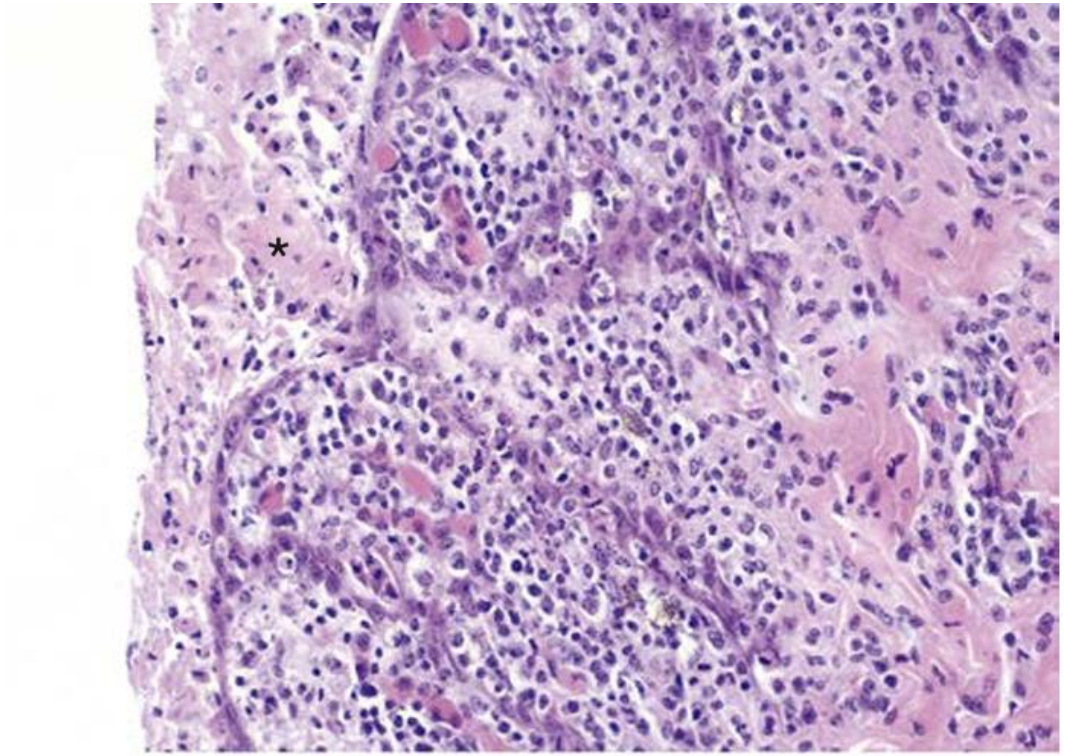
Disease Agent	Main Species Affected	Transmission	Morbidity	Carrier State	Contamination of Meat and By-Products
Foot-and-mouth disease virus	Swine, cattle, sheep, goats, African buffaloes; some strains are host restricted	Aerosol, contact, fomites	High	Cattle, sheep, goats, African buffaloes	Frozen meat, lymph nodes, bone marrow, milk products
Swine vesicular disease virus	Swine, humans	Contact, fomites	Moderate	No	Virus persists in cured meat and gland products
Vesicular exanthema of swine/San Miguel sea lion viruses	Swine, various marine animals	Contact, fomites	Moderate	No	Meat
Vesicular stomatitis virus	Horses, cattle, swine, humans	Biting insects; some by contact	Moderate to low	No	Not documented

Pathogenesis of Vesicular Diseases

- Viral entry via mucosal surfaces or skin lesions.
- Replication in epithelial cells causes vesicle formation.
- Vesicles rupture, leading to erosions and secondary bacterial infections.

- **Gross Findings**:
- Vesicles, ulcers, and erosions on oral mucosa.
- Sloughing of epithelium and excessive salivation.

- **Microscopic Findings**:
- Ballooning degeneration of epithelial cells.
- Inflammatory infiltrates and necrosis.



Foot-and-Mouth Disease (FMD)

- Infectious agent:

- *Aphthovirus* (Picornaviridae).

- Pathogenesis:

- Rapid viral replication in epithelial cells.

- Clinical signs:

- Vesicles on **mouth, feet, teats**; lameness.





Foot-and-Mouth Disease (FMD)

- Lesion Distribution and Clinical Manifestations of Vesicular Disease

-Severe vesicular lesions are observed on

Lips, dorsal surface of the tongue, and palate.

Skin near the coronary band, particularly in interdigital spaces.

Hairless areas, including the vulva, teat, and udder.

Conjunctiva and forestomach.

- Affected species:

-Primarily seen in young calves and lambs, but also occurs in pigs and young goats.

-Myocardial Lesions in **Young Animals**:

-Irregular small, grayish foci observed on the left ventricular wall and septum.

-Indicative of myocardial degeneration and necrosis, appearing as a striped pattern (**"tiger heart"**).

(Not a specific lesion for Foot-and-Mouth Disease (FMD)—pathogenesis remains unclear)

Vesicular Stomatitis Virus (VSV)

• Infectious agent:

- *Vesiculovirus* (Rhabdoviridae).

• Pathogenesis:

- Transmitted via insect vectors.

• Clinical signs:

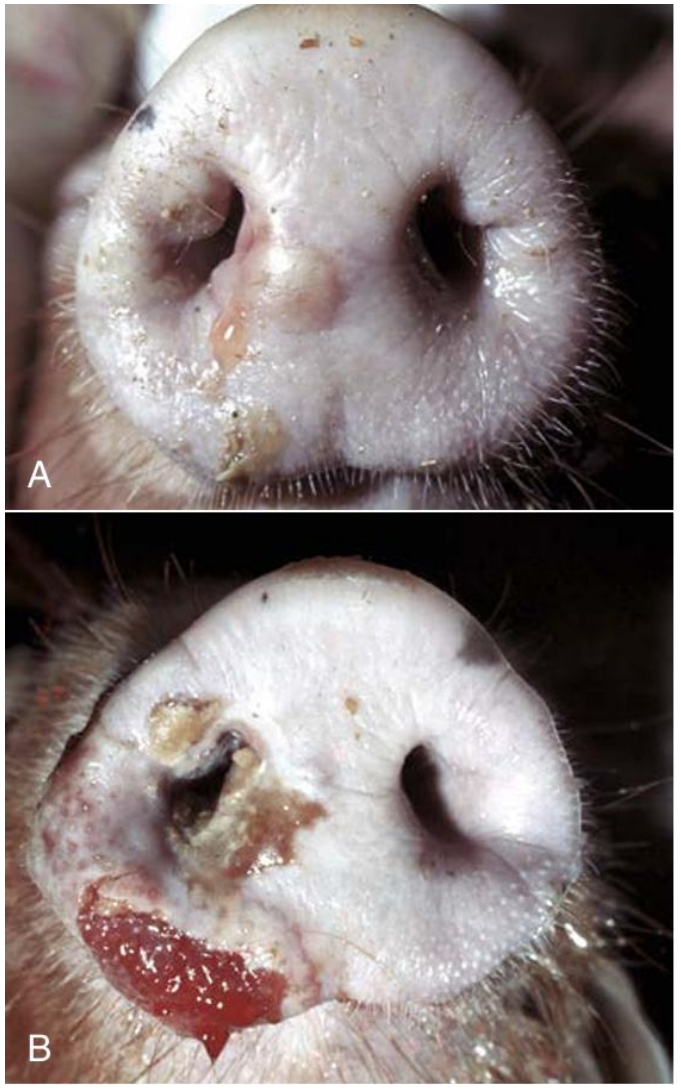
- Vesicles on **tongue, lips, coronary bands**.

Swine Vesicular Disease (SVD)

• Infectious agent:
- *Enterovirus* (Picornaviridae).

• Pathogenesis:
- Spread through contaminated feed or direct contact.

• Clinical signs:
- Vesicles on **snout, lips, hooves**.

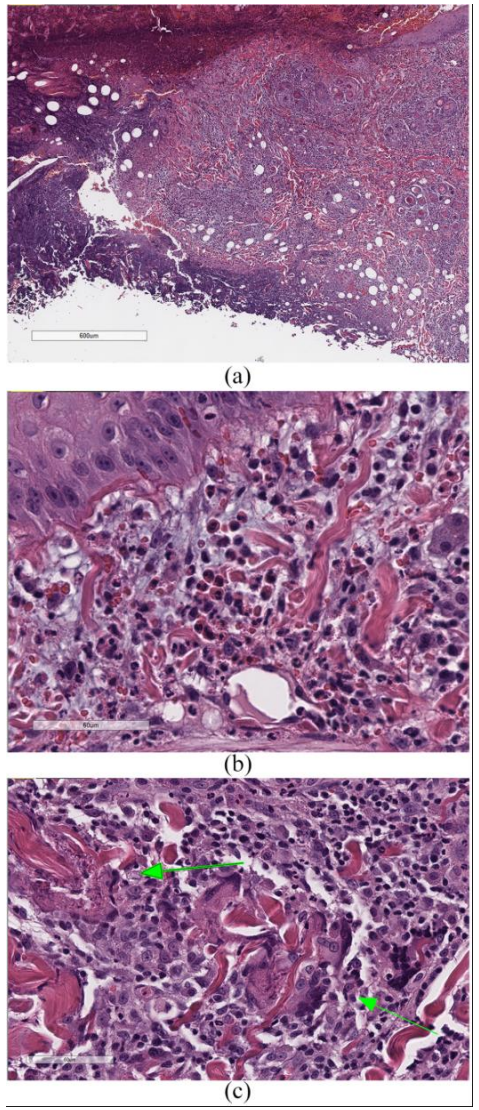


Eosinophilic Stomatitides

- Commonly affects cats (oral eosinophilic granulomas) and some dog breeds.
- Immune-mediated pathogenesis suspected, possibly a hypersensitivity reaction.
- Antibodies to intercellular material are often present.
- Associated with increased circulating eosinophils.

- **Gross Findings:**
  -Lip lesions, often near the **philtrum in cats**.
  -Oral lesions may occur on the **gingiva, hard and soft palates, tongue, and pharynx**.

- **Microscopic Findings:**
  -Central collagenolysis (collagen destruction, not necrosis).
  -**Surrounding eosinophilic inflammation**, mast cells, multinucleated giant cells



Novel presentation of eosinophilic granuloma complex in a cat. 2019

Lymphoplasmacytic Stomatitis

- **Chronic inflammatory condition** primarily affecting **cats**.

- Hypothesized associations with **bacteria, feline calicivirus, FeLV, and FIV**.

- **Characterized by:**
-Severe gingival inflammation
-Halitosis
-Inappetence

Oral Mucosal Hyperplasia

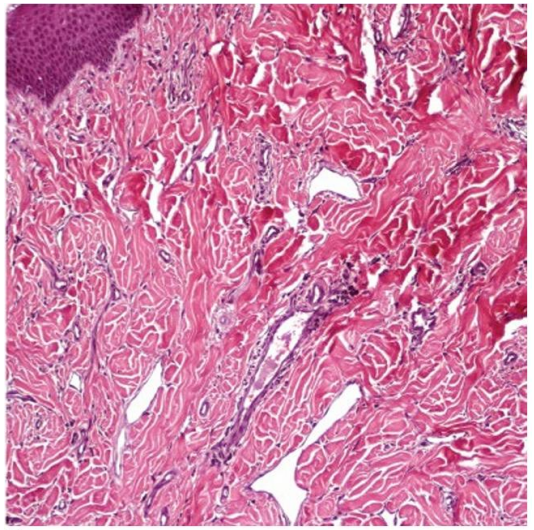
•Gingival hyperplasia (a.k.a. **Fibrous hyperplasia)** is **a benign fibrous overgrowth** of the gingiva.

•Often associated with **chronic inflammation** or genetic predisposition (e.g., brachycephalic breeds).

•Can obscure teeth and affect mastication and dental hygiene.



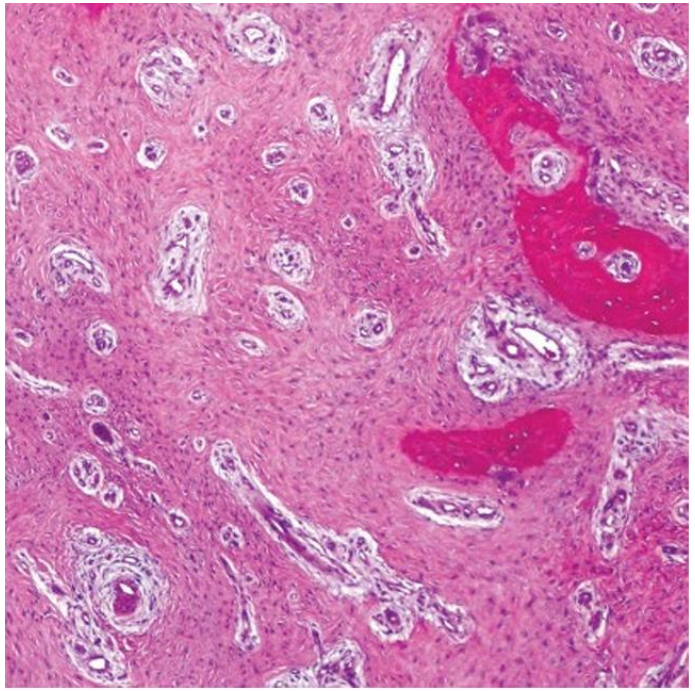
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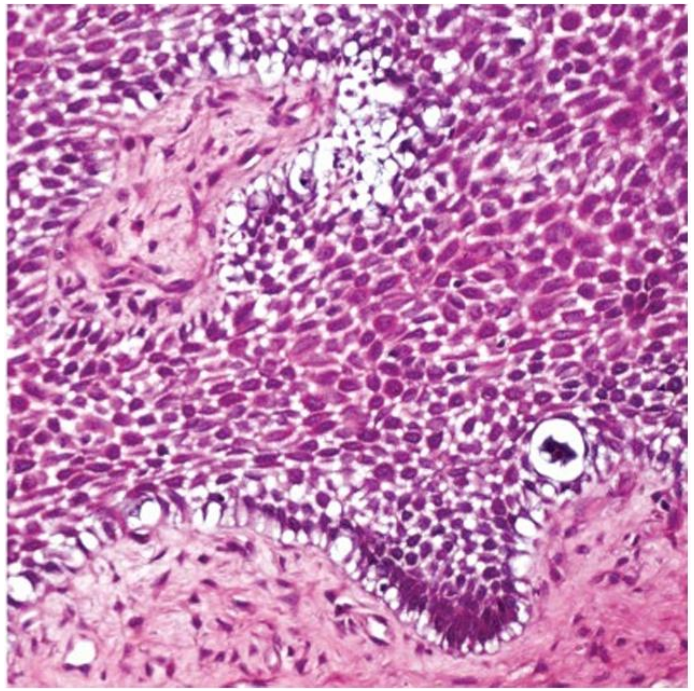


B

Oral Neoplasia: Common Tumors

• **Benign Lesions**:
-Odontogenic fibroma (a.k.a. fibromatous epulis)
: Firm, periodontal growth.
-Acanthomatous ameloblastoma
: Locally invasive, destroys bone.



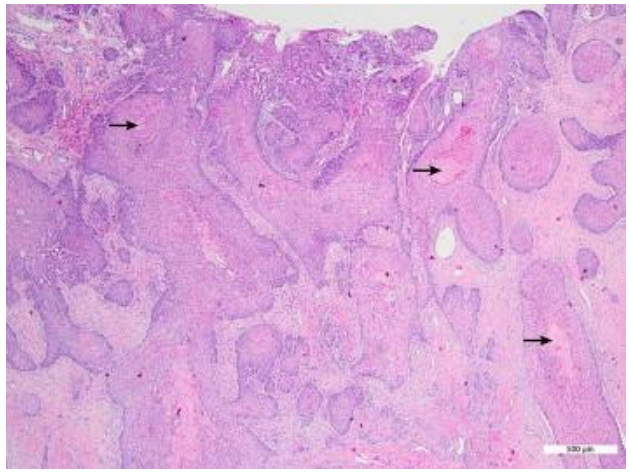


Oral Neoplasia: Common Tumors

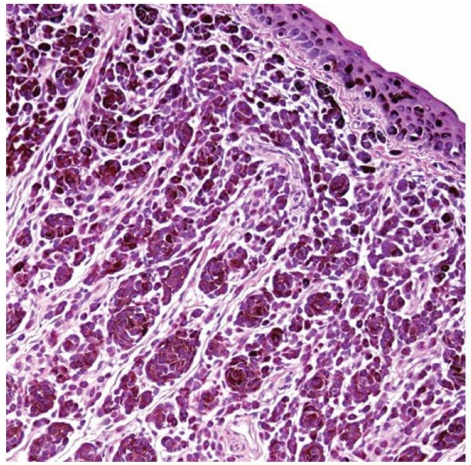
- **Malignant Tumors**:

-Squamous cell carcinoma: Common in older cats.

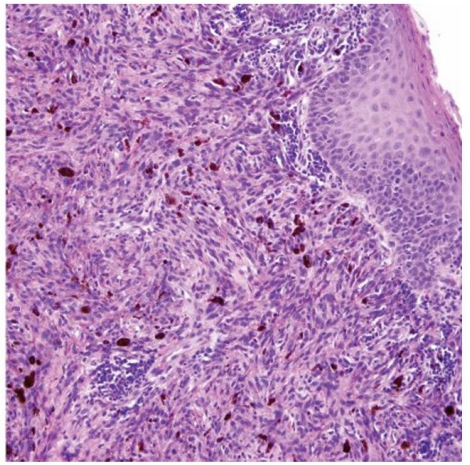
-Melanoma: Highly malignant in dogs.



VS

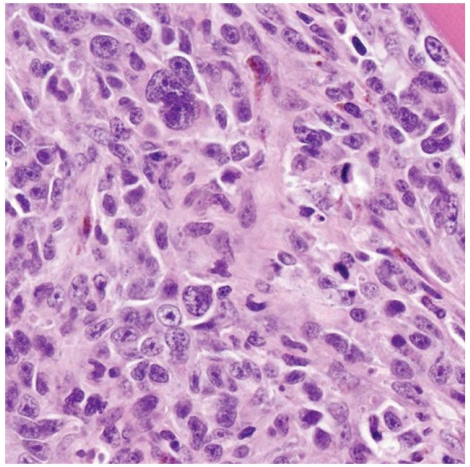


A



B

VS



Esophageal Disorder

Diseases of the Esophagus: Overview

• The esophagus is prone to congenital anomalies, infections, trauma, and neoplasia.

• Major categories:

-Congenital and Acquired Megaesophagus

-Esophagitis (Reflux, Infectious, Traumatic)

-Foreign Body Obstruction (Choke, Trauma)

-Neoplasia and Parasitic Infestations

Congenital and Acquired Megaesophagus

• Congenital Megaesophagus

: Due to persistent right aortic arch (vascular ring anomaly).

Affects German Shepherds, Irish Setters, Greyhounds.

• Acquired Megaesophagus

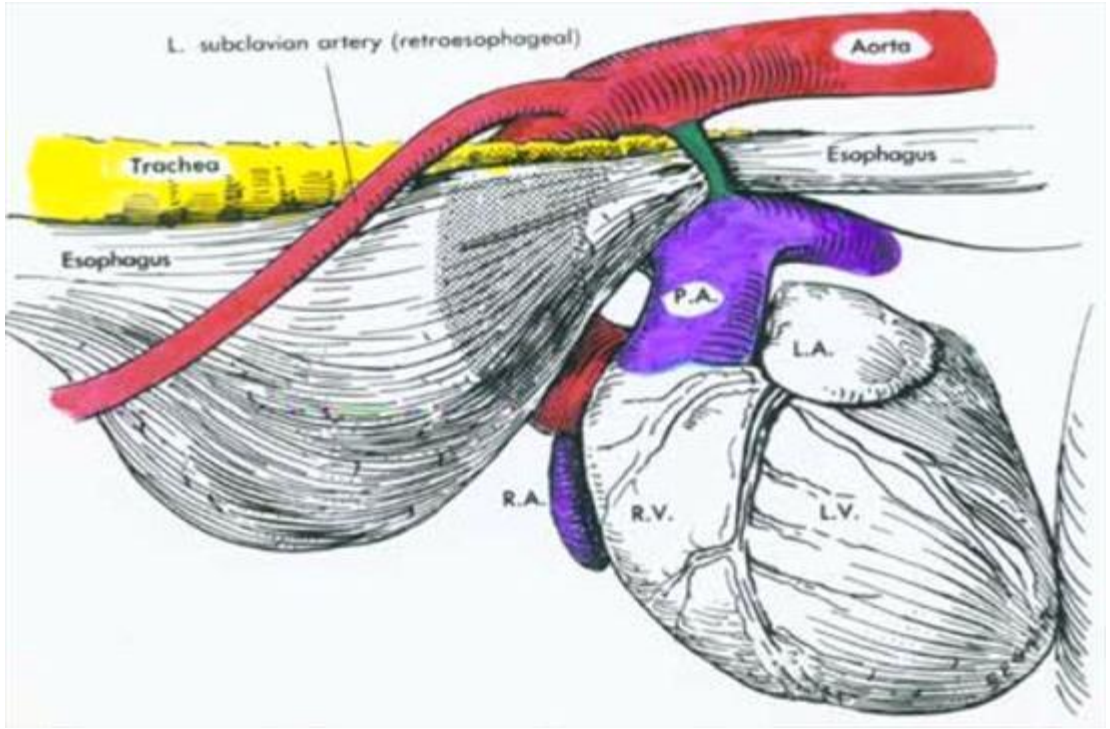
: Secondary to myasthenia gravis, hypothyroidism, vagal nerve disorders.

• Gross Findings

: Dilated, atonic esophagus, putrid ingesta accumulation.

• Microscopic Findings

: Degeneration of vagus nerve fibers (variable).



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Acid Reflux Esophagitis

• Caused by gastric acid reflux leading to mucosal injury.

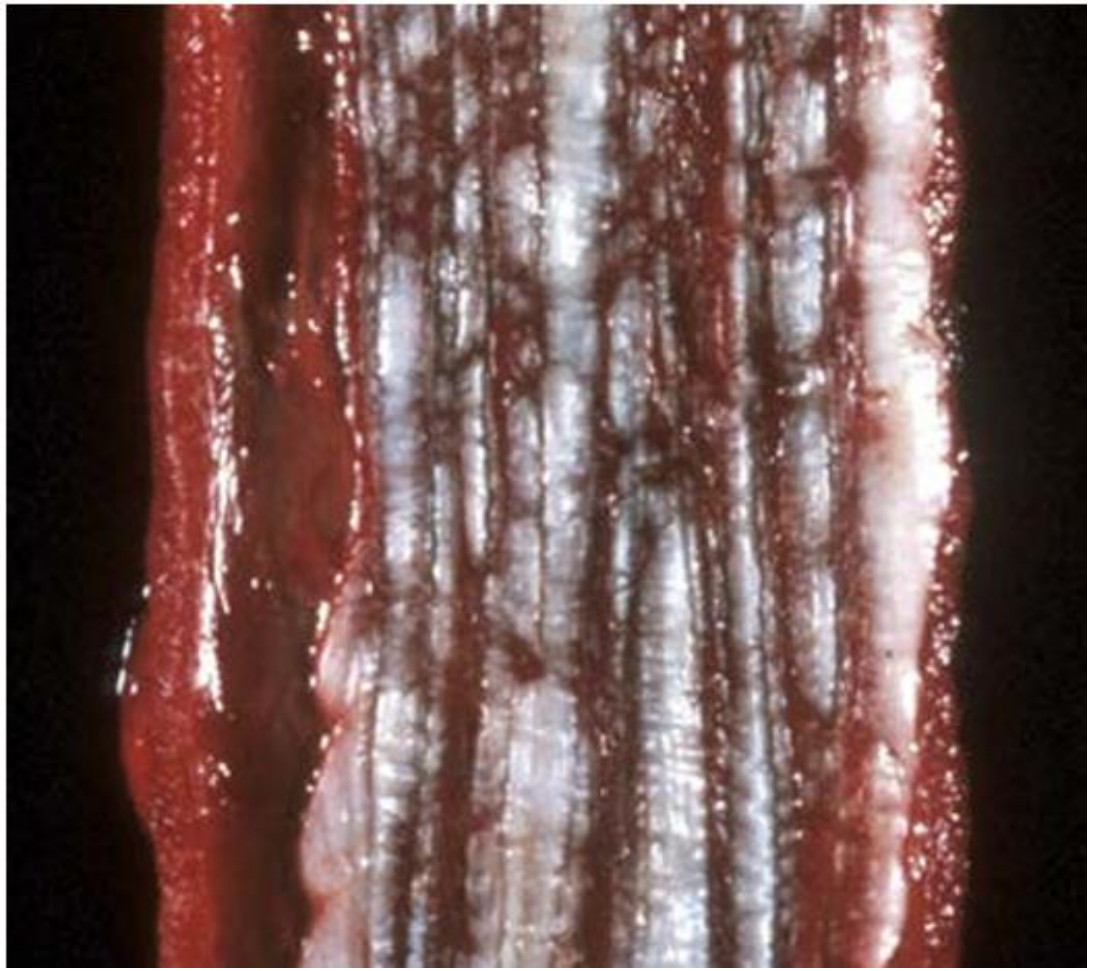
• More common in horses, dogs, and animals under anesthesia.

• Gross Findings

: Red linear streaks in the distal esophagus.
Erosion of the epithelium near the gastric cardia.

• Microscopic Findings

: Mucosal ulceration, epithelial hyperplasia, fibrosis in chronic cases.



Infectious Esophagitis (BVDV, Candida)

- Bovine Viral Diarrhea Virus (BVDV)

: Causes ulcerative esophagitis.

- Gross Findings: Multiple shallow ulcers.

- Candida spp. (Thrush)

: Opportunistic infection in immunocompromised animals.

- Microscopic Findings

: Budding yeast, pseudohyphae in the epithelium.

Foreign Body Obstruction (Choke)

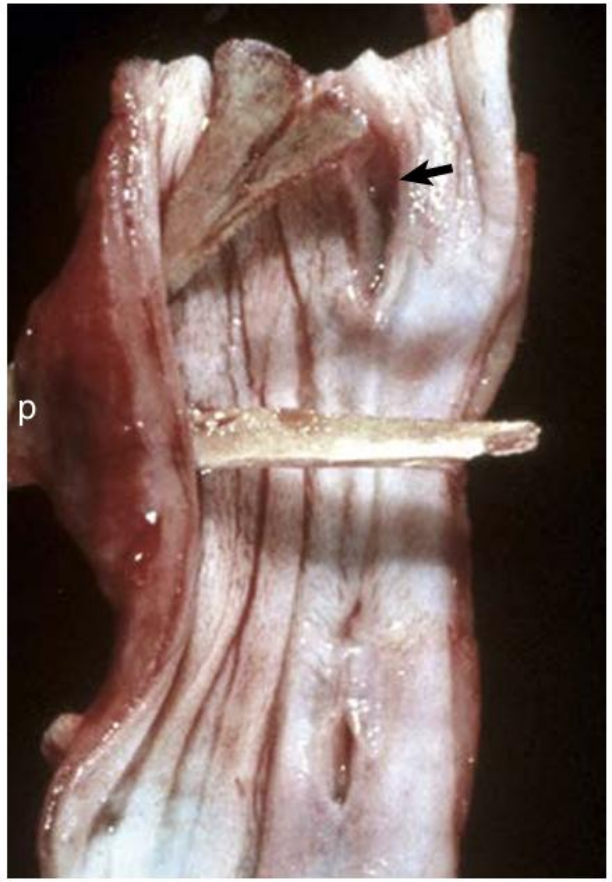
• Common in cattle and horses due to ingestion of corn cobs, apples, bones.

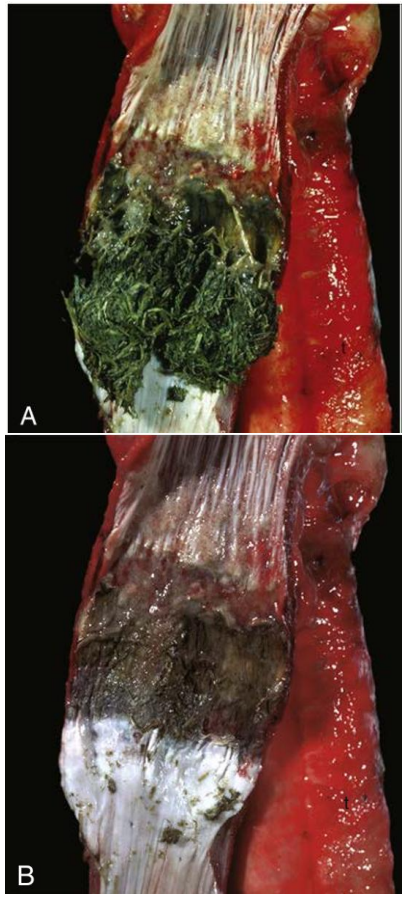
• Prolonged obstruction can cause esophageal necrosis and perforation.

• Gross Findings

: Esophageal dilation proximal to the obstruction.

Ulceration and perforation in severe cases.





Esophageal Neoplasia

- Rare in domestic animals but includes

  Squamous cell carcinoma (SCC): Most common in cattle, associated with bracken fern.

  Leiomyoma/Leiomyosarcoma: Smooth muscle tumors.

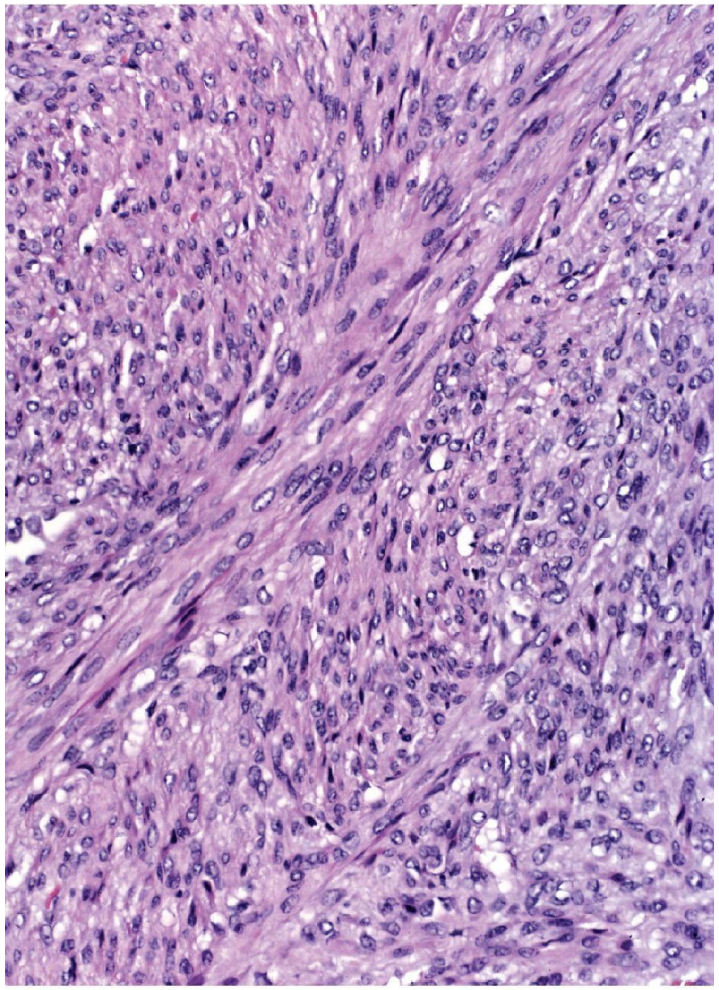
- Gross Findings

: Exophytic, ulcerated mass obstructing the lumen.

- Microscopic Findings

-SCC: Keratin pearls, pleomorphic epithelial cells.

-Leiomyosarcoma: Spindle-shaped cells with interwoven fascicles.



A

https://veteriankey.com/tumors-of-muscle/

Parasitic Infestation: Spirocerca lupi

• Canine esophageal nematode, endemic in warm climates.

• Life cycle

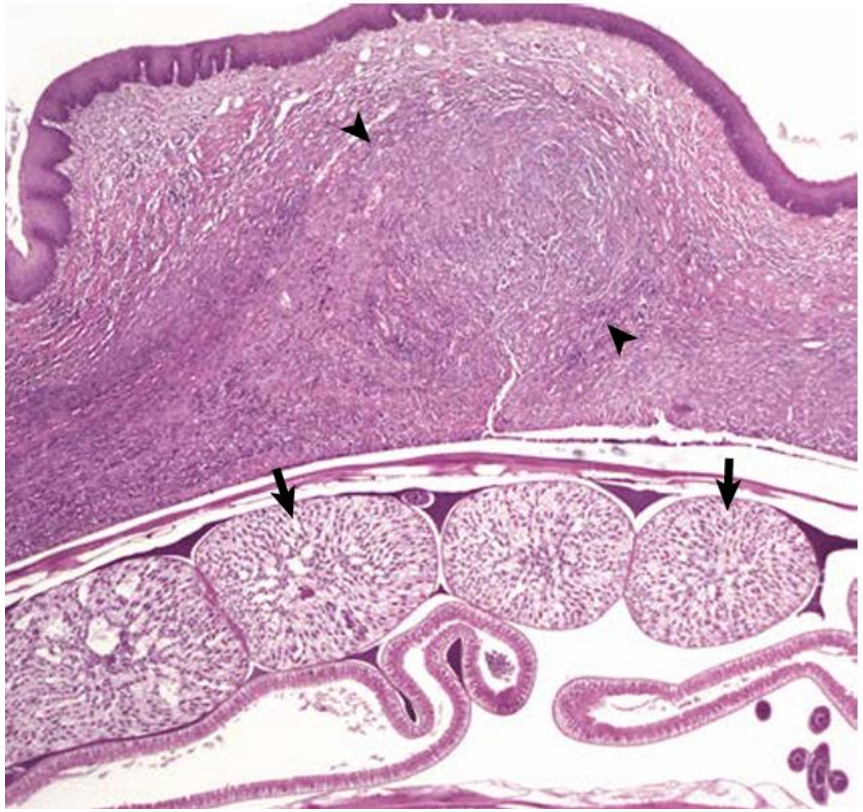
: Larvae migrate from stomach to aorta → esophageal submucosa.

• Gross Findings

: Granulomatous nodules containing adult parasites.

• Microscopic Findings

: Fibrosis, chronic inflammation, potential malignant transformation to fibrosarcoma.



Other Esophageal Parasites

- Gongylonema spp. (Ruminants, pigs, horses)

: Serpentine mucosal migration, typically asymptomatic.

- Hypoderma lineatum (Cattle)

: Larvae migrate through esophageal adventitia before reaching the skin.

- Gasterophilus spp. (Horses)

: Attach via oral hooks, cause shallow erosions.

Hiatal Hernia

- Protrusion of the stomach into the thoracic cavity through the diaphragm.
  Can be sliding or paraesophageal.

- Clinical signs: Regurgitation, aspiration pneumonia.

- Gross Findings

: Cranial displacement of the gastric cardia, esophageal dilation.

- Microscopic Findings

: Chronic inflammation, fibrosis of the hiatus

Summary: Key Points on Esophageal Disorders

- Megaesophagus: Congenital (vascular anomaly) vs. Acquired (neuromuscular disease).
- Esophagitis: Acid reflux, BVDV, Candida, and traumatic causes.
- Foreign Body Obstruction: Leads to ulceration, necrosis, perforation.
- Neoplasia: SCC (cattle, bracken fern), Leiomyosarcoma (dogs).
- Parasitic Infections: Spirocerca lupi (dogs), Gongylonema spp. (ruminants, pigs).

Stomach and Abomasum

Overview

- Function: Enzymatic digestion and absorption.

- Susceptible to ulcers, displacement, inflammation, and neoplasia.

- Common diseases
  -Gastric ulcers
  -Abomasal displacement
  -Gastric dilation-volvulus (GDV)
  -Infectious gastritis

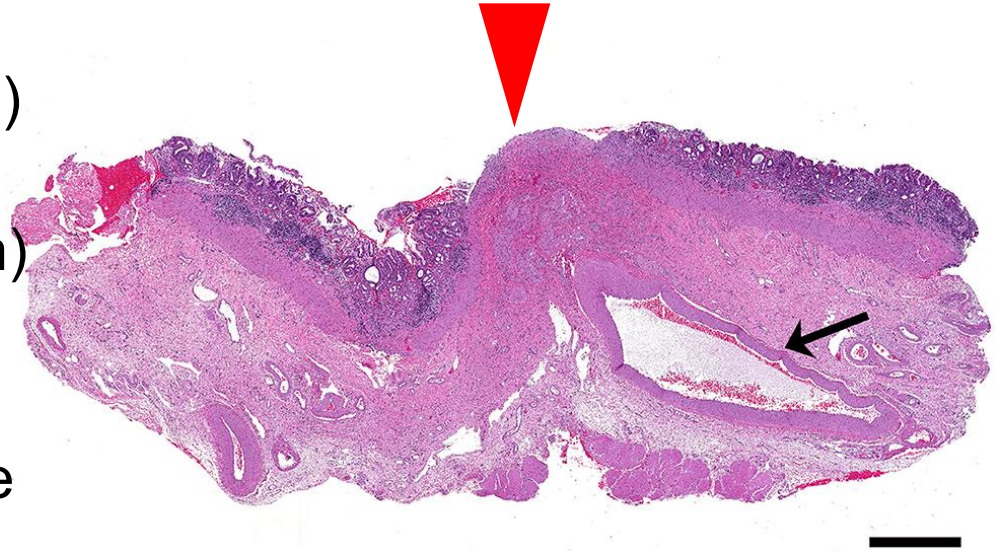
Gastric Ulcers

- Caused by an imbalance between mucosal protection and acid secretion

- Common causes
  -NSAIDs (inhibit prostaglandins → ↓ mucus production)
  -Helicobacter spp. (linked to chronic gastritis)
  -Stress and dietary changes (lactic acidosis, parturition)

- Gross findings
  -Erosions, ulcers → risk of perforation and hemorrhage

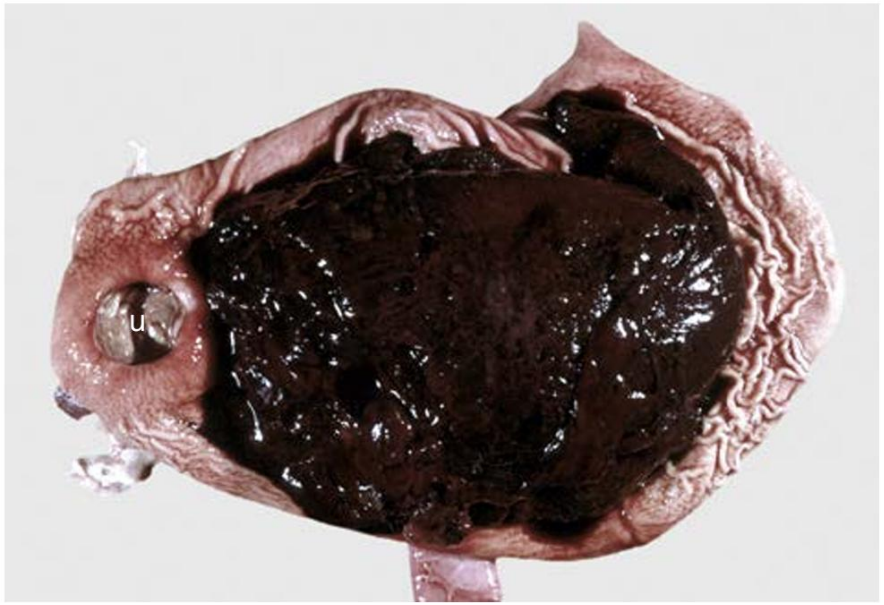
- Microscopic findings
  -Necrotic epithelium, inflammatory cell infiltration.



Case report: The first description of a Dieulafoy's lesion in the gastric mucosa of a dog

Gastric Ulcers

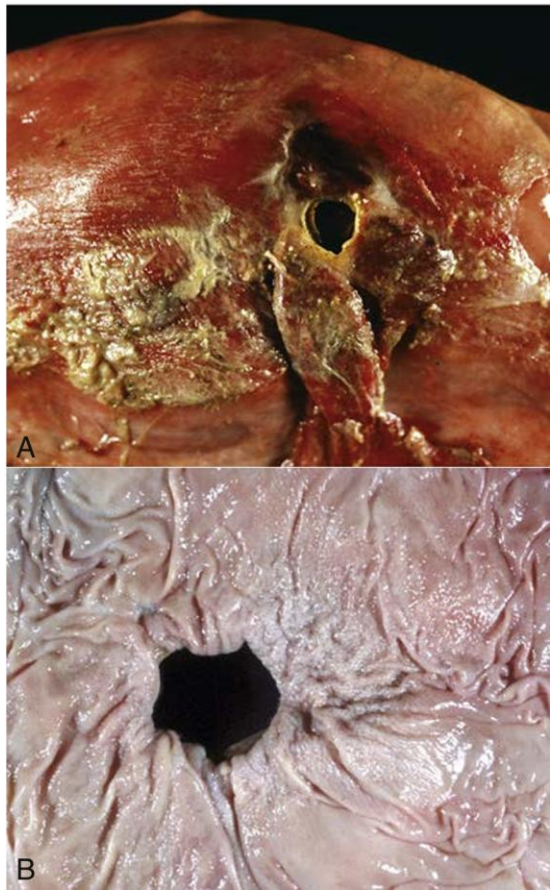
Dog



Pig



Cow

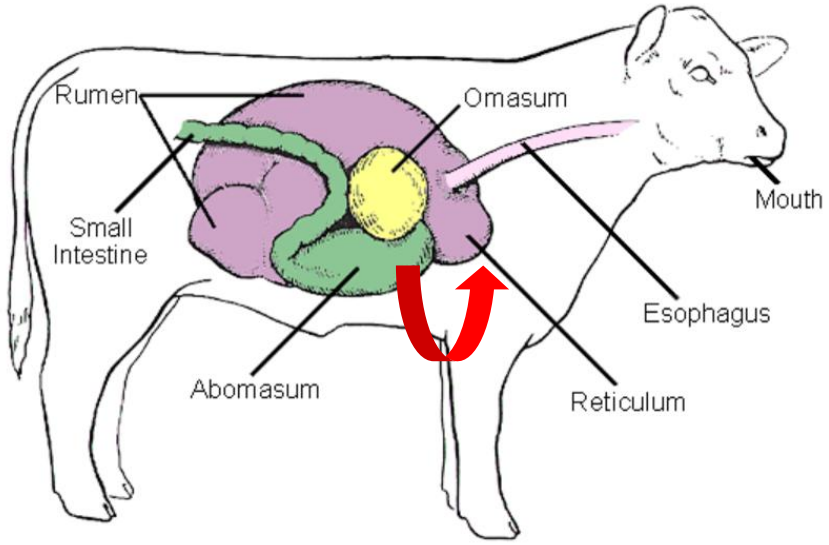


Abomasal Displacement

- Left displaced abomasum (LDA)
  -More common, gas accumulation, reduced motility

- Right displaced abomasum (RDA)
  -Risk of volvulus → Ischemia, necrosis

- Common in postpartum dairy cows



- Pathogenesis
  -Gas accumulation distends the abomasum → displacement under the rumen.
  -Hypomotility and hypocalcemia increase risk

- Consequences
  -Anorexia, dehydration, metabolic alkalosis, ketosis

Gastric Dilation and Volvulus (GDV)

- Common in deep-chested dog breeds (e.g., Great Danes, German Shepherds).

- Pathogenesis

  -Gas distension → Stomach rotates (torsion) → Vascular compromise → Ischemia.

- Gross findings

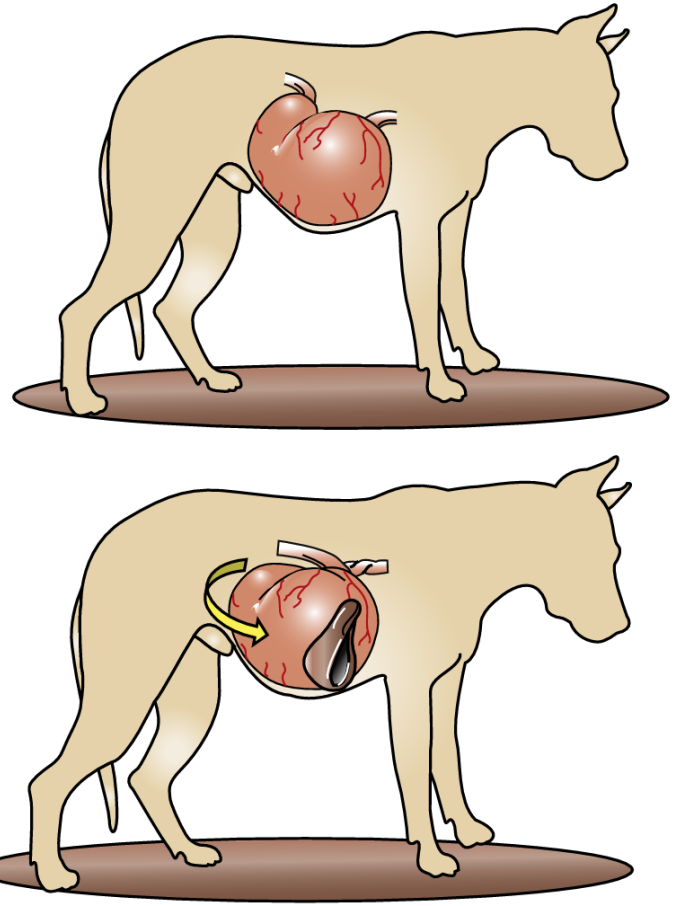
  -Severely distended stomach, congested mucosa, necrotic wall.

- Microscopic findings

  -Mucosal hemorrhage, thrombosis, necrosis

- Treatment

  -Emergency decompression, surgical repositioning, gastropexy.



Infectious Gastritis

- Bacterial causes

  -Helicobacter spp. (chronic gastritis, ulcers)

  -Clostridium perfringens (necrotizing gastritis)

- Viral causes

  -Bovine herpesvirus-1 (Infectious Bovine Rhinotracheitis)

Infectious Gastritis: Parasitic

- Ruminants
  -Ostertagia ostertagi (abomasal parasites)



- Pigs
  -Hyostrongylus rubidus (causes chronic gastritis).

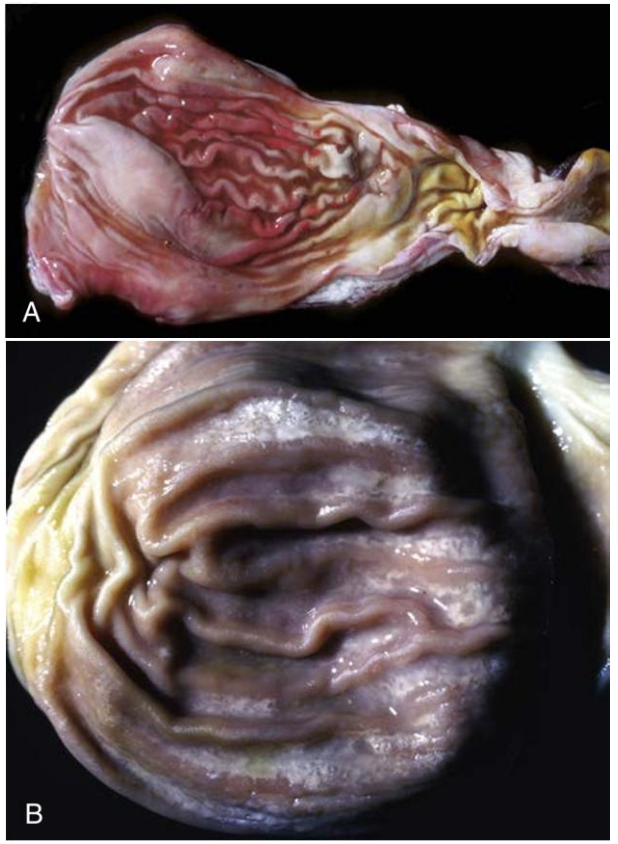
- Gross findings
  -Thickened mucosa, Moroccan leather appearance (Ostertagia)

- Microscopic findings
  -Glandular hyperplasia, eosinophilic inflammation.

Miscellaneous Disorder

- Uremic gastritis
  -Most frequent in carnivores as a result of chronic renal disease
  -Characterized by mineralization of the glands and vessels

- Pyloric stenosis
  -Inability of the pyloric sphincter; congenital or acquired
  -Common in dogs (brachycephalic breeds), Siamese cats, and horses
  -Can be identified in recently weaned animals; vomiting and gastromegaly
  -Microscopic findings
    : Muscular hypertrophy, submucosa edema, vascular ectasia, and degeneration of myenteric ganglion cells



Neoplasia

- Spindle cell tumor

  -Mainly **leiomyoma**, leiomyosarcoma, or GIST, but possibly from fibroblast or neuronal cells

- Lymphoma

  - Cattle: is often caused by the bovine leukemia virus and has a predilection for the **abomasum, the myocardium, and the uterus**

- Squamous cell carcinoma

  -The stratified squamous (esophageal) portion

  of the stomach, relatively common in the horse

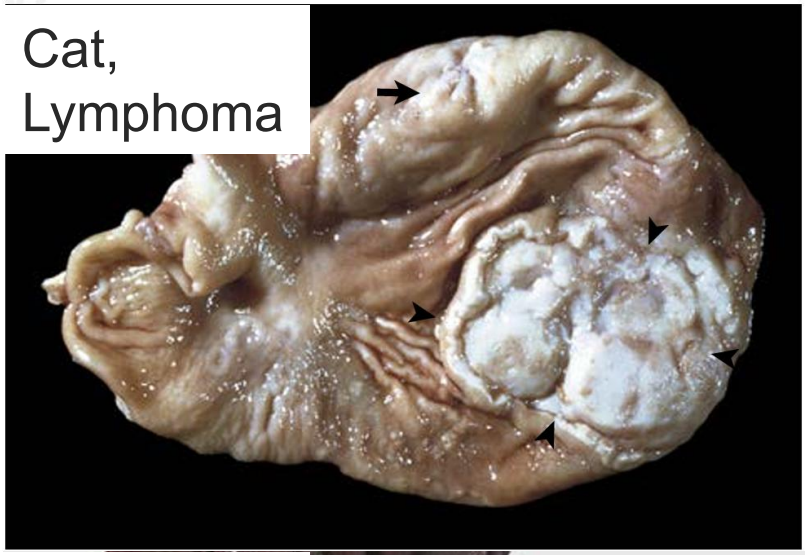
  -Highly aggressive, with extensive metastases and abdominal carcinomatosis.

Neoplasia

Dog, Leiomyoma



Cat, Lymphoma



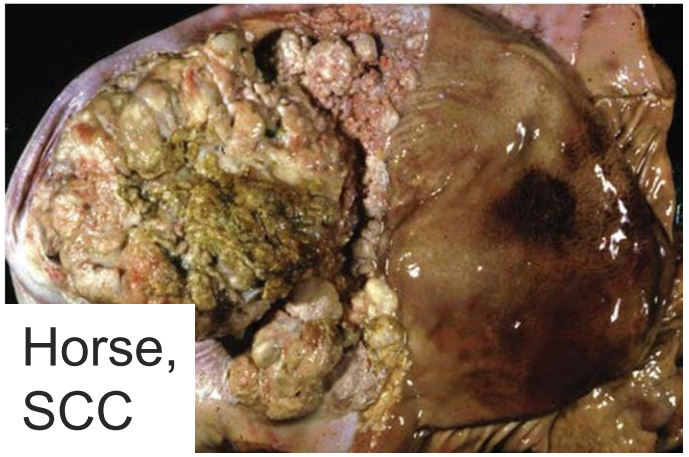
Horse, Lymphoma







Cow, Lymphoma



Horse, SCC

Intestine

Overview

- Functions: Nutrient absorption, immune defense, and gut microbiota homeostasis

- Susceptible to inflammation, infections, malabsorption, and neoplasia

- Major disease categories

  -Viral, bacterial, and parasitic infections

  -Malabsorption syndromes

  -Neoplastic conditions

Viral Enteritis in Pigs and Ruminants

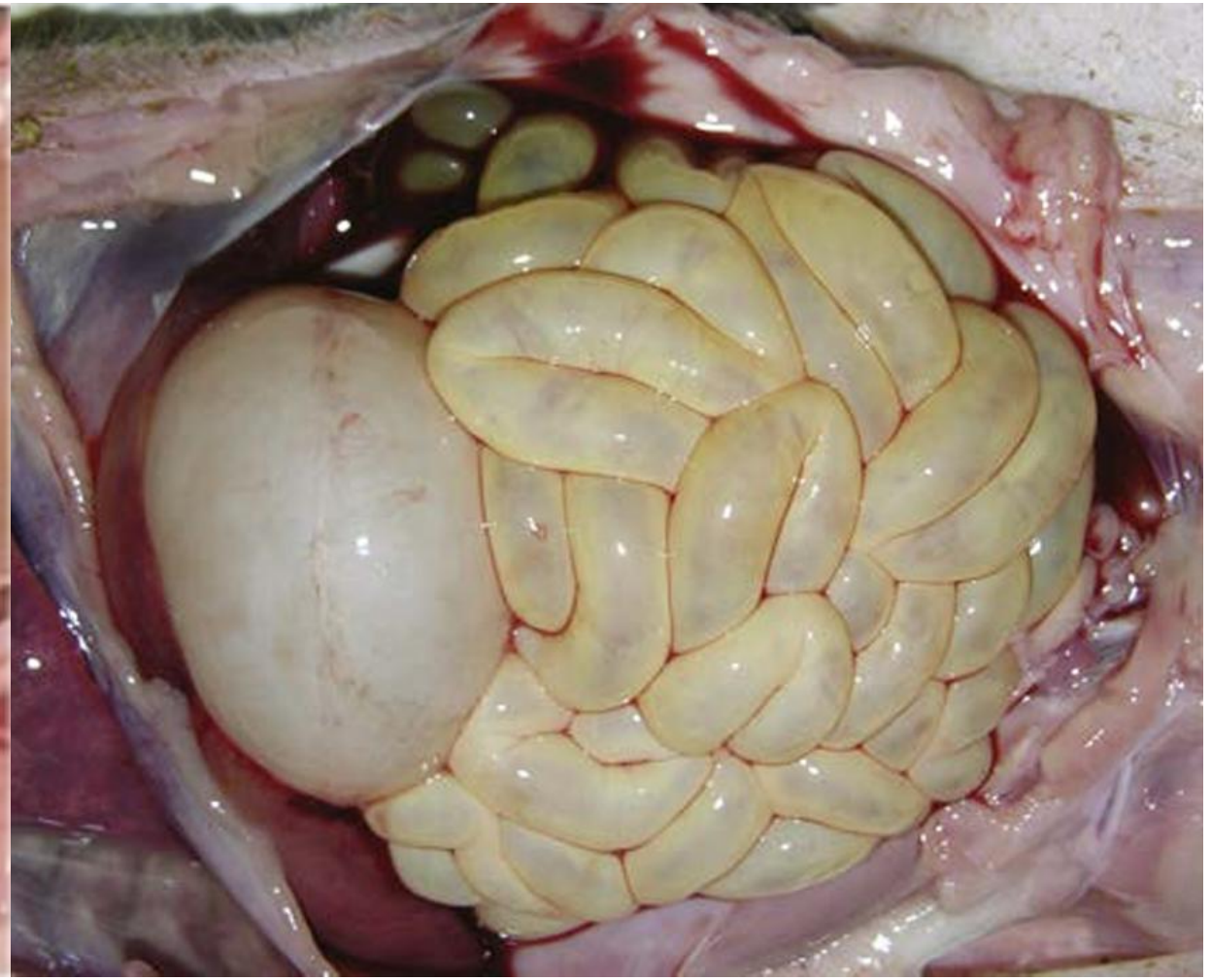
- Transmissible Gastroenteritis Virus (TGEV) – Pigs
  -Highly contagious coronavirus affecting neonatal pigs (<10d)
  -Sunlight-sensitive → frequent in winter
  -Severe villous atrophy → Malabsorptive diarrhea.

- Bovine Viral Diarrhea Virus (BVDV) – Cattle
  -Targets Peyer's patches, leading to mucosal ulceration

- Rotavirus and Coronavirus - Multiple Species
  -Affect young animals → Villous enterocyte destruction → Watery diarrhea.

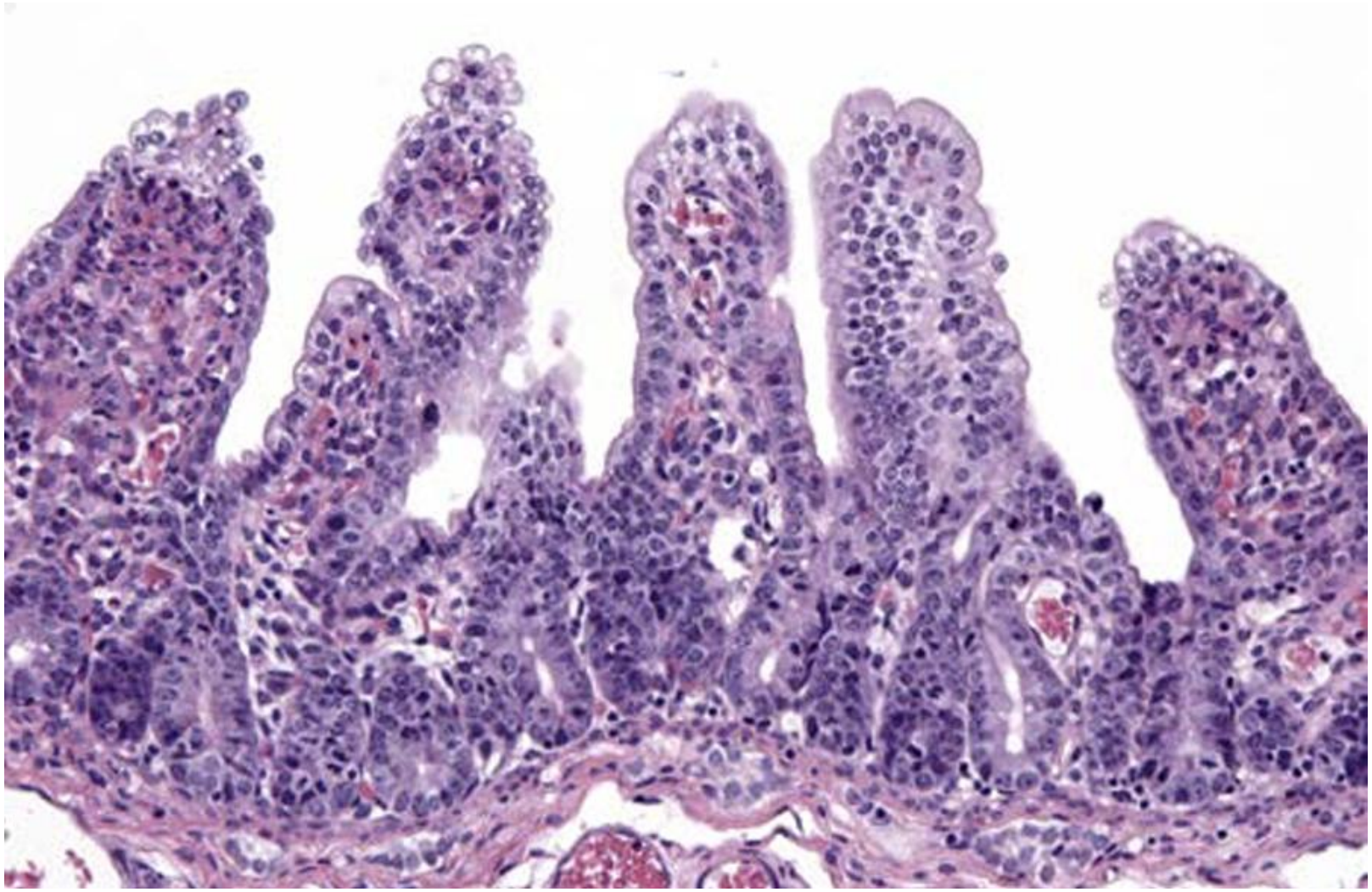
TGE, Small intestine, Piglet

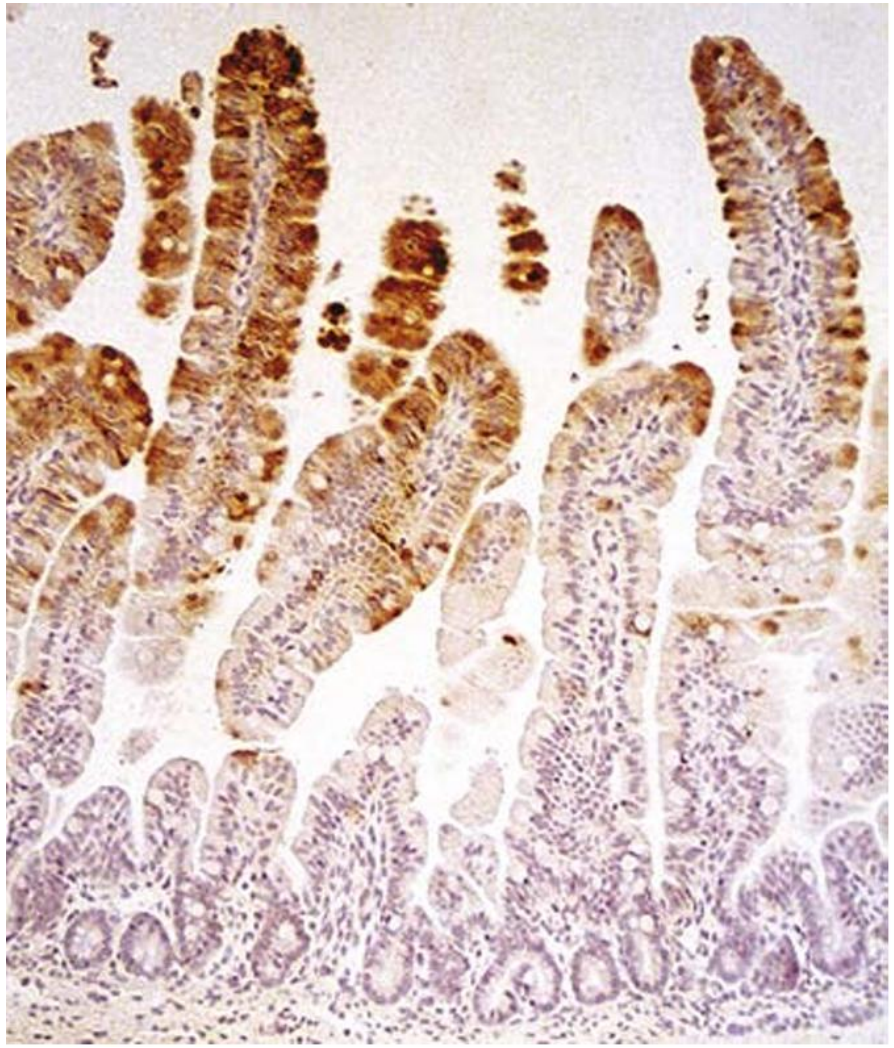




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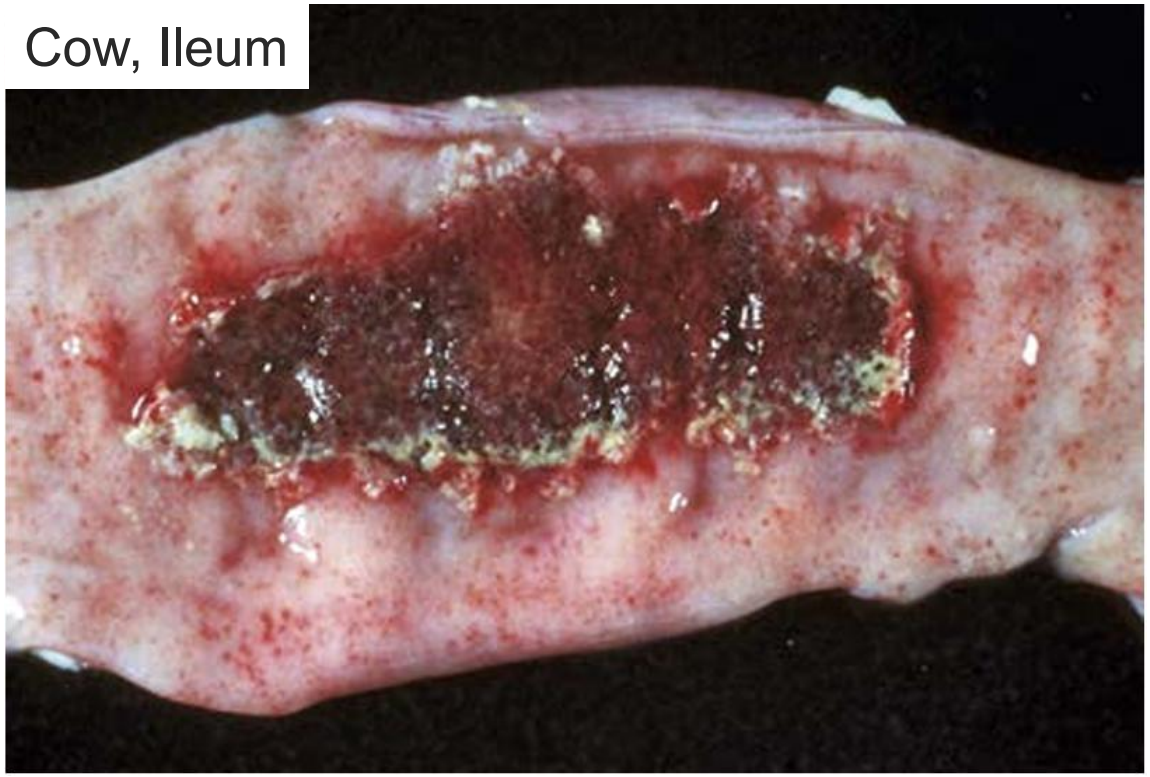
Rotaviral enteritis in piglets





BVDV

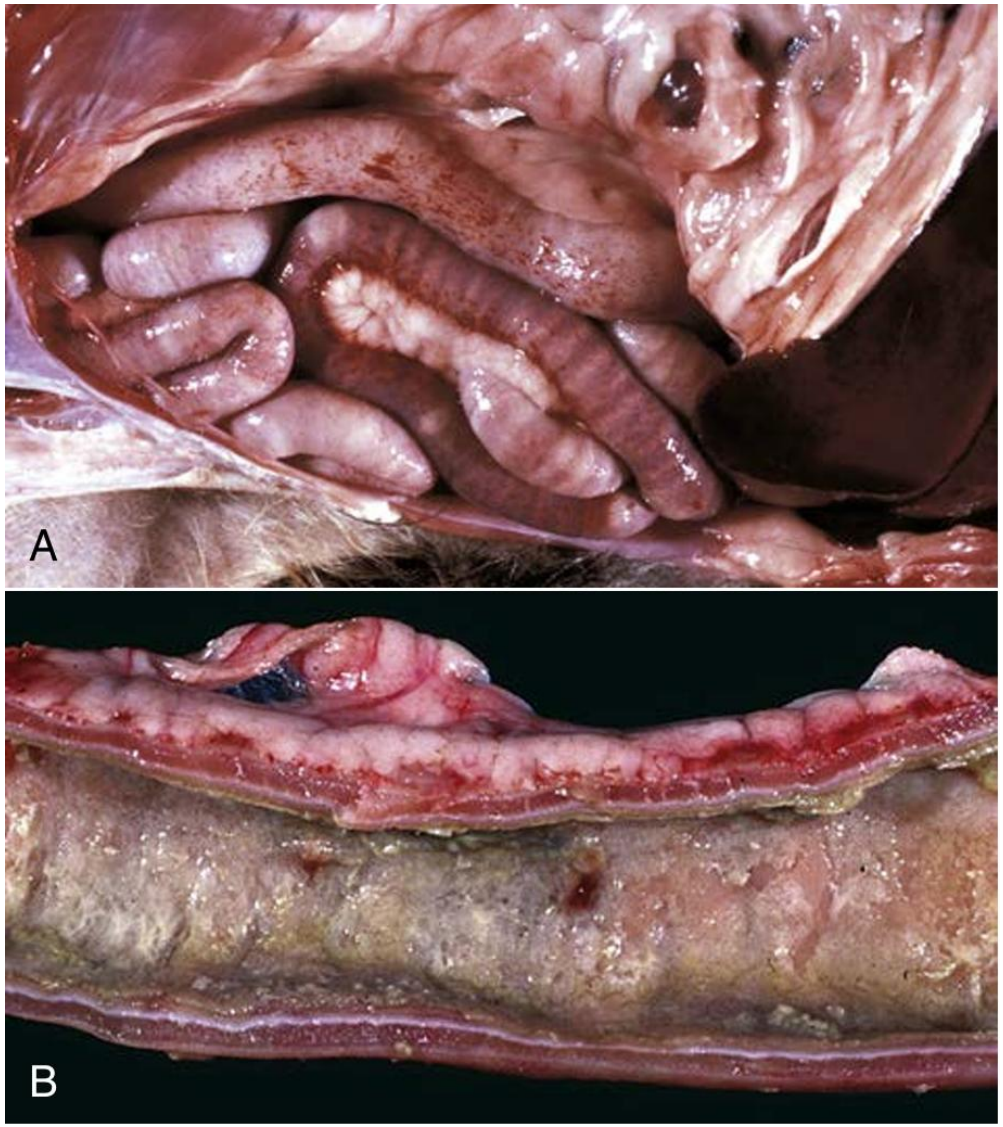
Cow, Ileum



Bison, Colon



Parvoviral enteritis in dogs

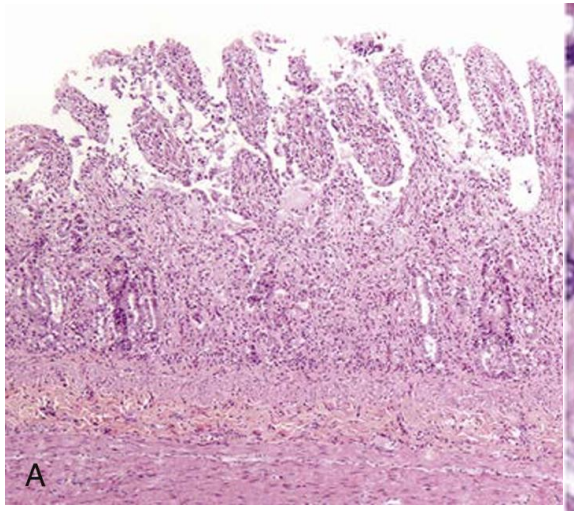


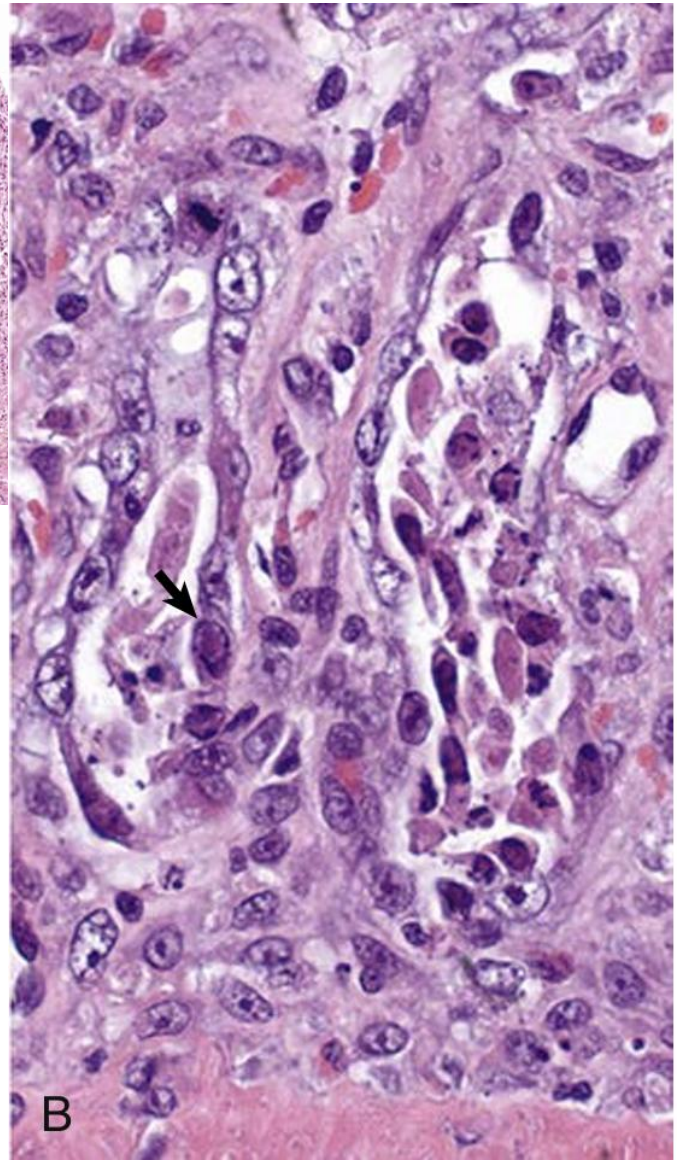
Canine Parvovirus-2 (CPV-2)

Pathogenesis

1. **Oral Ingestion** of CPV-2 → Virus enters **tonsils** and **lymphoid tissues**.
2. Systemic Viremia (2-5 days post-infection) → Infects **rapidly dividing cells**.
3. Primary Target Organs:
   - Small Intestinal **Crypt** Epithelium → Severe crypt necrosis → Villous atrophy → Malabsorption and diarrhea.
   - **Bone Marrow** and **Lymphoid Tissue** (Peyer's Patches) → Leukopenia and immunosuppression.
   - Fetal Myocardium (Neonatal Puppies) → Myocarditis (uncommon due to maternal immunity).

Parvoviral enteritis in cats





Feline Parvovirus (Feline Panleukopenia Virus)

Pathogenesis

1.Oral Ingestion of FPV → Virus enters **oropharyngeal lymphoid tissue**

2.Systemic Viremia (2-7 days post-infection) → Virus targets rapidly **dividing cells**

3.Primary Target Organs:

- Bone Marrow & Lymphoid Tissue → Severe leukopenia & immunosuppression.
- Intestinal Crypt Epithelium → Crypt necrosis → Villous atrophy → Malabsorptive diarrhea.
- **Cerebellum in Neonatal Kittens → Cerebellar hypoplasia (if infected in utero).**

Bacterial Enteritis - E. coli and Salmonella

- Enterotoxigenic E. coli (ETEC)
  -Neonatal diarrhea
  -Produces heat-labile (LT) and heat-stable (ST) toxins → Secretory diarrhea

- Enterohemorrhagic E. coli (EHEC)
  -Edema disease in pigs
  -Shiga toxin-producing strains → Vascular damage → Systemic edema

- Salmonella enterica
  -Invades M cells → **Fibrinonecrotic enteritis** in ruminants and pigs.

Boxer colitis



Salmonellosis in the Large Intestine

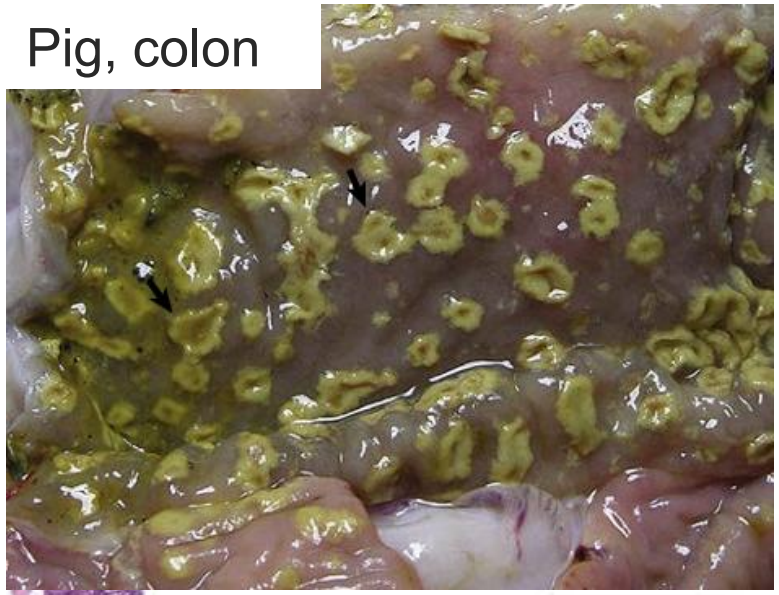
- Salmonella typhimurium, Salmonella choleraesuis
- Pathogenesis: Invades M cells, survives in macrophages
- Gross findings

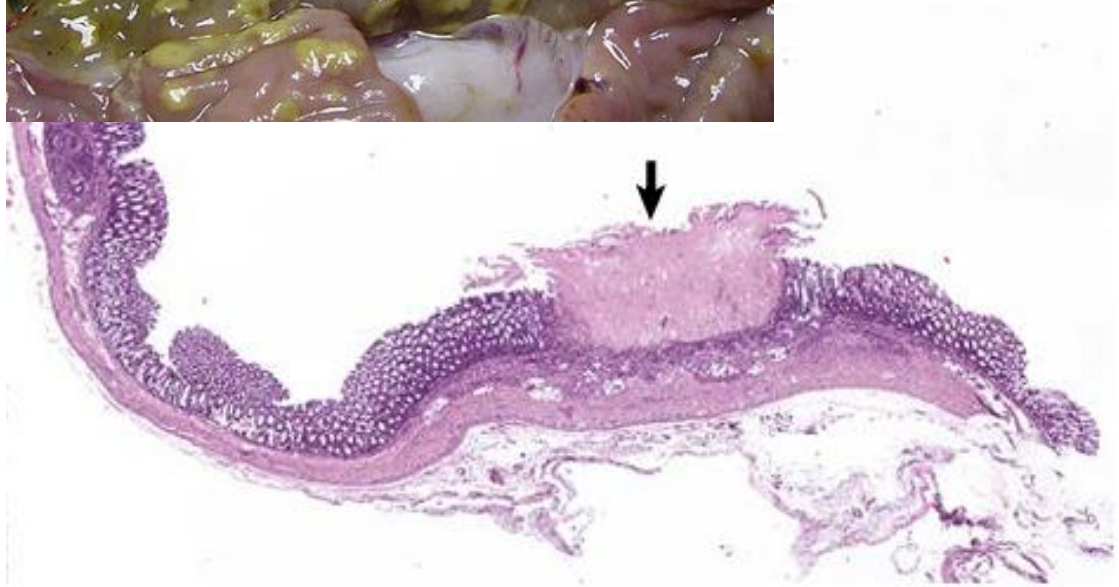
  -Fibrinous colitis, button ulcers
- Microscopic findings

  -Necrosis, inflammatory infiltrates, thrombi in blood vessels.

Pathognomonic!!

Pig, colon





Clostridial Enteritis and Enterotoxemia

- Clostridium perfringens Type C

  -Produces beta toxin, causing hemorrhagic necrotizing enteritis in neonatal pigs and calves

- Clostridium difficile Toxin A and B → Pseudomembranous colitis

- Gross Findings: Hemorrhagic, fibrinonecrotic enteritis

- Microscopic Findings: Crypt necrosis, fibrin thrombi formation.

Parasitic Enteritis

- Cryptosporidium parvum

  -Attaches to intestinal epithelium, causing villous atrophy

  Common in calves, lambs, and immunocompromised hosts

- Coccidiosis (Eimeria spp., Isospora suis)

  -Protozoal infection of intestinal crypts → **Hemorrhagic diarrhea**

- Gross Findings

  -Thickened, congested intestinal mucosa.

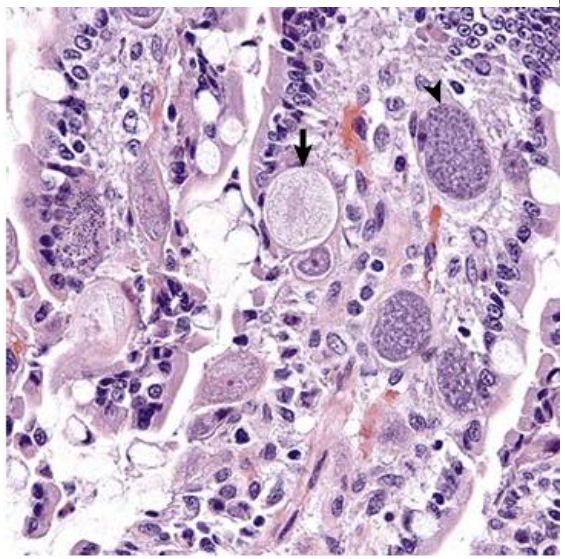
- Microscopic Findings

  -Protozoal organisms within intestinal epithelial cells

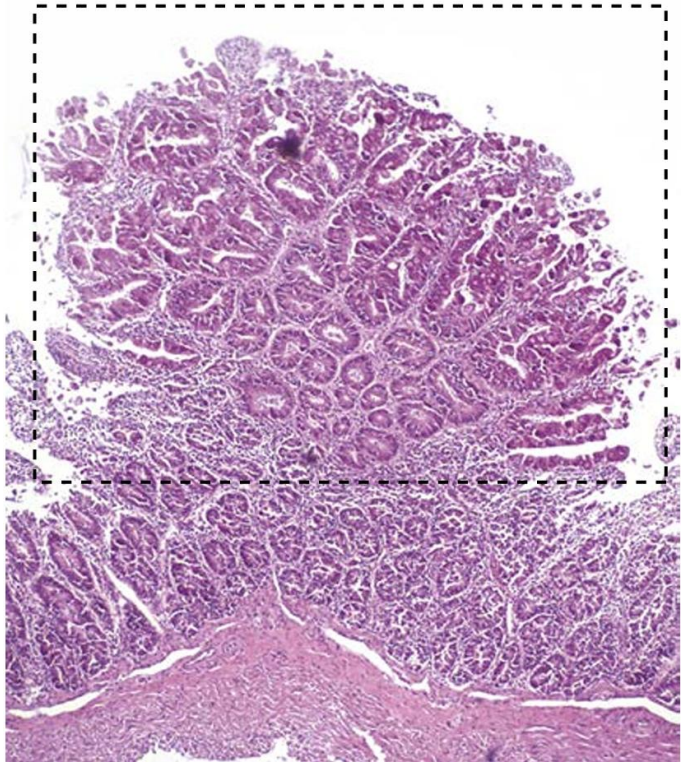
Calf, small intestine



Cow, small intestine



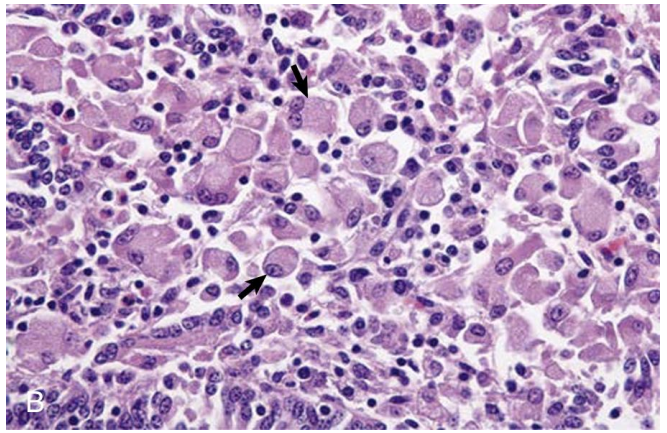
Goat, small intestine

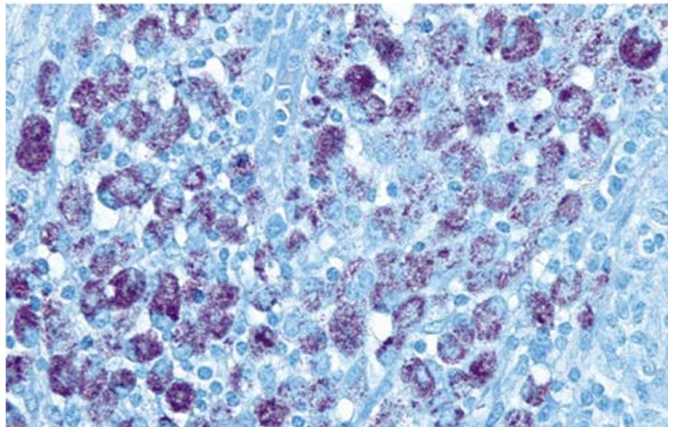


Johne's Disease

- Mycobacterium avium subsp. paratuberculosis
- Chronic granulomatous enteritis in cattle, sheep, and goats
- Causes chronic **wasting** and diarrhea
- Gross Findings: Thickened intestinal wall
- Microscopic Findings: Granulomatous inflammation in Johne's Disease.







Neoplastic Diseases - Intestinal Lymphoma

- Intestinal Lymphoma (Cats, Dogs, Cattle)

  -Most common small intestinal neoplasm in cats

  -Associated with chronic inflammation (IBD-related lymphoma)

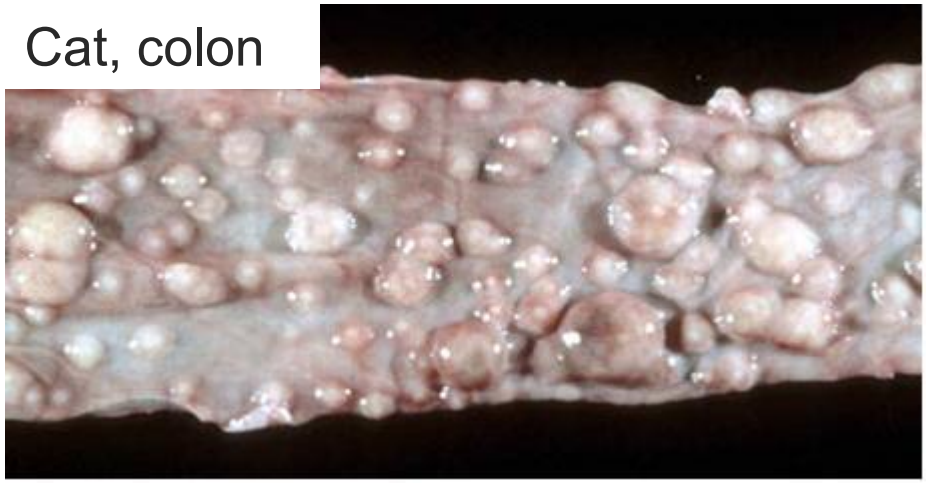
- Gross Findings

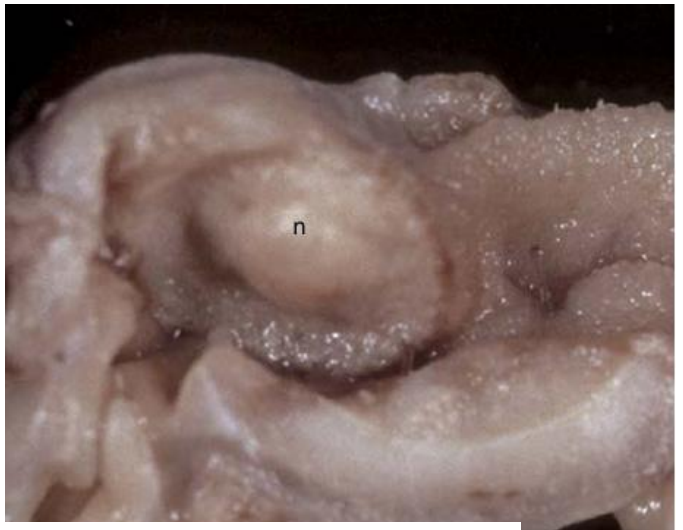
  -Thickened intestinal segments, nodular lesions

- Microscopic Findings

  -Monomorphic lymphoid cell infiltrates replacing normal epithelium.

Cat, colon





Cat, Small intestine

Intestinal Adenocarcinoma and Gastrointestinal Stromal Tumors (GIST)

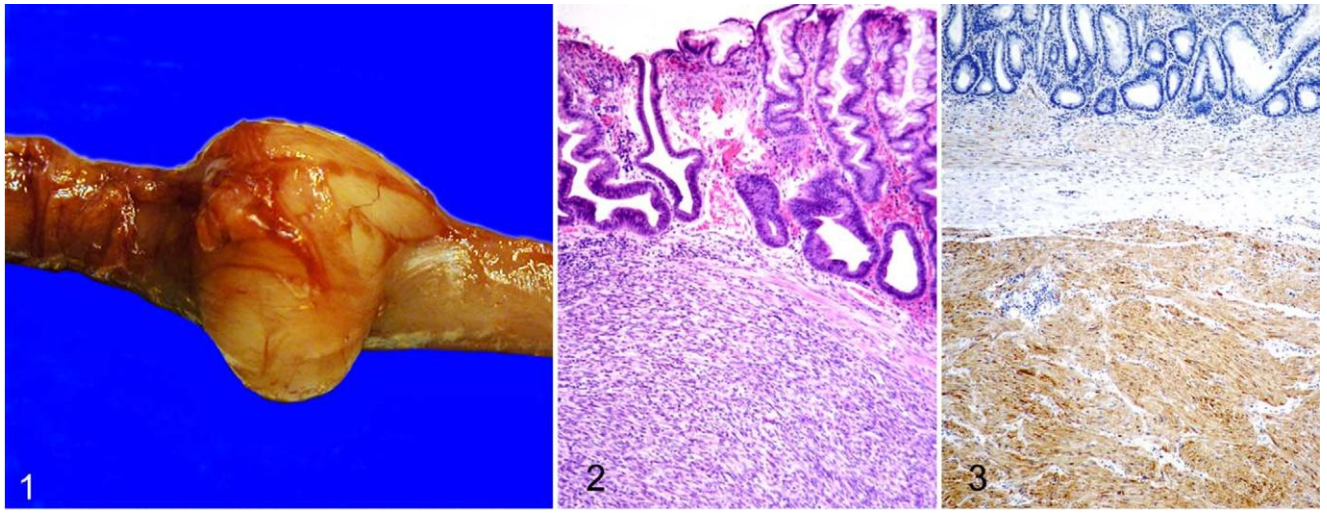
- Adenocarcinoma (Dogs, Cats, Sheep)
  -Highly invasive → Metastasis to lymph nodes and peritoneum

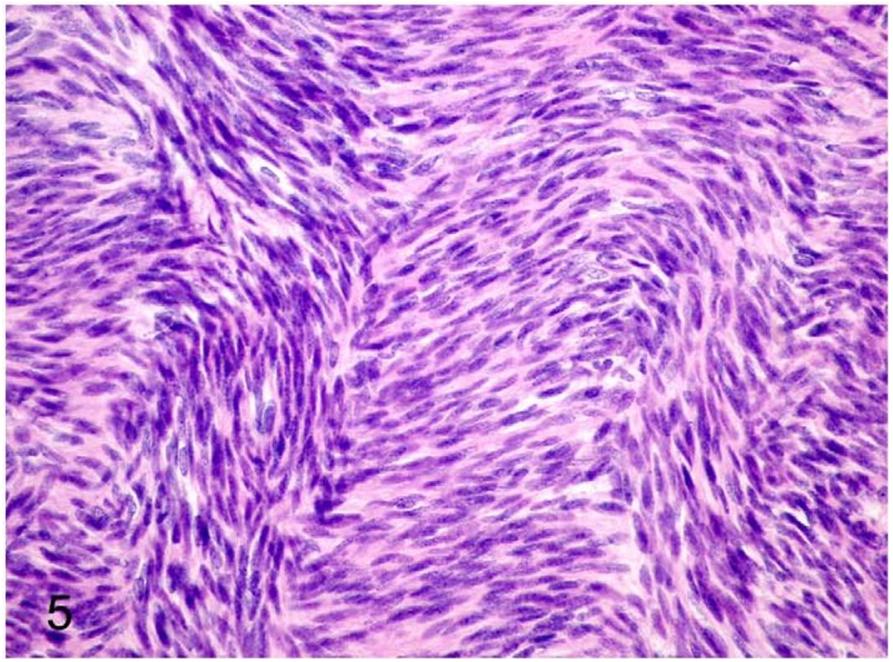
- Gastrointestinal Stromal Tumor (GIST)
  -Arises from interstitial cells of Cajal
  -c.f.) non-angiogenic, non-lymphogenic intestinal mesenchymal tumor (NIMT)

- Gross Findings: Firm, infiltrative masses causing luminal narrowing

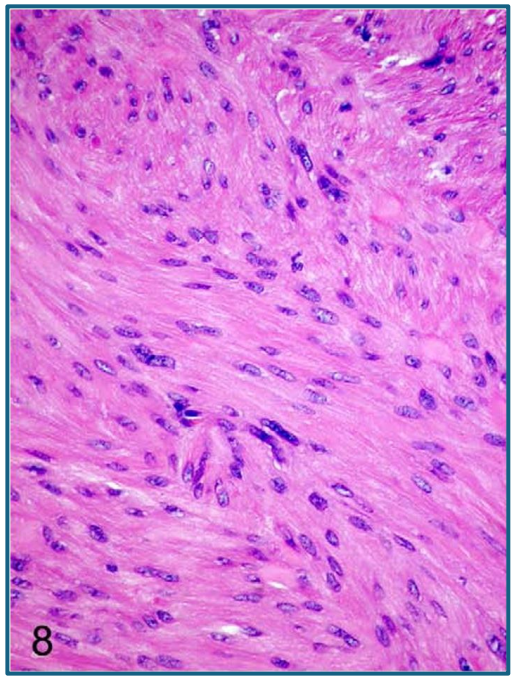
- Microscopic Findings
  Invasive neoplastic glands (adenocarcinoma)
  Spindle cell proliferation (GIST).

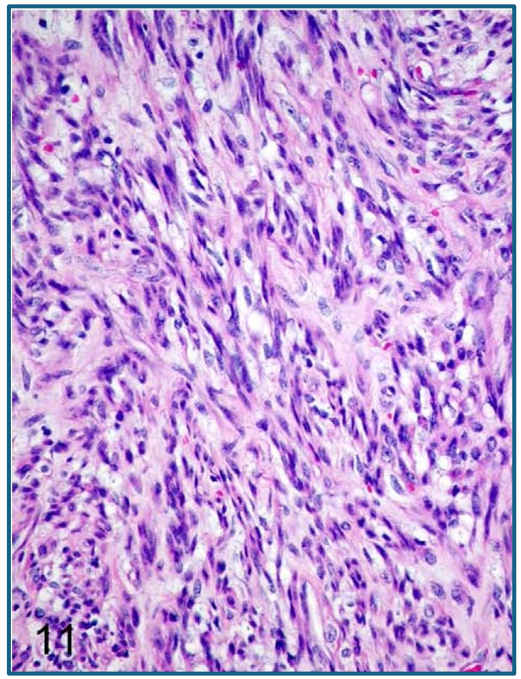
Spindle cell tumor in the intestine





GIST





Leiomyosarcoma

hayes-et-al-2013-classification-of-canine-nonangiogenic-nonlymphogenic-gastrointestinal-sarcomas-based-on-microscopic

Peritoneal and Mesenteric Diseases - Overview

- The peritoneum and mesentery support the intestines

- Common diseases

-Peritonitis (bacterial, parasitic)

Bacterial: Escherichia coli, Actinobacillus spp., Trueperella pyogenes

Viral: Feline Infectious Peritonitis (FIP, caused by Feline Coronavirus)

Parasitic: Echinococcus granulosus (hydatid cysts), Setaria spp.

-Fat necrosis

Nutritional (Vitamin E deficiency) → Common in cats fed high fish-based diets (rich in unsaturated fatty acids)

Pancreatic (Lipase activation)

Traumatic

-Ascites

Transudate vs Exudate

Mesothelioma

- Idiopathic in most animals

- Pathogenesis

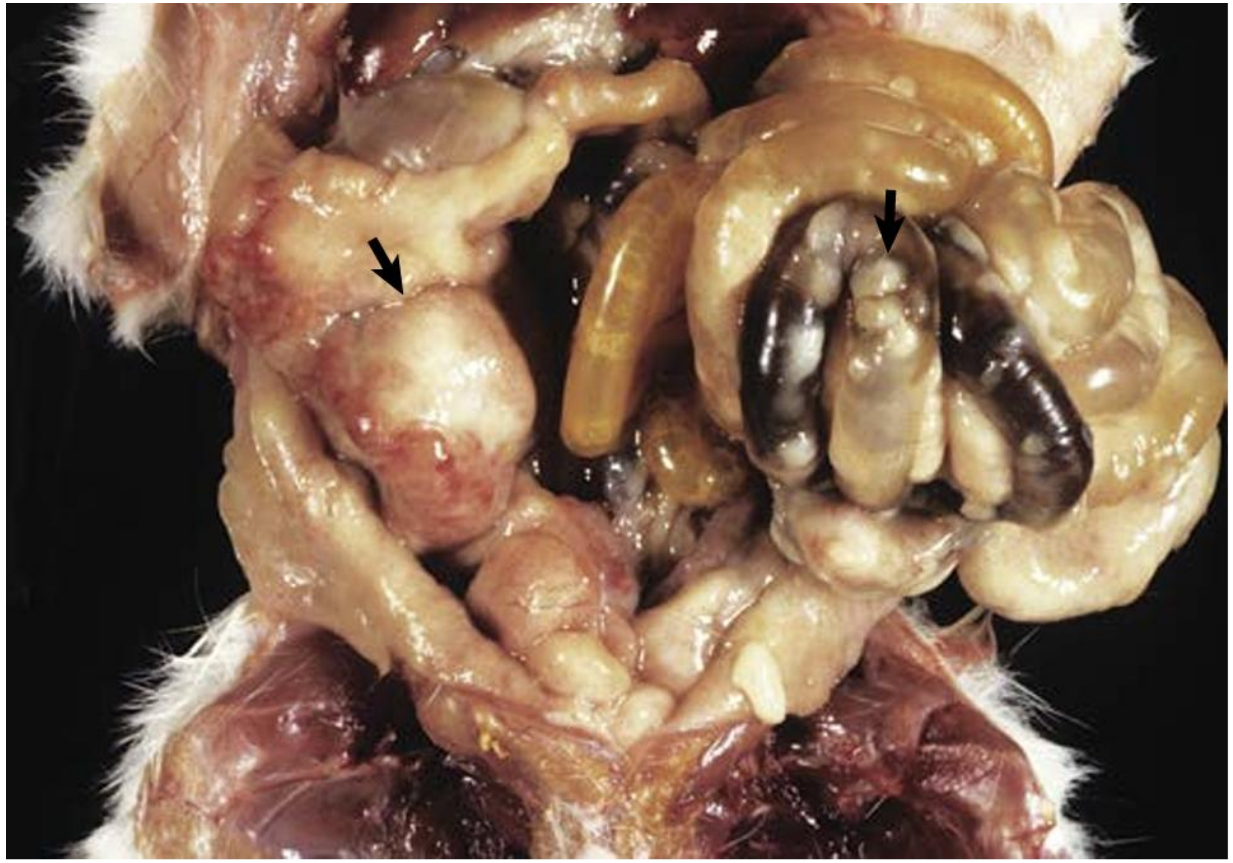
  Neoplastic transformation of mesothelial cells in serous membranes

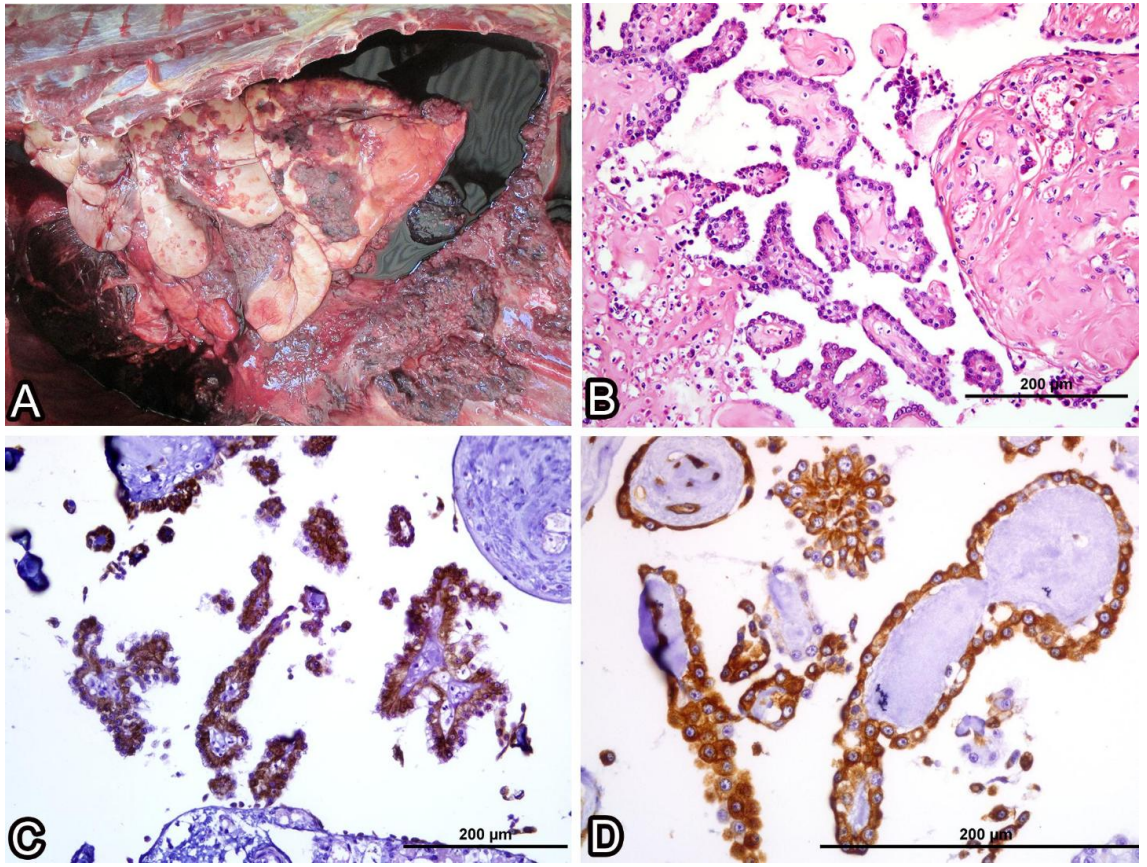
  → Tumor spreads along serosal surfaces, forming diffuse, coalescing nodules

  → Malignant mesothelial cells produce pleural, pericardial, or peritoneal effusions

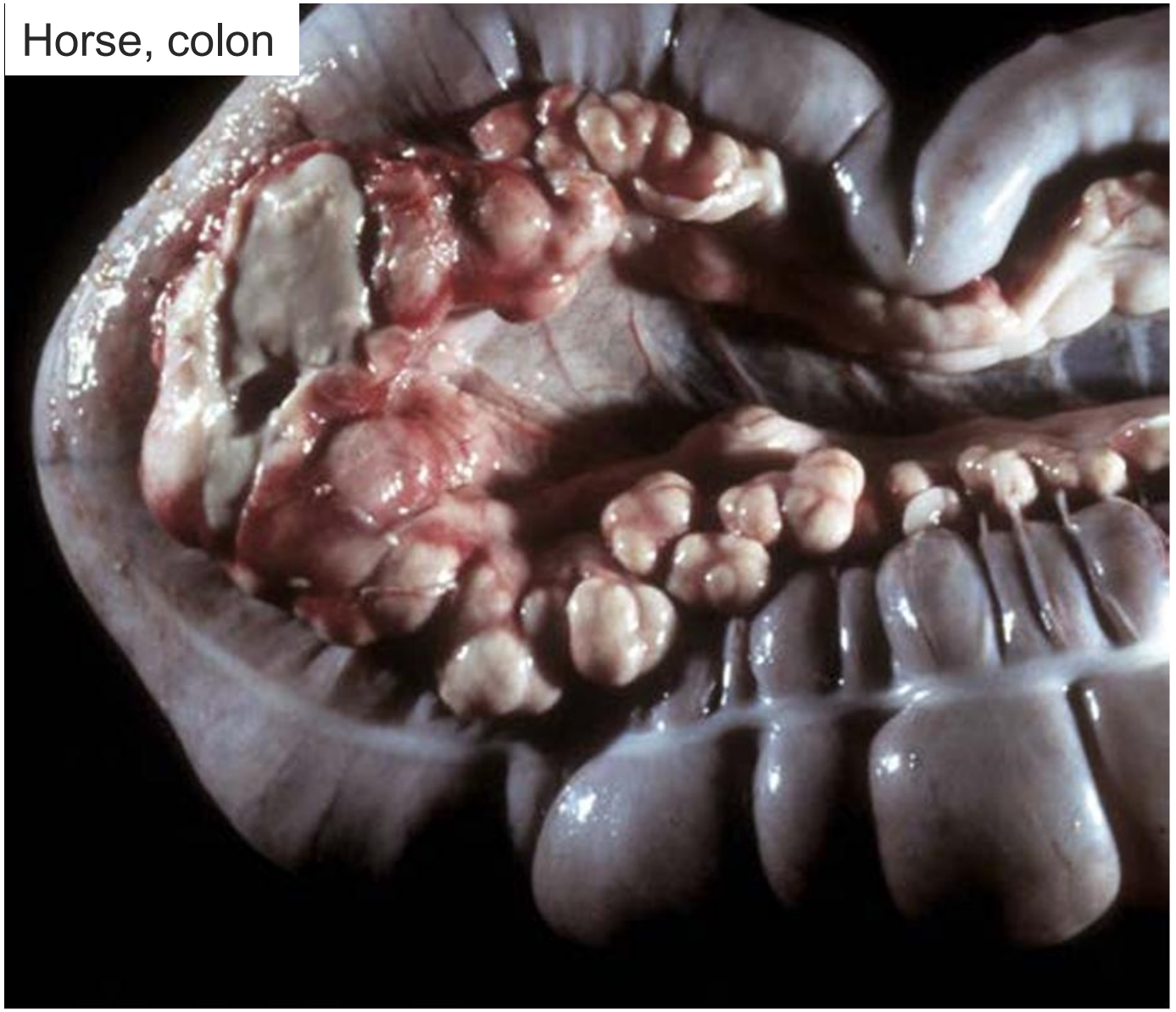
  → Infiltration into adjacent tissues can cause organ dysfunction

Mesothelioma





What is it?



Intestinal Volvulus and Torsion

- Pathogenesis

  -Rotation of intestinal loops → Vascular strangulation

- Predisposing Factors

  -Excess fermentation, rapid diet changes (ruminants)

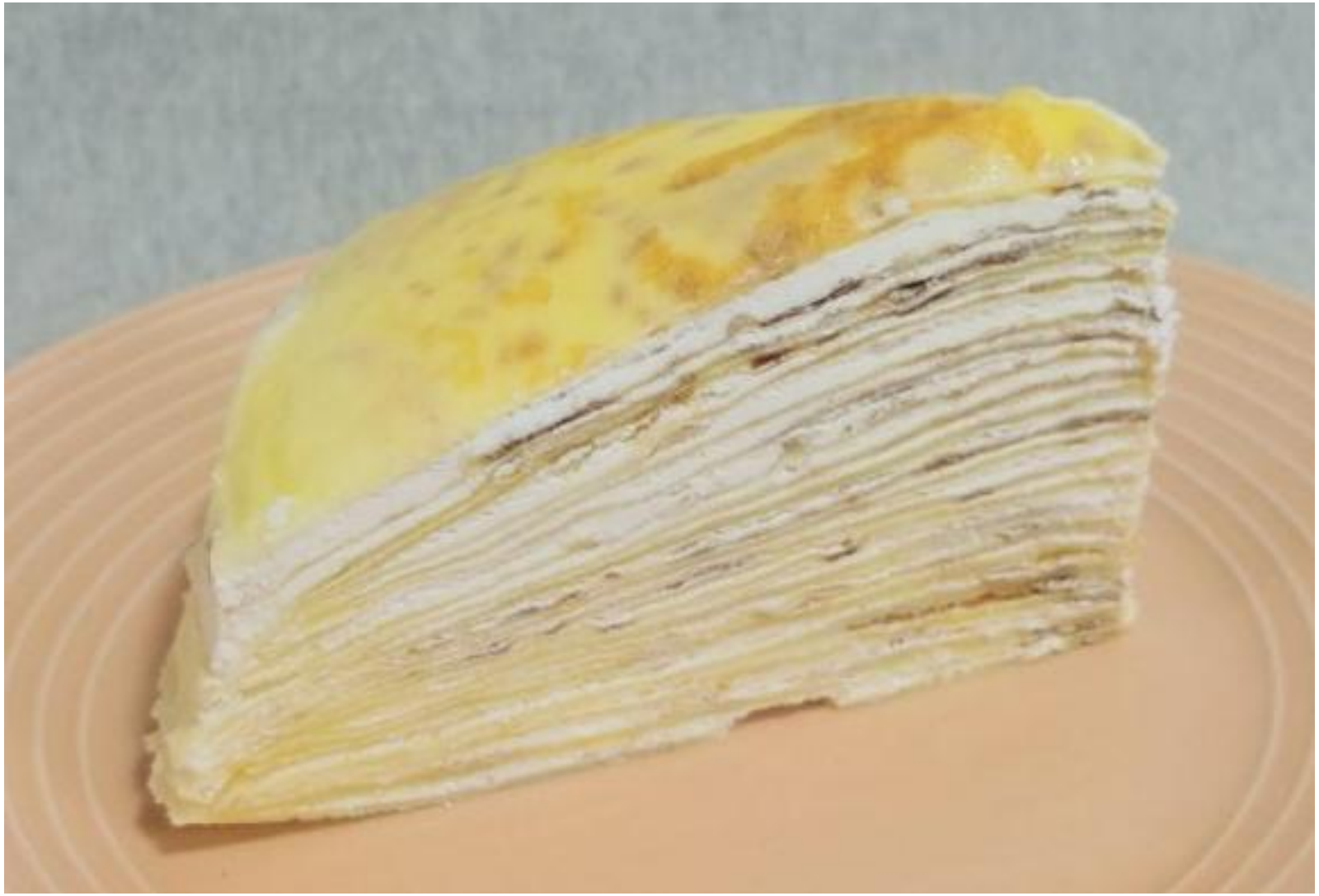
  -Deep-chested dogs at risk.

- Gross Findings

  -Dark red, congested, ischemic loops of bowel.

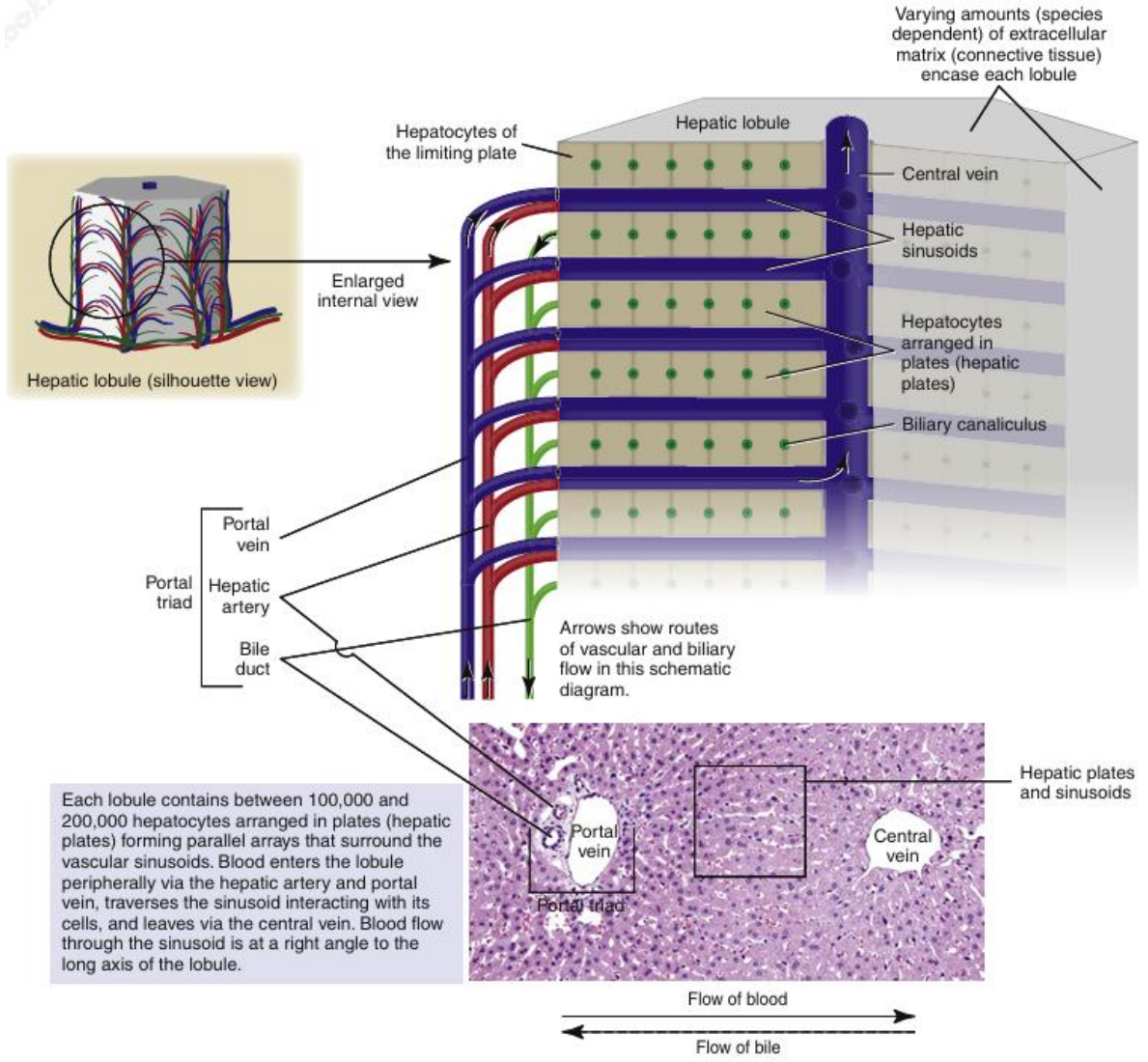
Hepatobiliary System and Exocrine Pancreas

Liver and Intrahepatic Biliary System



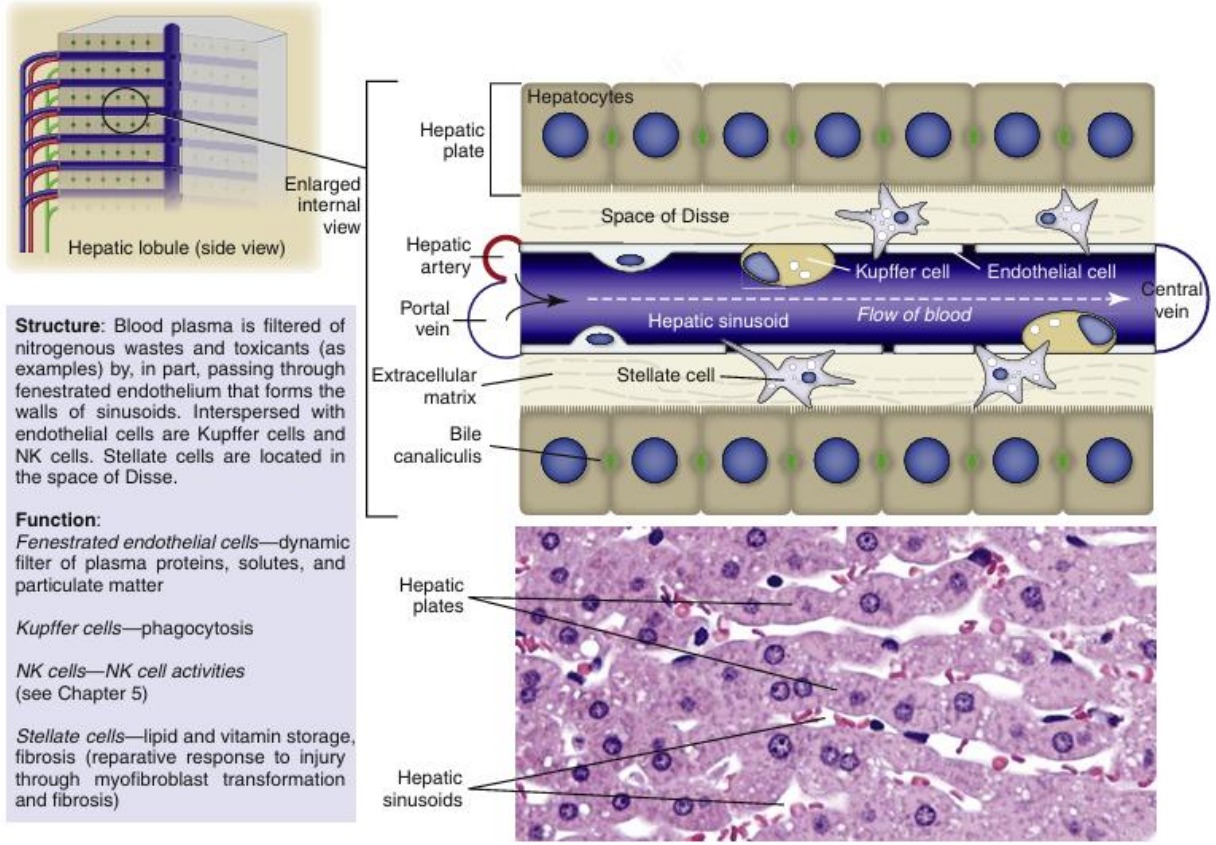
Liver and Intrahepatic Biliary System

- Liver, gallbladder, and biliary duct system
- Connected via the intrahepatic canalicular system
- Functions: metabolism, detoxification, storage, bile production and excretion



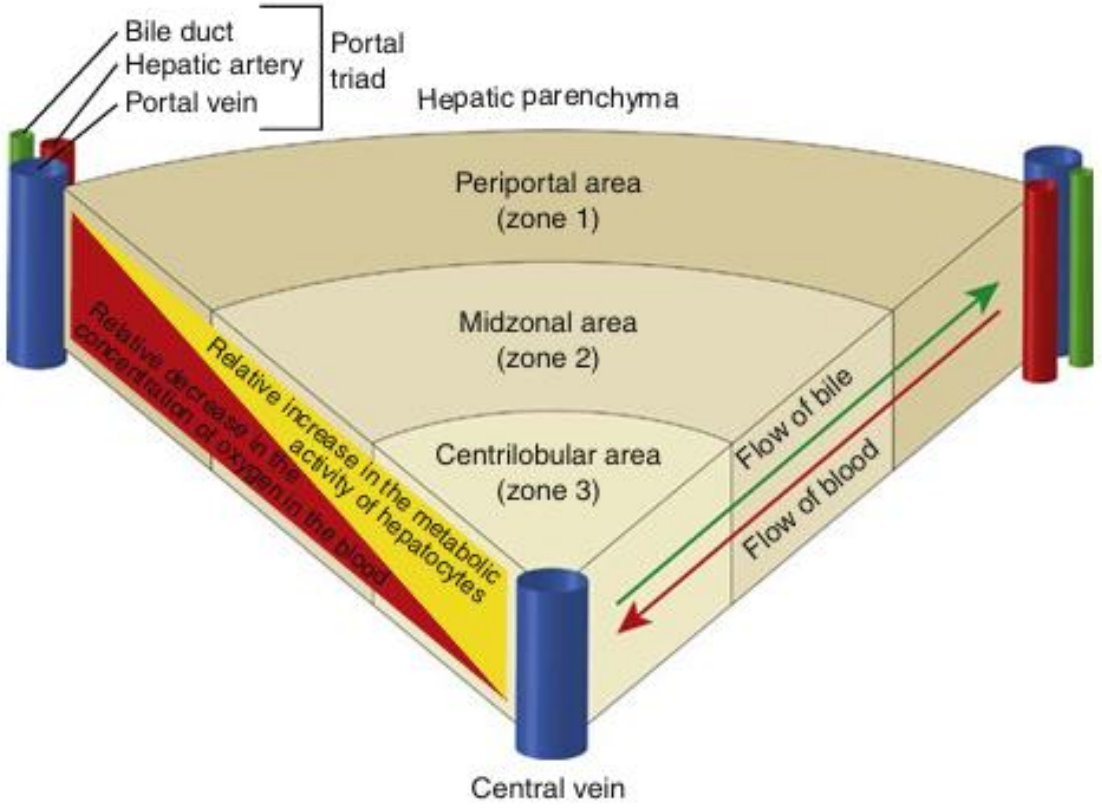
Microscopic Structure of the Liver

- Functional unit: Hepatic lobule
- Radiating hepatic plates around central vein
- Sinusoids between plates lined with fenestrated endothelium and Kupffer cells
- Space of Disse lies between hepatocytes and sinusoids, facilitates exchange

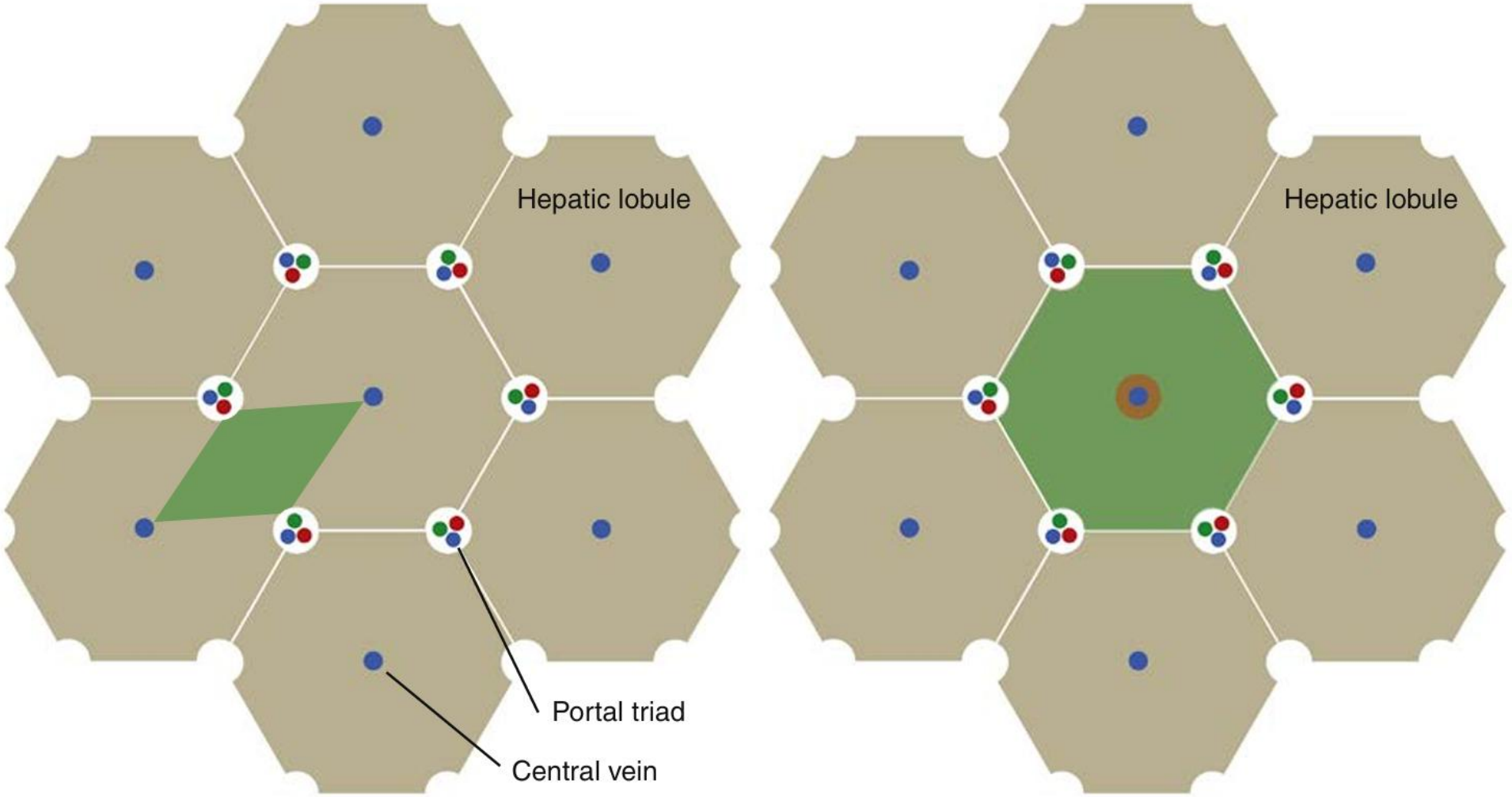


Portal Triad and Hepatic Circulation

- Portal triad: portal vein, hepatic artery, bile ductule
- Dual blood supply:
  - Portal vein (~75%) delivers nutrient-rich blood from intestines
  - Hepatic artery (~25%) supplies oxygenated blood
- Blood drains through sinusoids into central vein



Concept of hepatic lobule and acinar

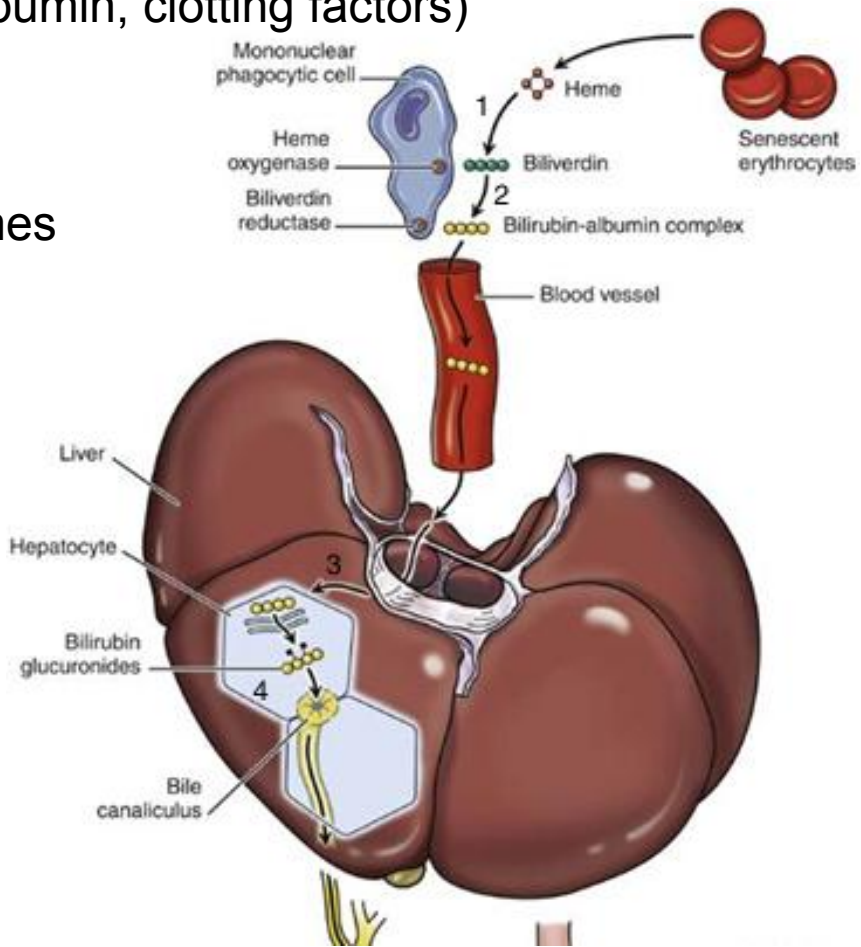


Zonal pattern - acinar

Zonal pattern - lobular

Functions of the Liver

- **Metabolism**:
  - Carbohydrates: stores glucose as glycogen, performs gluconeogenesis
  - Lipids: synthesizes cholesterol, triglycerides, lipoproteins
  - Proteins: deaminates amino acids, produces plasma proteins (e.g., albumin, clotting factors)
- **Detoxification**:
  - Converts ammonia to urea (urea cycle)
  - Metabolizes drugs, hormones, and toxins via cytochrome P450 enzymes
- **Bile Production**:
  - Bile acids synthesized from cholesterol
  - Excretes bilirubin (from hemoglobin breakdown)
- **Storage**:
  - Glycogen, vitamins (A, D, B12), iron, and copper
- **Immune Function**:
  - Kupffer cells remove bacteria and debris from blood
  - Acts as a filter for gut-derived antigens and pathogens



Bile Formation and Flow

- Hepatocytes secrete bile into canaliculi
- Bile flow: canaliculi → bile ductules → hepatic ducts → common bile duct
- Composition: bile salts, bilirubin, cholesterol, electrolytes
- Essential for fat emulsification and absorption

Injury Responses

Pathophysiology – Liver Injury

- Hepatocytes are highly metabolic and vulnerable to hypoxia and toxins
- Injury pathways: oxidative stress, mitochondrial dysfunction, inflammatory cytokines
- Bile flow obstruction causes cholestasis
- Stellate cell activation leads to fibrosis

Box 8.2 Mechanisms of Liver Injury

- Metabolic bioactivation of chemicals via cytochrome P450 to reactive species
- Stimulation of autoimmunity
- Stimulation of apoptosis
- Disruption of calcium homeostasis leading to cell surface blebbing and lysis
- Canalicular injury
- Mitochondrial injury

Histologic Patterns – Liver

- Steatosis: lipid droplets in hepatocytes

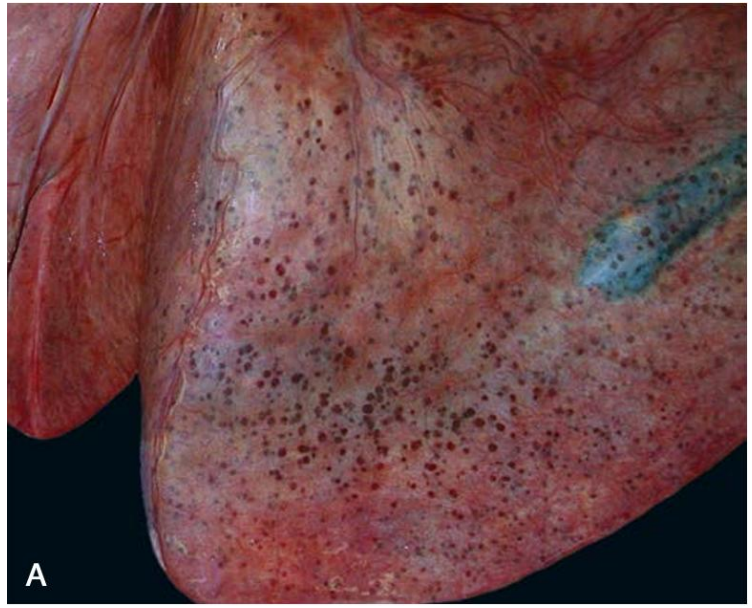
- Random hepatocellular degeneration and/or necrosis
  - Infectious agents (viruses, bacteria, and certain protozoa)

- Zonal necrosis
  -centrilobular (toxic/hypoxic): anemia, right-sided heart failure
  -paracentral/periacinar: anemia, right-sided heart failure → proceeds to centrilobular
  -midzonal (the least common pattern, aflatoxicosis in pigs and horses and hexachlorophene in cats)
  -periportal (toxic but do not require bioactivation)

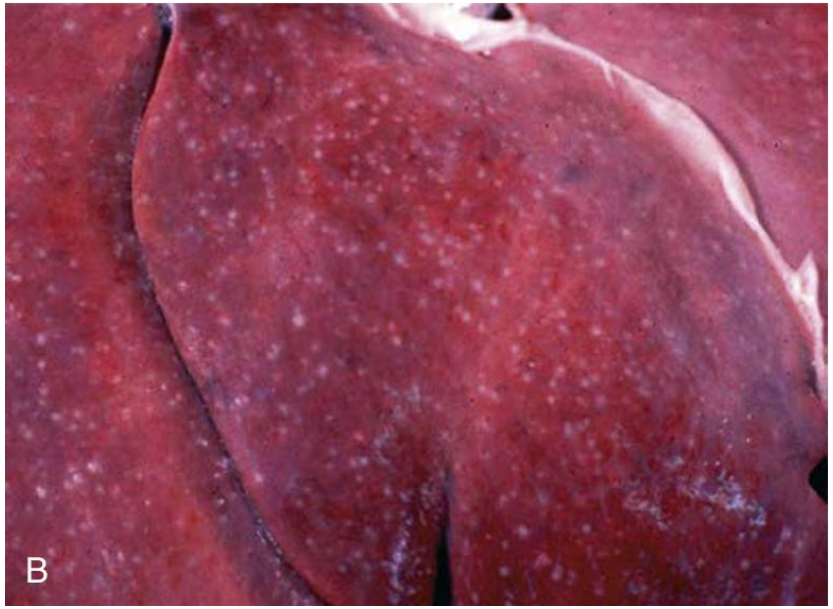
- Fibrosis: portal, bridging, cirrhosis

- Regeneration: mitotic activity, nodular hyperplasia

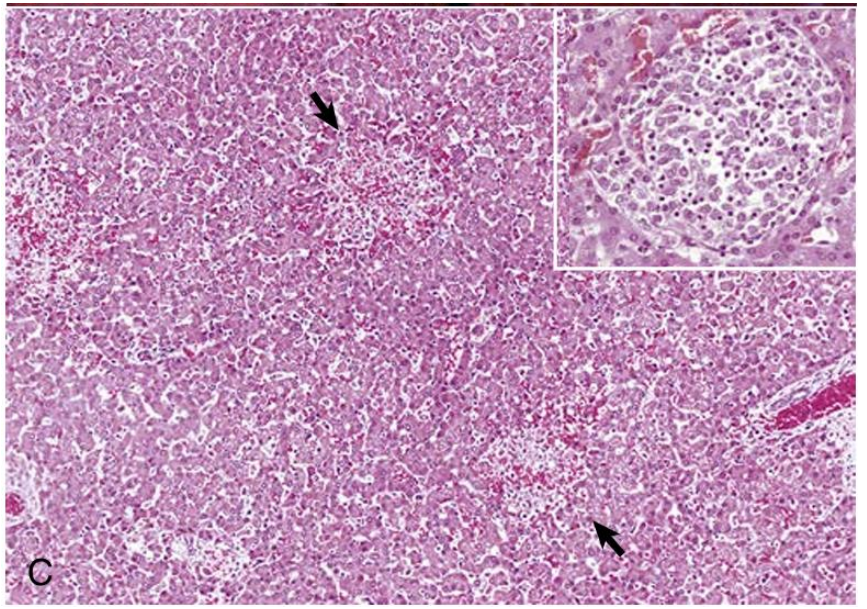
Histologic Patterns – Random



Tyzzer's disease (*Clostridium piliforme* infection, Horse)

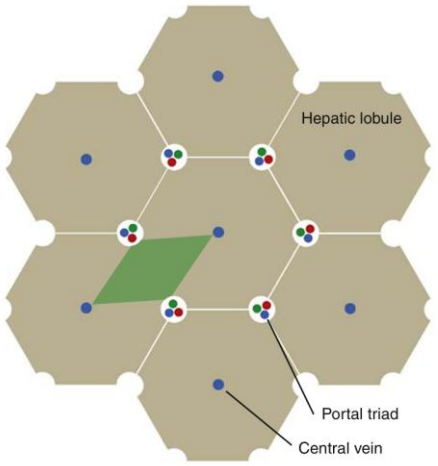


Equine herpesvirus infection

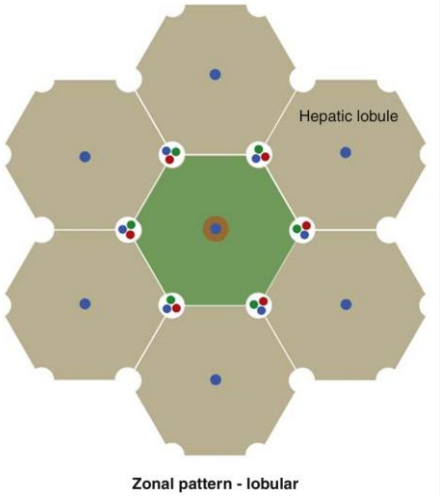


Salmonellosis, pig

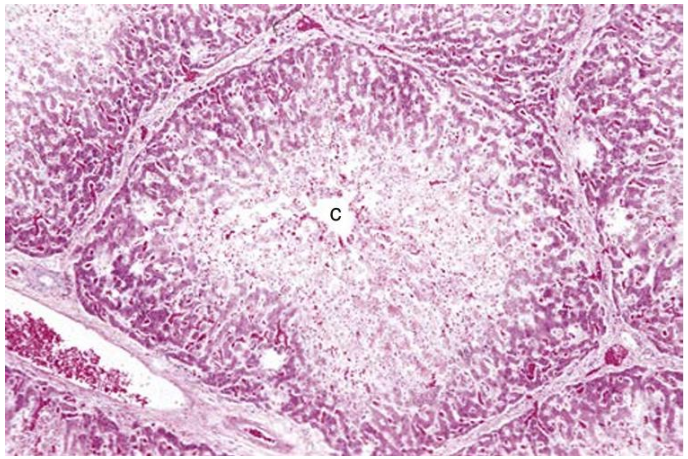
Histologic Patterns – Zonal



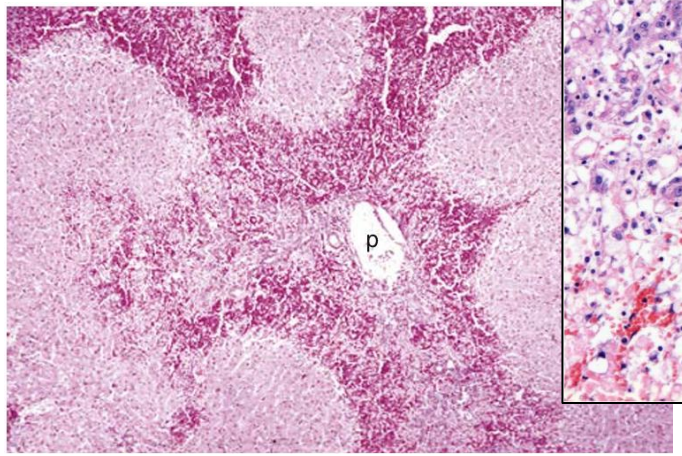
Zonal pattern - acinar



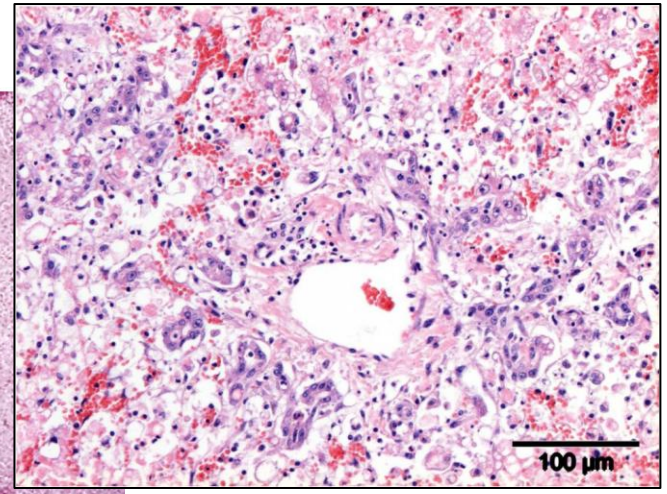
Zonal pattern - lobular

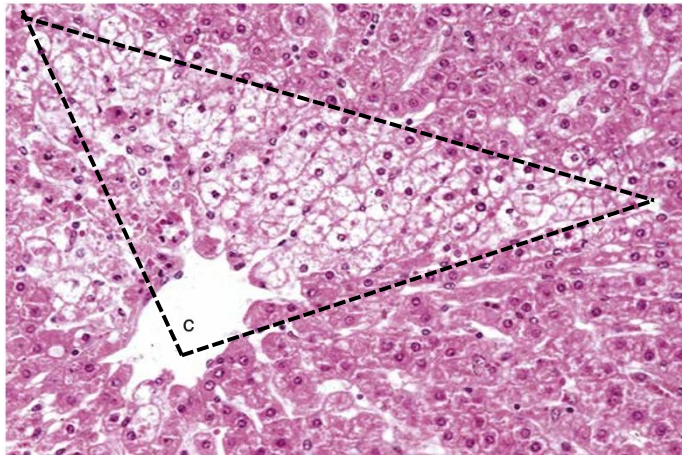


Centrilobular necrosis, pig

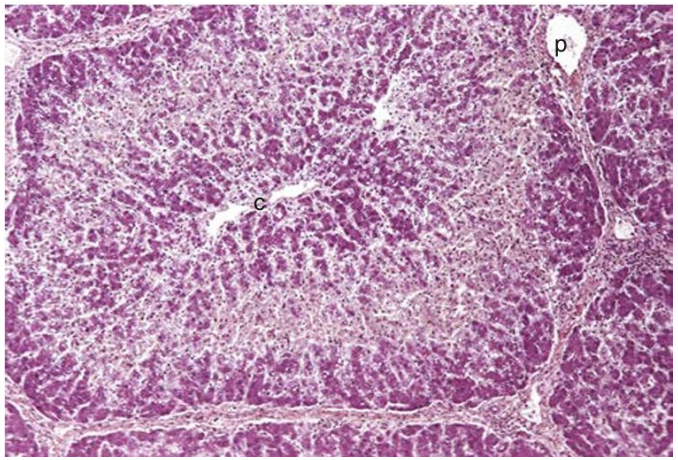


Periportal





Paracentral (periacinar)



Midzonal necrosis, horse

Morphological classification of hepatobiliary disease

Inflammatory Hepatic Disease (Hepatitis)

- Acute hepatitis: neutrophilic inflammation, often infectious

  -Characterized by hepatocellular necrosis and apoptosis

  -Particularly in bacterial or protozoal infections

  -Random foci of neutrophilic hepatitis due to embolic localization of infectious agents

  -Viral infection (i.e., herpesvirus): a random distribution of necrosis and apoptosis with minimal inflammation, including neutrophil infiltration

Morphological classification of hepatobiliary disease

Viral hepatitis

- The liver maintains an **immunologically tolerant** environment to prevent overreaction to gut-derived antigens.
- Viral infections (e.g., HBV, HCV, herpesvirus) often cause hepatocyte **apoptosis, not necrosis**

  → minimal neutrophilic response.
- **Cytotoxic T lymphocytes** (CD8+) mediate hepatocyte killing **without strong proinflammatory cytokine release**.
- **Kupffer cells** release **anti-inflammatory cytokines** (e.g., IL-10, TGF-β), suppressing innate immune activation.

- Bacterial/protozoal infections trigger TLR-mediated inflammation and neutrophil influx.

Morphological classification of hepatobiliary disease

Inflammatory Hepatic Disease (Hepatitis)

- Chronic hepatitis: mononuclear infiltrates, fibrosis, ductular reaction, and regeneration

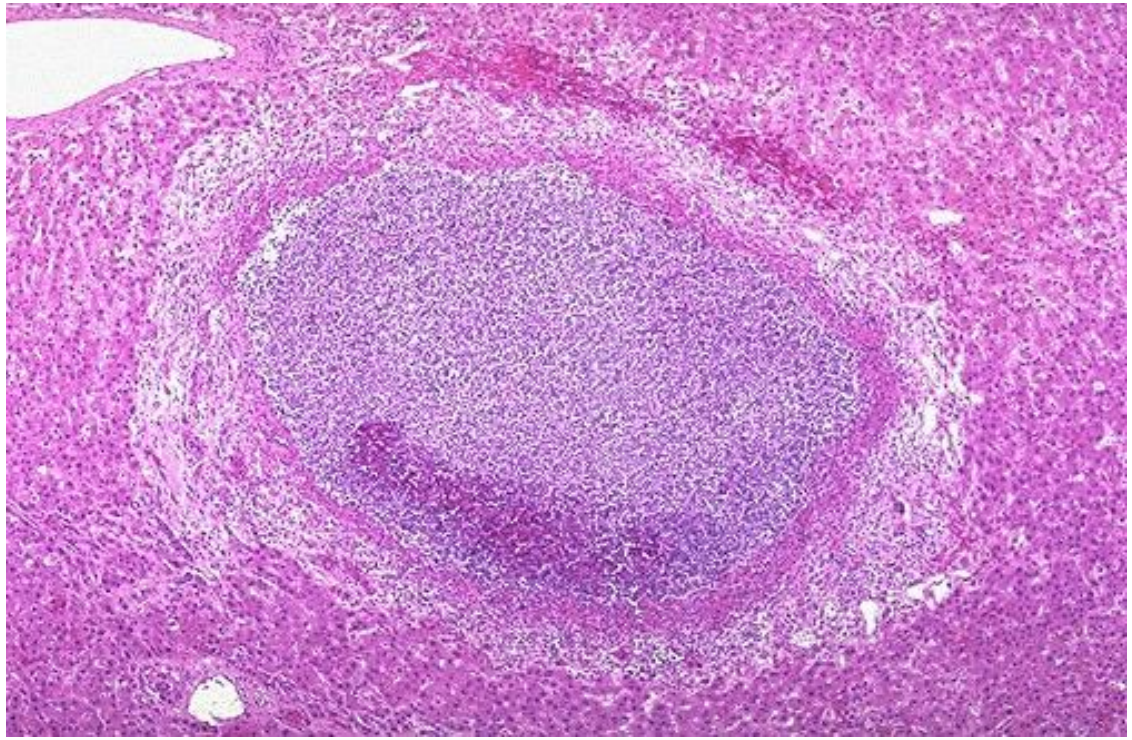
  -Granulomatous (grossly)

  -Chronic suppurative: abscess

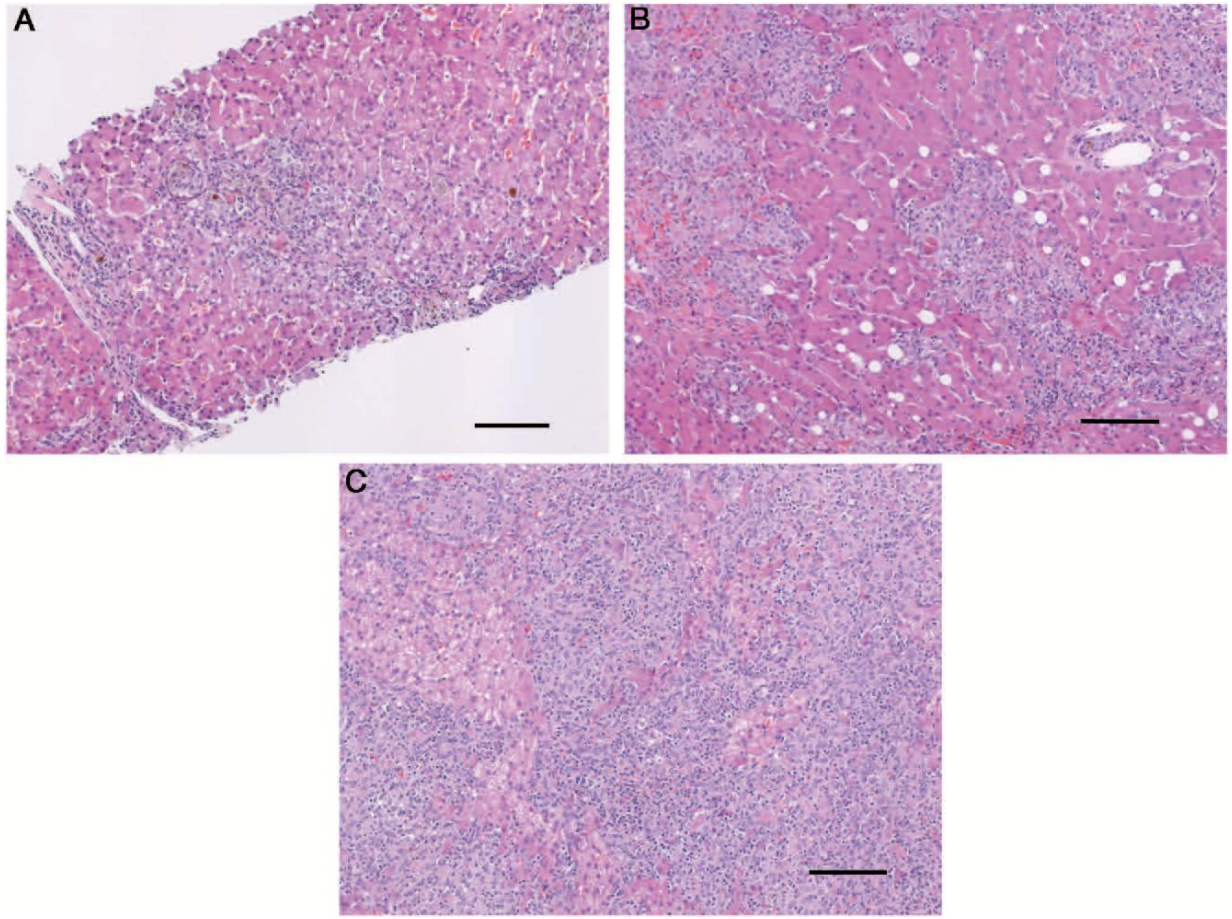
  -Proceed to end-stage hepatic disease → liver failure

- Interface hepatitis: inflammation at limiting plate, not specific in animals

Chronic abscess vs Pyogranulomatous hepatitis



https://pathologyapps.com/histology.php?id=548

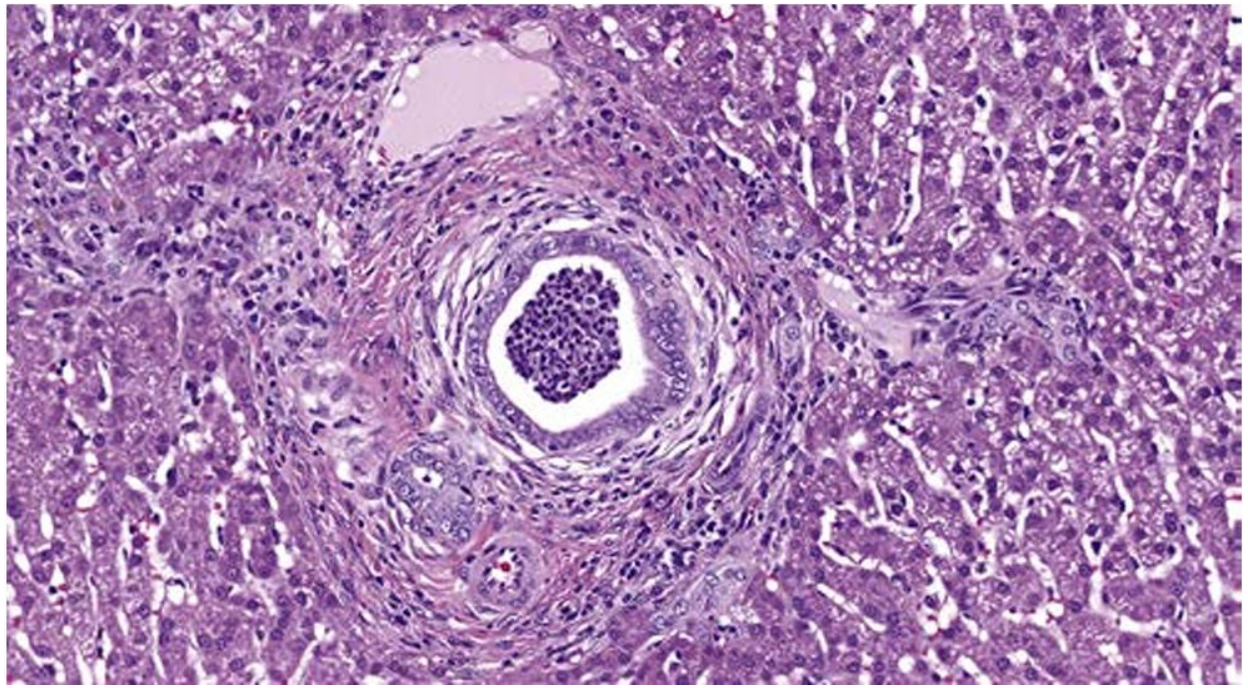


Limited yield of diagnoses of intrahepatic infectious causes of canine granulomatous hepatitis from archival liver tissue, JVDI, 2012

Morphological classification of hepatobiliary disease

Biliary disease

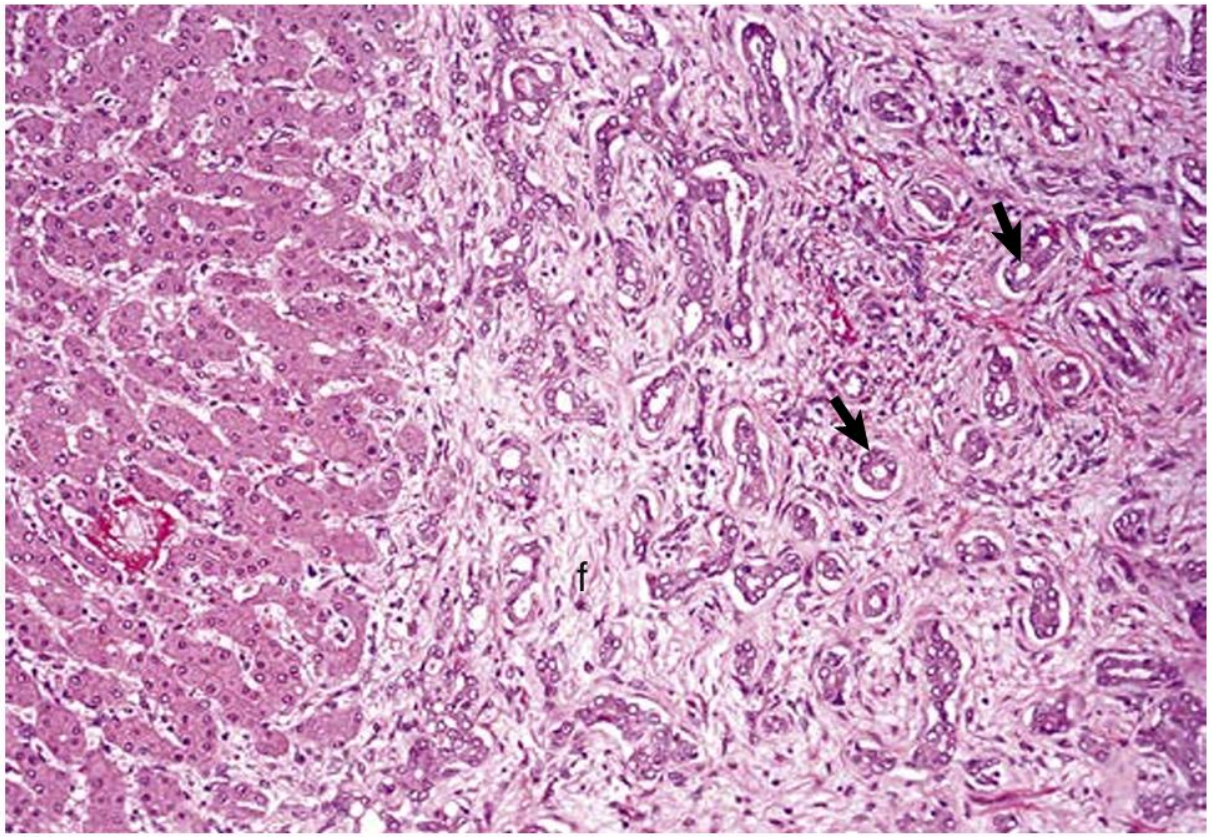
- Cholangitis: inflammation of bile ducts
- Cholangiohepatitis: inflammation of bile ducts and adjacent parenchyma (commonly due to an extension of cholangitis
- Biliary hyperplasia and ductular reaction
- An ascending bacterial infection from the intestine via common bile duct



-*Escherichia coli* or *Enterococcus*, *Bacteroides*, *Streptococcus*, or *Clostridium* spp

Disturbance of bile flow and icterus

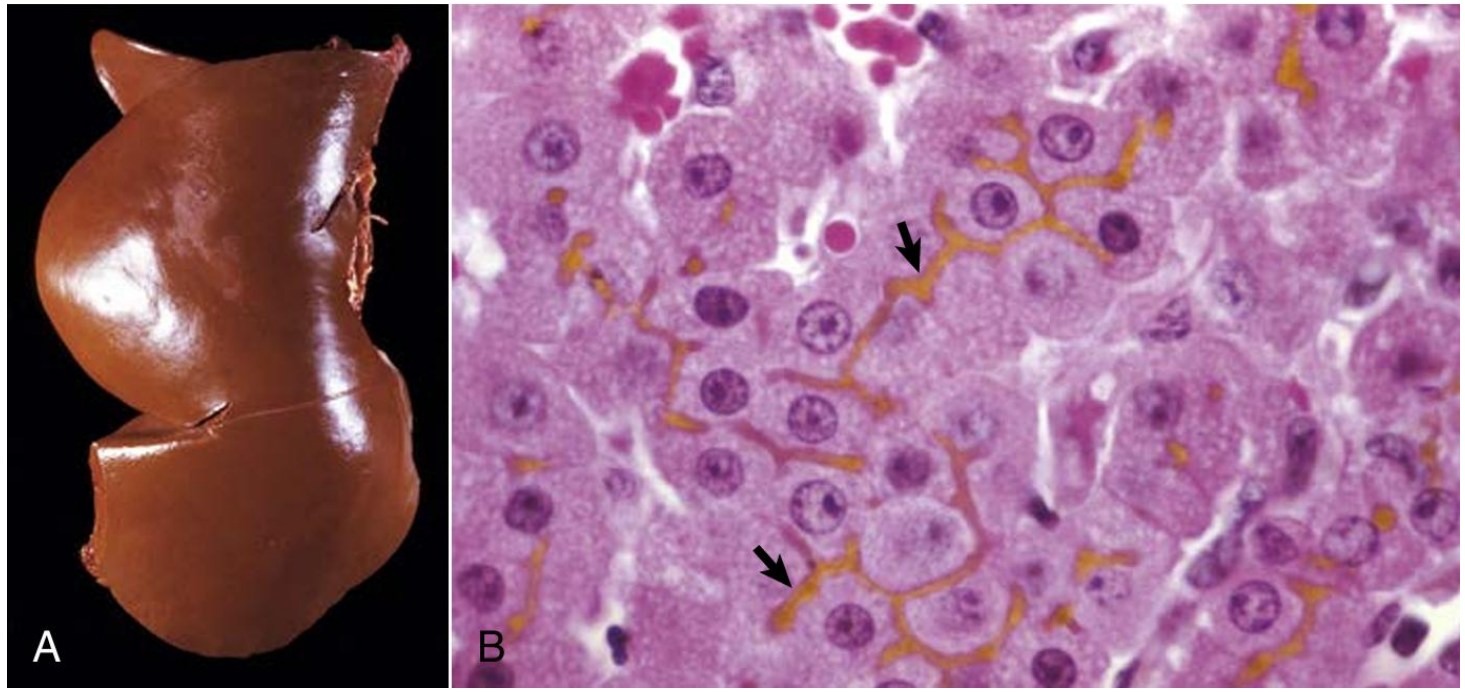
- Bile flow impairment = cholestasis (c.f., hyperbilirubinemia)
  - -Intrahepatic (liver injury or hemolysis: prehepatic hyperbilirubinemia)
  - -Extrahepatic (duct obstruction)
- Accumulation of bile components in hepatocytes and blood
- Leads to icterus (jaundice): yellow discoloration of tissues



Extrahepatic cholestasis, chronic, cholelithiasis, horse

Microscopic Features of Cholestasis

- Bile plugs in canaliculi
- Bile pigments in hepatocytes (green-brown)
- Kupffer cell hyperplasia
- Portal tract inflammation if prolonged



Acute hemolysis, Babesiosis, Calf

Icterus



- **Icterus versus Jaundice?**

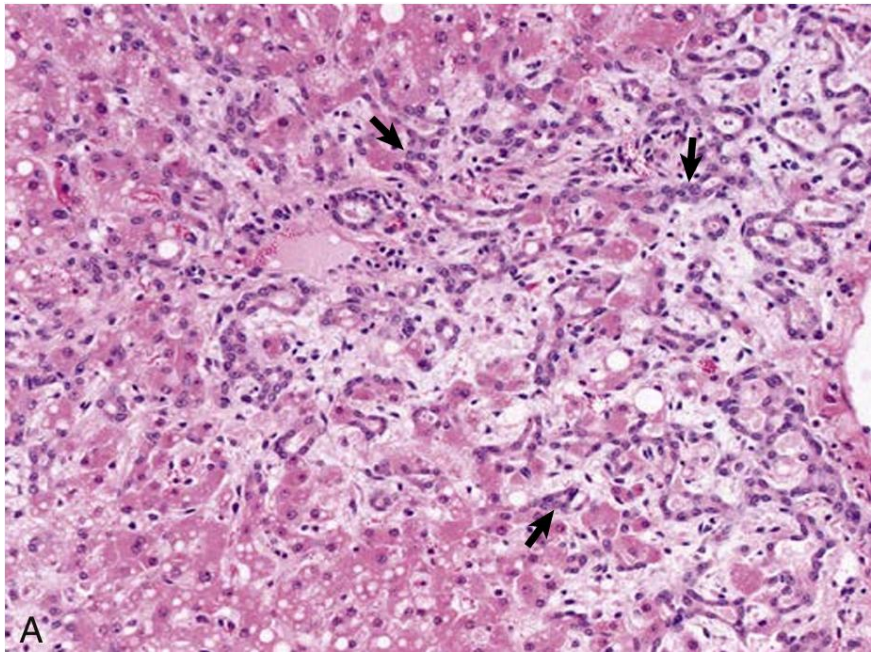
- **Prehepatic**: excessive hemolysis → ↑ unconjugated bilirubin
- **Hepatic**: hepatocellular dysfunction → impaired conjugation & excretion
- **Posthepatic**: biliary obstruction → ↑ conjugated bilirubin
- Different types reflect underlying cause of bilirubin accumulation

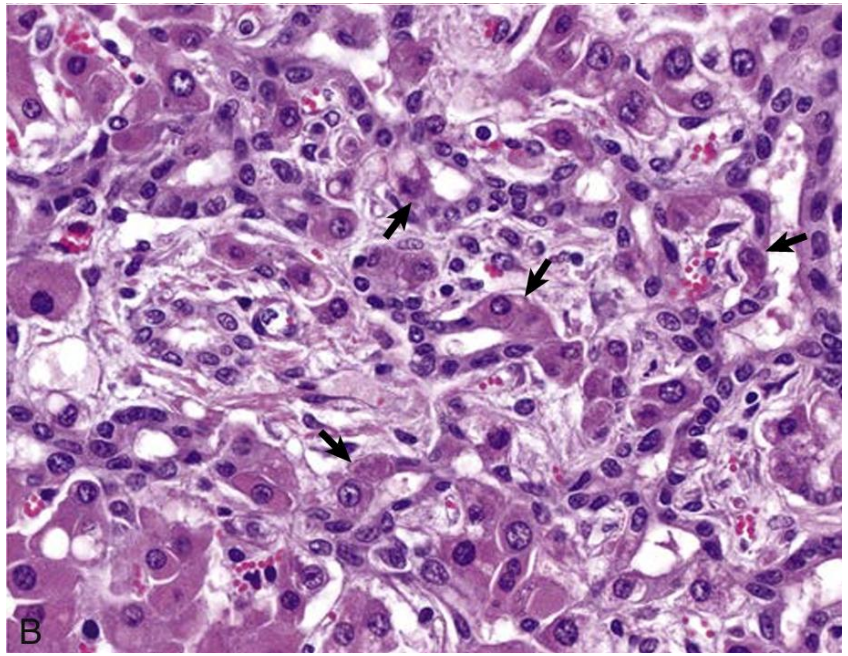
Consequences of Chronic Cholestasis

- Biliary fibrosis and **ductular reaction**
  -Proliferation of bile ductules in response to injury
  -Occurs in periportal areas
  -Seen in cholestatic liver disease, fibrosis, and cirrhosis
  -Involves hepatic progenitor (oval) cells

- Hepatocyte injury due to bile acid toxicity
- Portal-portal bridging fibrosis in prolonged cases
- Can progress to biliary cirrhosis

Ductular reaction (Biliary hyperplasia)

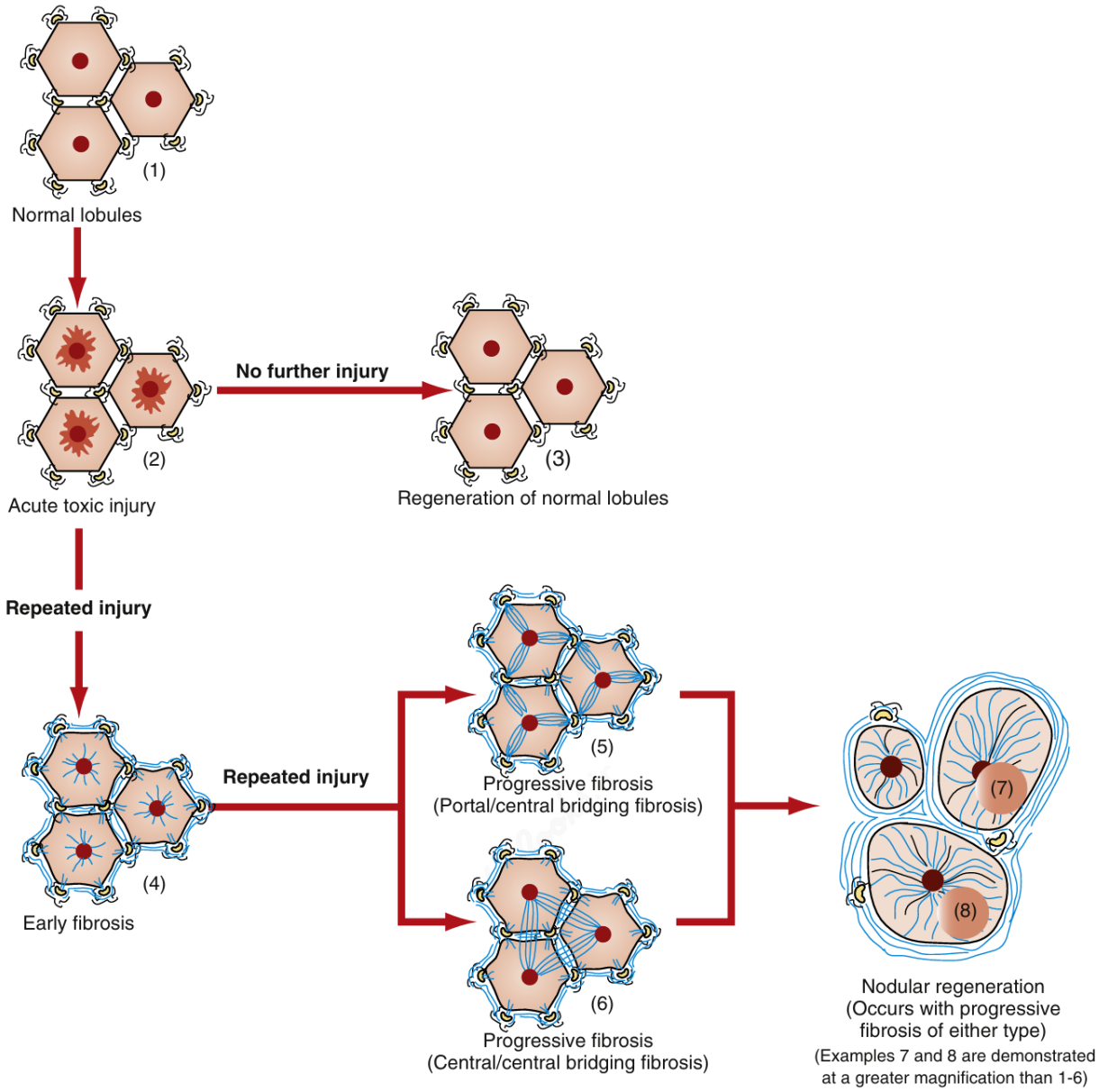




- Small duct-like structures in periportal regions
- Cuboidal epithelium, mitotic activity
- Often embedded in fibrous matrix
- Accompanied by inflammatory infiltrates

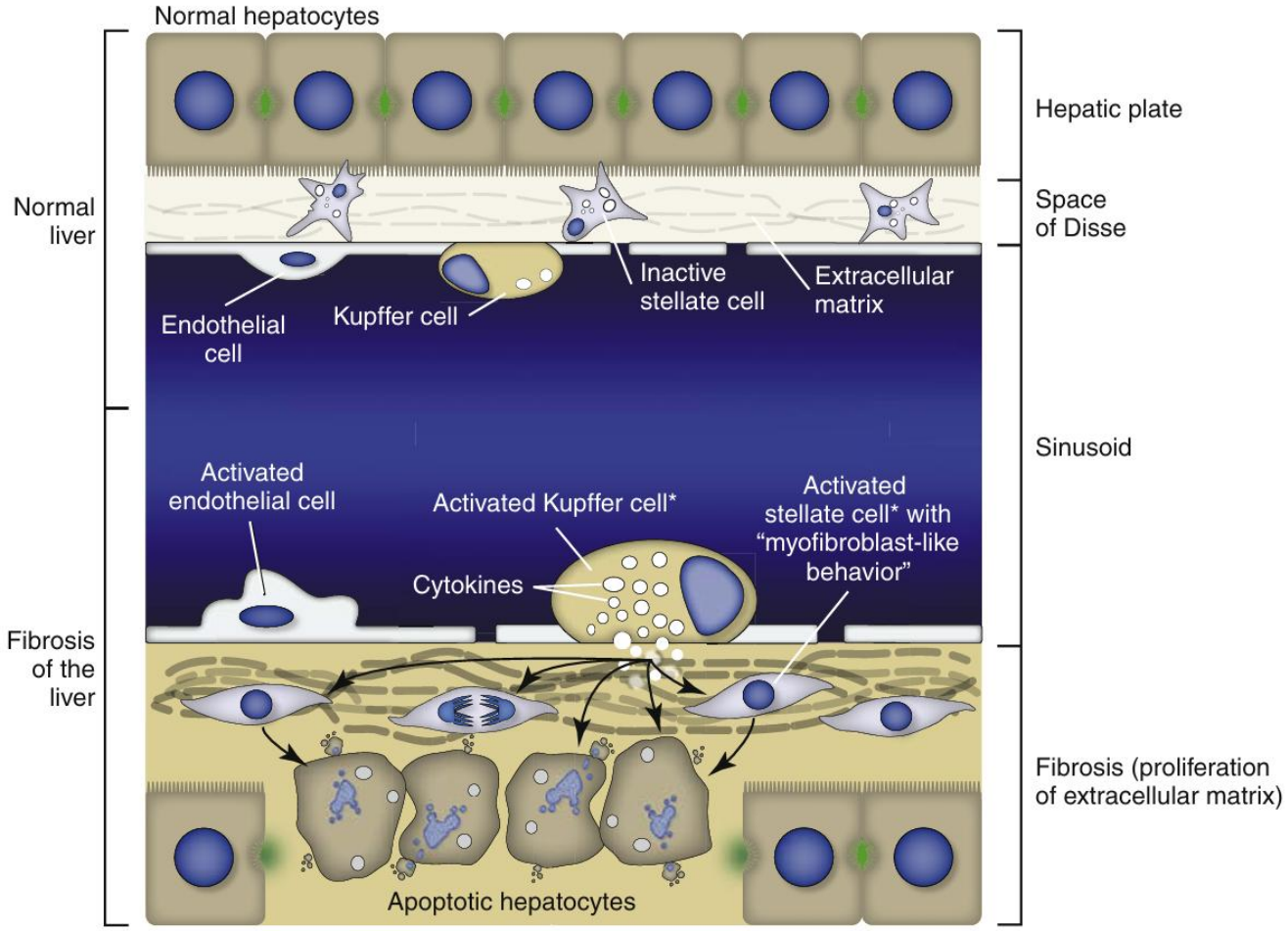
- Hepatic injury → impaired hepatocyte replication → ductule formation of progenitor cells
- Bile duct injury and cholestasis → proliferation of mature biliary epithelium

Fibrosis and Cirrhosis



- Fibrosis: collagen deposition following chronic injury
- Perisinusoidal: common in toxic injury
- Portal and periportal: seen in chronic hepatitis and cholangitis
- Bridging fibrosis: links portal–portal or portal–central areas
- Cirrhosis: end-stage, with nodular regeneration and distortion of architecture

Fibrosis and Cirrhosis



*Activated stellate and Kupffer cells release cytokines that promote: (1) cell dysfunction and death, (2) cell proliferation (PDGF, TNF), (3) cell contraction (ET-1), (4) chemotaxis (MCP-1, PDGF), and (5) fibrogenesis (extracellular matrix proliferation [fibrosis]) (TGF-β).

Pathogenesis

- Activation of hepatic stellate cells → myofibroblast-like phenotype
- Secrete collagen (mainly type I and III)
- Stimulated by TGF-β, PDGF, oxidative stress, endotoxins

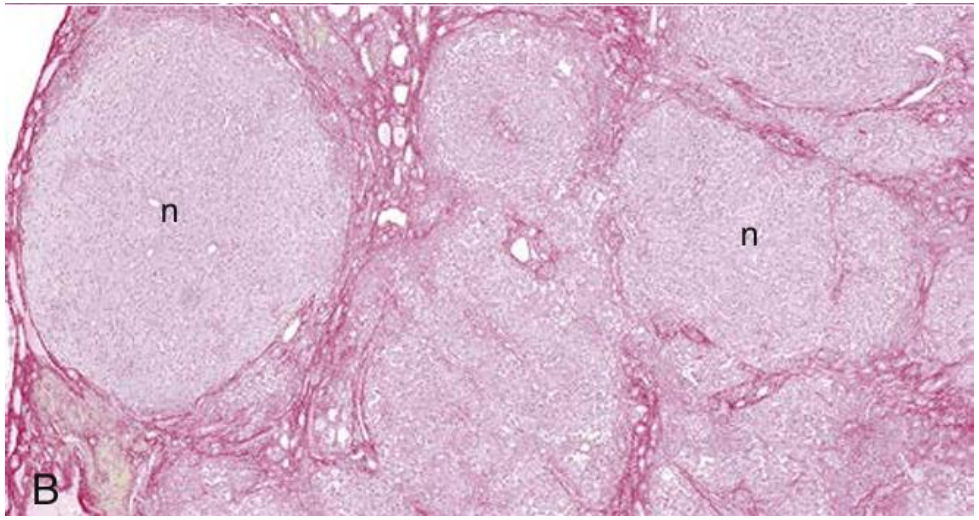
Fibrosis vs Cirrhosis?

: A diffuse process characterized by fibrosis and the conversion of the normal liver architecture into structurally abnormal lobules

WHO, 1977

Clinical Consequences

- Portal hypertension → ascites, shunting
- Impaired liver function → coagulopathy, encephalopathy
- Progression to cirrhosis if persistent injury continues

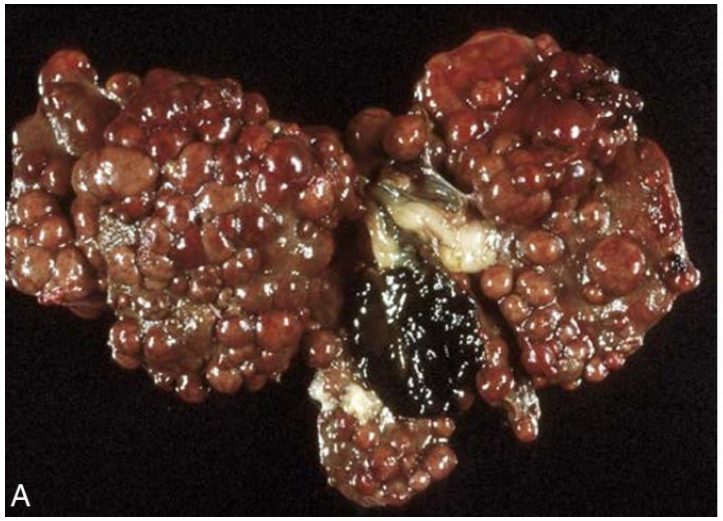


Most common in dogs

Cirrhotic liver w regenerative nodules



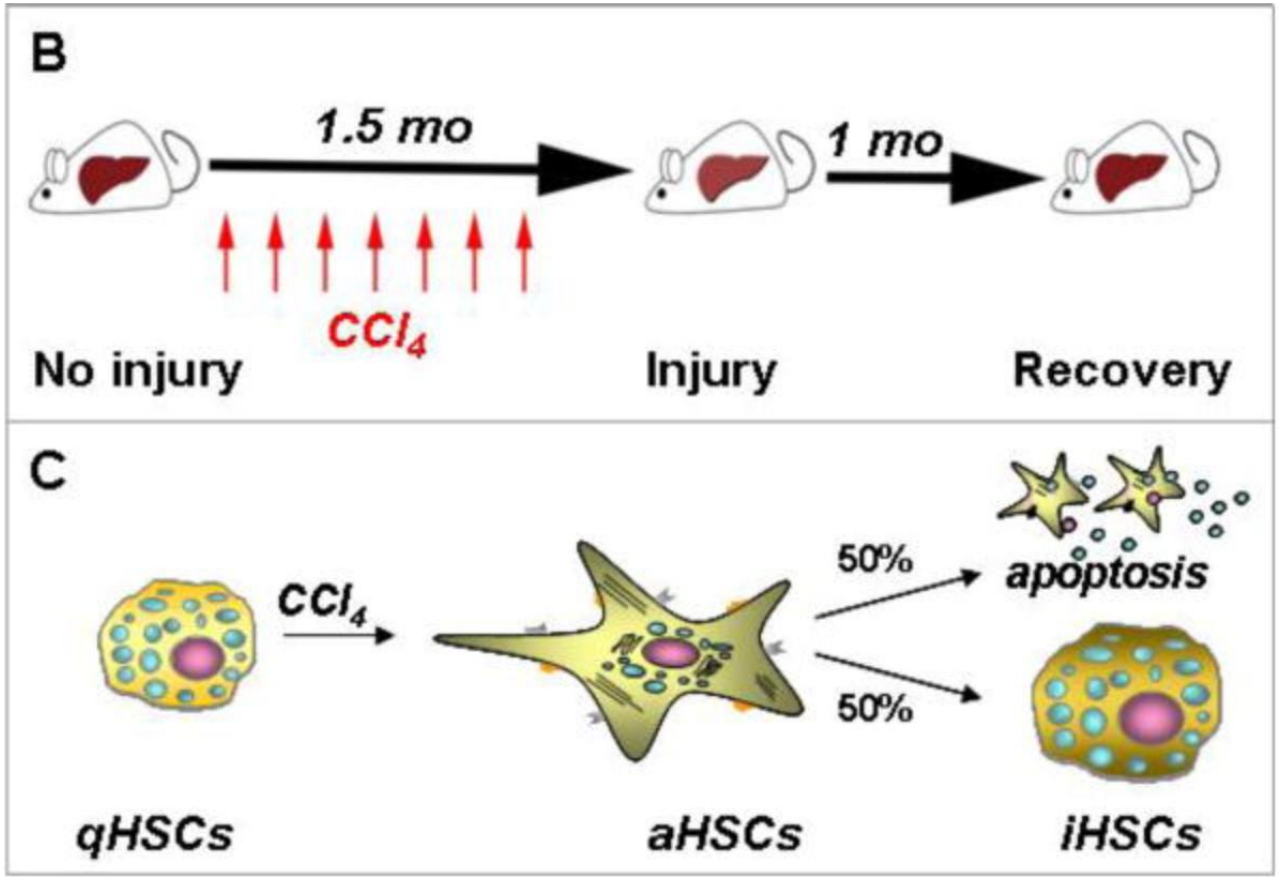
End-stage liver



Long-term phenobarbital-treated dog

Reversibility and Fibrosis Resolution

- Early-stage fibrosis can regress if the insult is removed
- Involves apoptosis of activated stellate cells
- Matrix metalloproteinases (MMPs) degrade ECM
- Clinical interventions aim to halt or reverse fibrogenesis



Reversibility of Liver Fibrosis and Inactivation of Fibrogenic Myofibroblasts, 2014

Liver failure_Overview

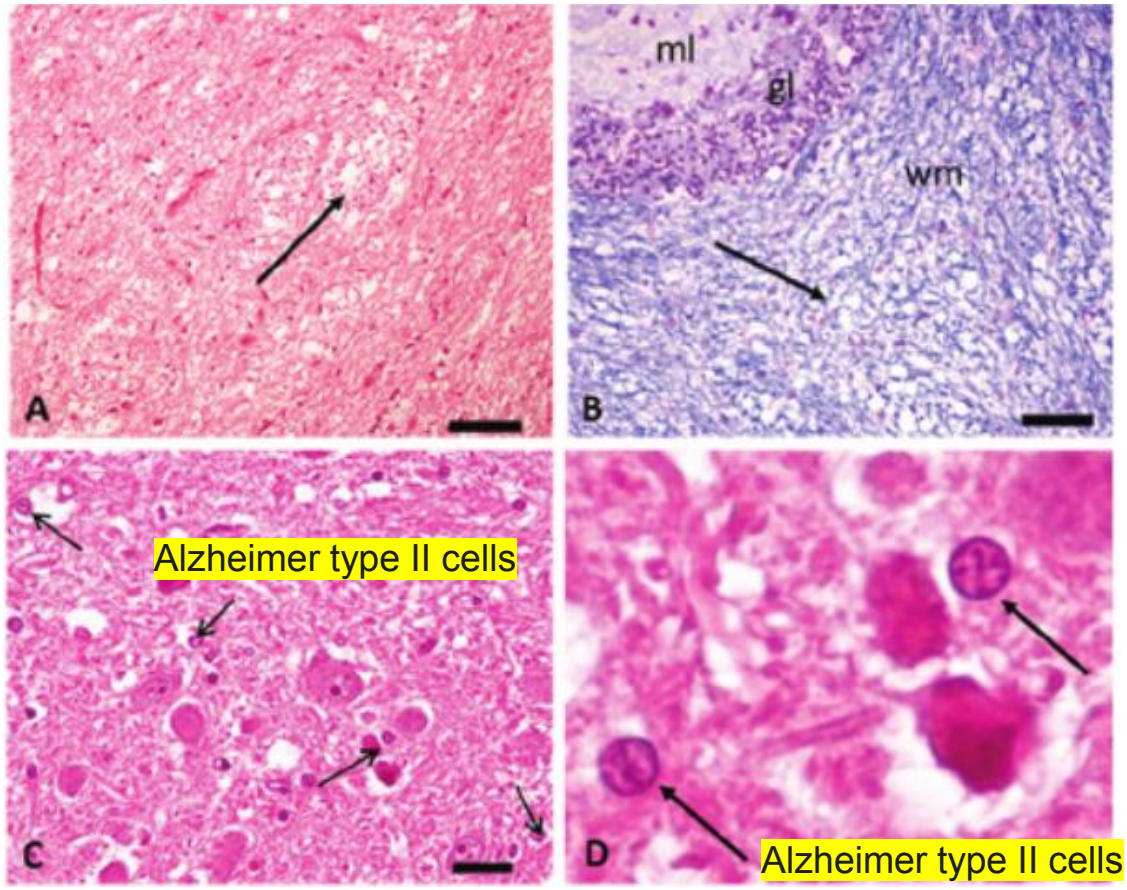
- Hepatic failure = loss of 70–80% of functional liver mass
- Results from acute massive necrosis or chronic progressive disease
- Can be fulminant or slowly progressive
- Clinical signs reflect multisystem involvement

E-Box 8.1 Consequences of Hepatic Failure

- Hepatic encephalopathy
- Coagulopathy (bleeding tendencies)
- Albuminemia
- Vascular and hemodynamic alterations (e.g., acquired portosystemic shunts)
- Edema, ascites (secondary to hypoalbuminemia and/or portal hypertension)
- Hepatocutaneous syndrome
- Photosensitization
- Immunologic manifestations (e.g., endotoxemia)
- Hypoglycemia
- Icterus (hyperbilirubinemia)
- Polyuria/polydipsia

Hepatic Encephalopathy

- Liver failure or shunt bypasses detoxification→ Toxins (esp. ammonia) from intestinal metabolism enter systemic circulation
- Ammonia crosses the blood-brain barrier→ Converted to glutamine in astrocytes → osmotic imbalance and swelling (astrocyte dysfunction and edema)
- Neurotransmission is altered
  -Imbalance in GABAergic and glutamatergic activity
  -Increased production of false neurotransmitters (e.g., octopamine)
- Cerebral edema
  -Mainly from increased intracellular glutamine, especially in acute fulminant liver failure

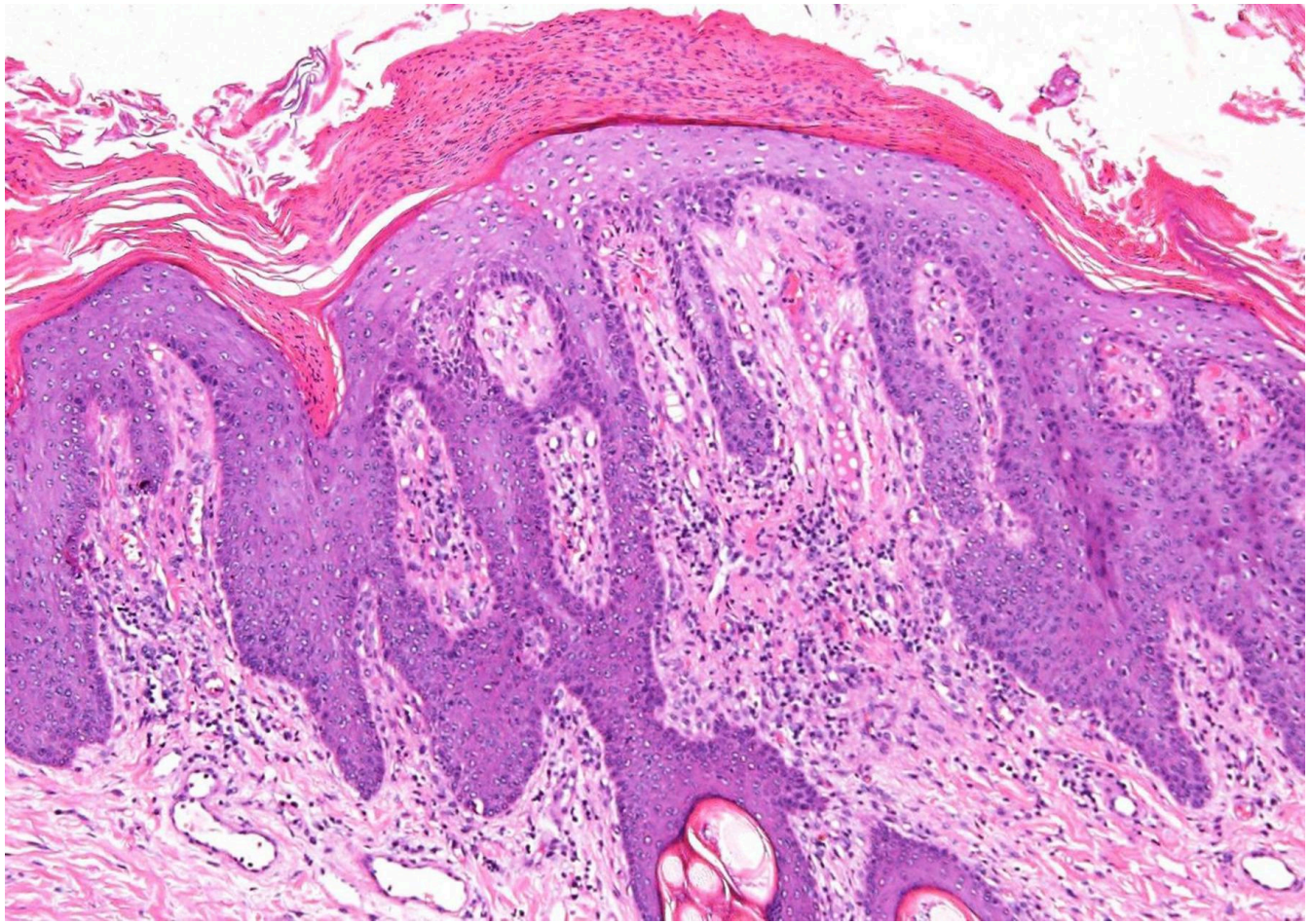


Hepatocutaneous syndrome

- Also known as superficial necrolytic dermatitis (SND)
- Impaired hepatic metabolism → ↓ amino acid synthesis, storage
- Inadequate supply for keratinocyte health
- Contributes to epidermal necrosis and poor skin barrier
- Parakeratosis, epidermal necrosis, and crusting
- Affects footpads, face, perianal skin, pressure points
- Histology: 'red, white, and blue' pattern
  - Red: hyperkeratosis
  - White: edema/spongiosis
  - Blue: basal layer hyperplasia



Hepatocutaneous syndrome



Hepatocutaneous syndrome in a Maltese, diagnosis, treatment and the value of CT in the diagnosis, 2019

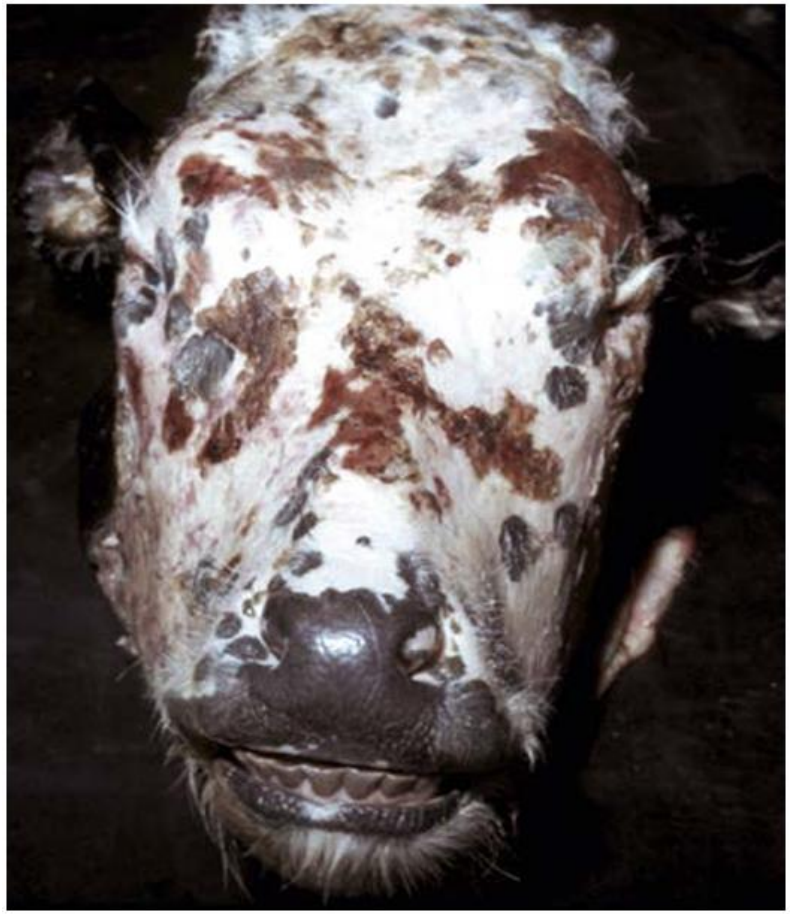
의뢰하신 우측 발바닥 조직에 대하여 각각 2단면을 내어 병리조직학적 검사를 한 결과, 표피의 뚜렷한 **과증식, 과각화 소견을 동반한 발바닥의 피부염** 소견이 관찰되었습니다.
발바닥에서 뚜렷한 과각화를 동반한 피부염은 다소 다양한 원인들에 의하여 나타날 수 있습니다. **만성적인 외부 자극/마찰이나 감염**에 의한 피부염이 있을 때, 2차적으로 과각화를 동반한 피부염이 나타날 수 있습니다. 한편, 1) **zinc-responsive dermatoses**, 2) **pemphigus foliaceus**, 3) **lupus erythematosus**, 4) **canine distemper**, 5) **superficial necrotizing dermatitis (hepatocutaneous syndrome)** 질환이 있을 시에도 발바닥의 뚜렷한 과각화 소견을 동반한 피부염이 관찰될 수 있는데, 이러한 질환들의 경우 일반적으로 과각화 소견과 더불어 해당 질환과 연관된 다른 병리조직학적 소견을 동반하게 됩니다.
발바닥의 과각화 소견은 Irish terrier 품종에서 유전적 소인에 의하여 나타날 수도 있거나, 많은 품종의 개에서 노령성 변화로 관찰될 수도 있다고 알려져 있습니다.

Photosensitization

- Primary Photosensitization
  -Occurs after ingestion of plants or drugs containing photodynamic compounds (e.g., St. John's Wort, phenothiazines)
  -The liver is not involved.

- **Hepatogenous (Secondary) Photosensitization**
  -Most common form in cattle.
  -Caused by liver damage that prevents excretion of phylloerythrin (a chlorophyll breakdown product)
  -Phylloerythrin accumulates in the blood and skin, becoming phototoxic

- Congenital Photosensitization
  -Due to inherited disorders of heme synthesis (e.g., porphyria)
  -Rare in cattle



Aging Changes in the Liver

- Mild hepatocellular atrophy and lipofuscin accumulation
- **Nodular hyperplasia** is common in older animals (esp. **dogs**)
- Reduced hepatic blood flow and regenerative capacity
- Clinical relevance is typically low unless compounded by disease

Hepatic nodular hyperplasia의 정확한 발병 원인은 알려져 있지 않으나, 주로 **노령성 병변**으로 여겨지며 특별한 **임상증상을 유발하지 않아** incidental finding으로 관찰되는 경우가 많다고 합니다. Nodular hyperplasia 병소 내부의 간세포는 종종 심한 공포화 소견을 보일 수 있는데, 본 예에서도 종괴 내부 간세포가 전반적으로 심하게 공포화 되어 있었으며, 이로 인하여 육안 상 pale한 노란색조로 관찰되었을 것이라 사료됩니다.
의뢰하신 간 조직에서 종양성 병변은 관찰되지 않았습니다. **다만 본 소견이 실제 병변에 대한 일부라면, 대표성에 대한 고찰도 필요할 것으로 사료됩니다.**

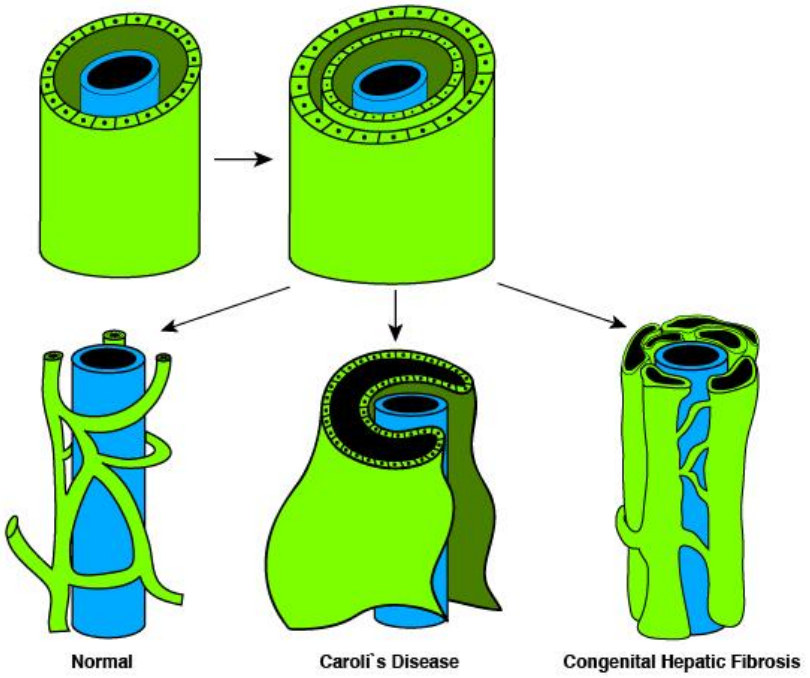
Developmental and Congenital Anomalies

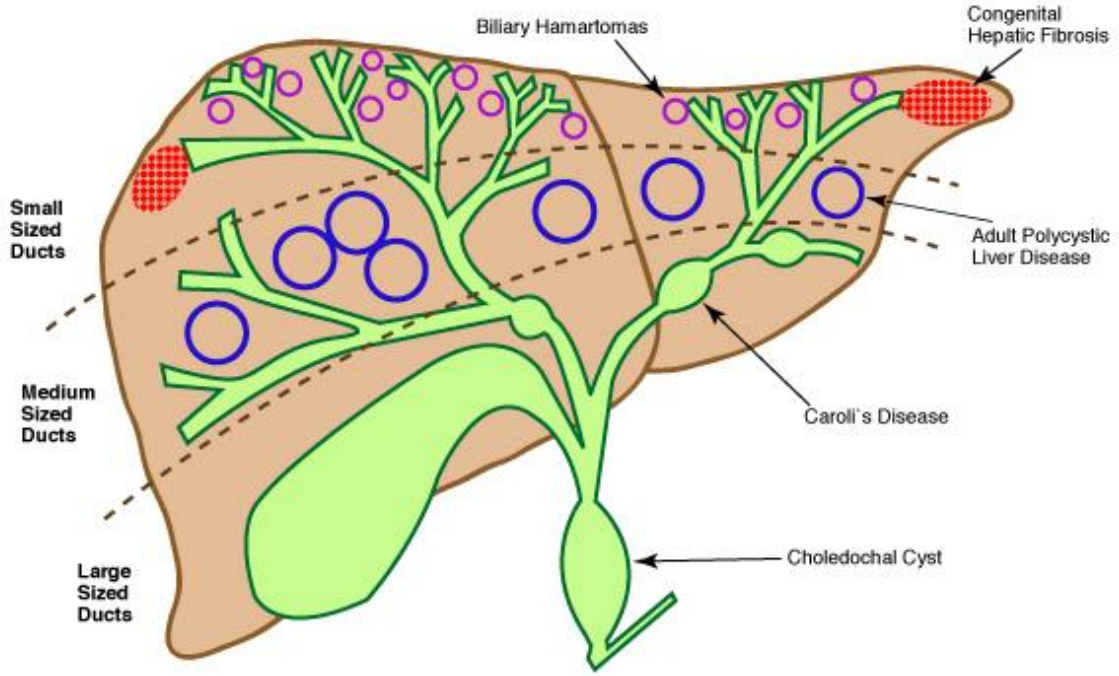
Portosystemic shunts: congenital or acquired

- Abnormal connection between portal and systemic circulation
- Extrahepatic (e.g. toy breeds) or intrahepatic (e.g. large breeds)
- Leads to hepatic atrophy, neurologic signs (hepatic encephalopathy)
- Small or absent portal veins histologically

Ductal Plate Malformations

- Disruption of embryonic bile duct remodeling
- Persistent embryonic ductal plates form fibrous bands
- Seen in congenital hepatic fibrosis and Caroli disease
- Can result in portal fibrosis and abnormal bile duct profiles

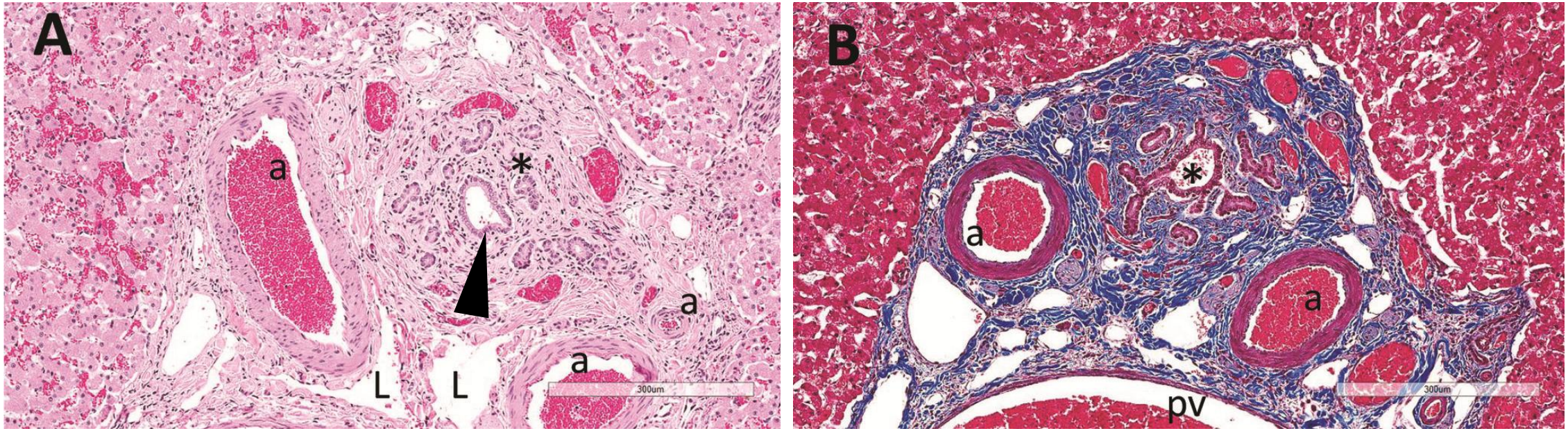




https://epos.myesr.org/poster/esr/ecr2015/C-0722/background

Congenital Hepatic Fibrosis

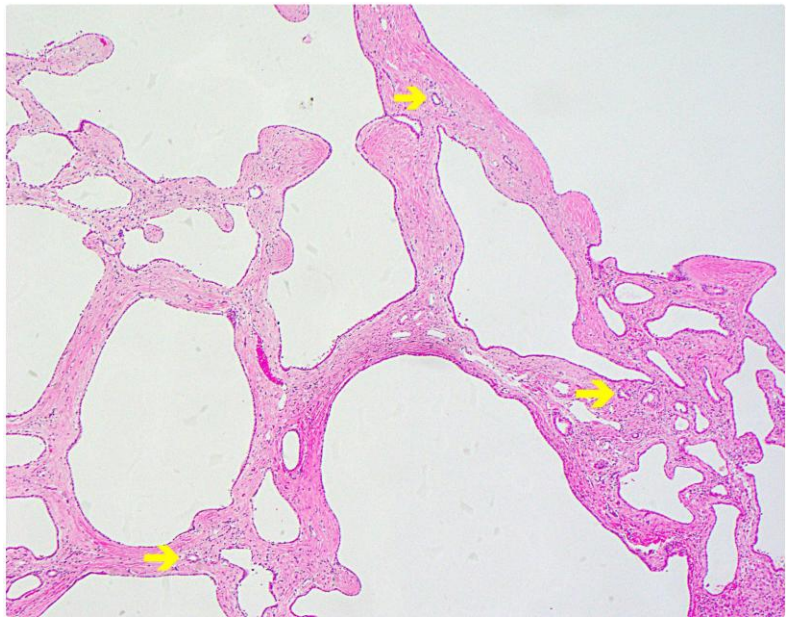
- Due to ductal plate malformation
- Portal-to-portal bridging fibrosis with bile duct proliferation
- Liver function may be preserved despite fibrosis
- Seen in multiple species including humans and dogs

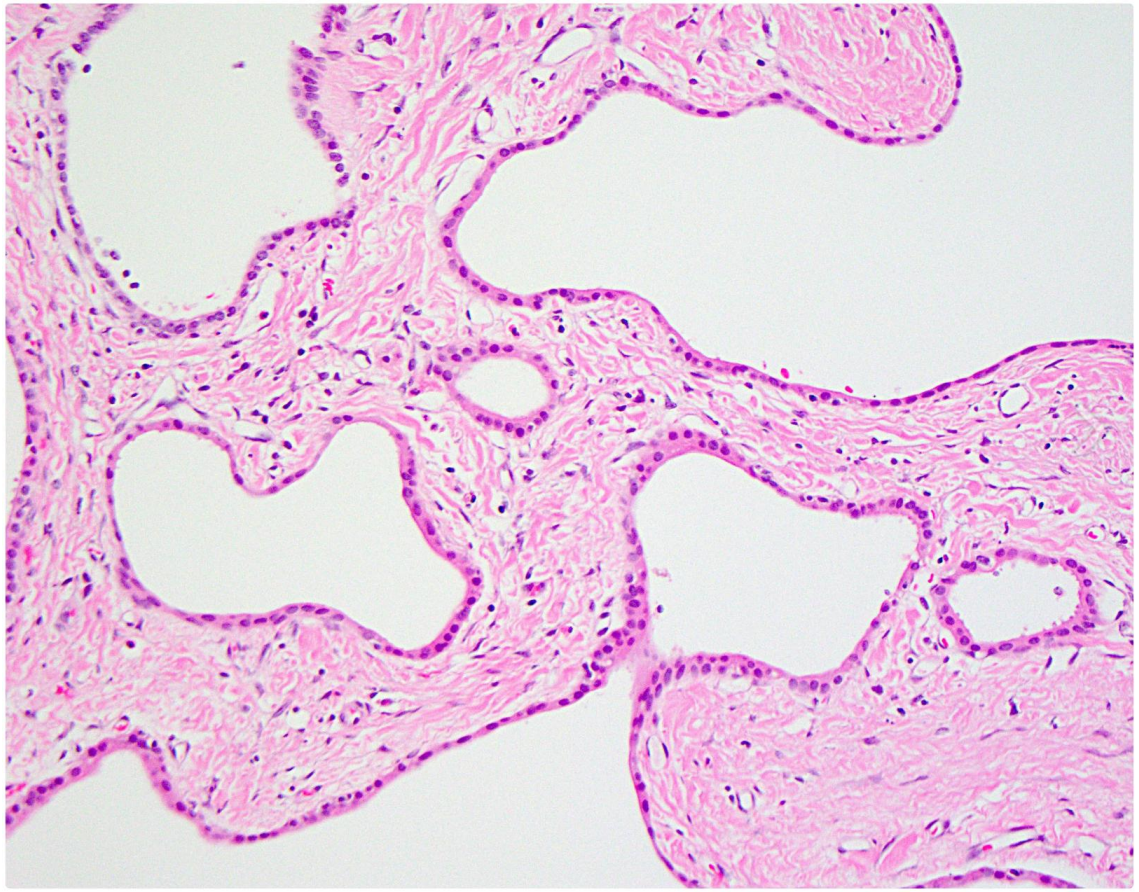


Relationships between congenital peritoneopericardial diaphragmatic hernia or congenital central diaphragmatic hernia and ductal plate malformations in dogs and cats, JAVMA 2021

Polycystic Liver Disease

- Inherited condition with numerous liver cysts
- Often associated with polycystic kidney disease (PKD)
- Seen in Persian cats, Cairn Terriers, others
- Cysts lined by biliary-type epithelium





https://www.pathologyoutlines.com/topic/liverpolycysticliverdisease.html

Biliary Atresia

- Failure of bile ducts to form or remain patent
- Progressive cholestasis, fibrosis, and cirrhosis
- A rare but severe cause of neonatal liver failure

Portals of Entry into the Liver and Biliary System

- Hematogenous spread: via portal vein (most common) or hepatic artery

  c.f. left liver lobe of sheep: severely affected by mycotoxin sporidesmin

- Retrograde biliary infection: bacteria ascending from intestine
- Direct extension: from adjacent organs (e.g., peritonitis, pancreatitis)
- Penetrating wounds or parasitic migration (e.g., traumatic reticuloperitonitis or foreign bodies in the reticulum)

Pathways of Spread Within the Liver

- Sinusoidal spread (via blood flow)
- Biliary canaliculi and ducts
- Parenchymal spread through contiguous hepatocyte necrosis
- Lymphatic and transcoelomic extension (e.g., peritoneal dissemination)

Hepatic and Biliary Defense Mechanisms

- Kupffer cells: phagocytosis of pathogens in sinusoidal blood
- Bile: detergent action flushes microbes from ducts
- Biliary epithelium: tight junctions and innate immune signaling
- Dual blood supply: portal and arterial circulation

Cellular and Molecular Barriers

- Hepatocytes: express PRRs (pattern recognition receptors)

  -Recognition: Yes (TNF-a, IL-6, MCP-1, activate immune response), **Phagocytosis: No**

- Stellate cells: modulate inflammation and fibrosis
- Cholangiocytes: produce antimicrobial peptides
- Cytokines and chemokines recruit immune cells

Multispecies Hepatic Infectious Diseases

• Leptospirosis: dogs, cattle, pigs → icterus, hepatitis

-Begins as vascular leptospirosis that extends into the kidney, liver, lungs, cardiovascular system, etc.

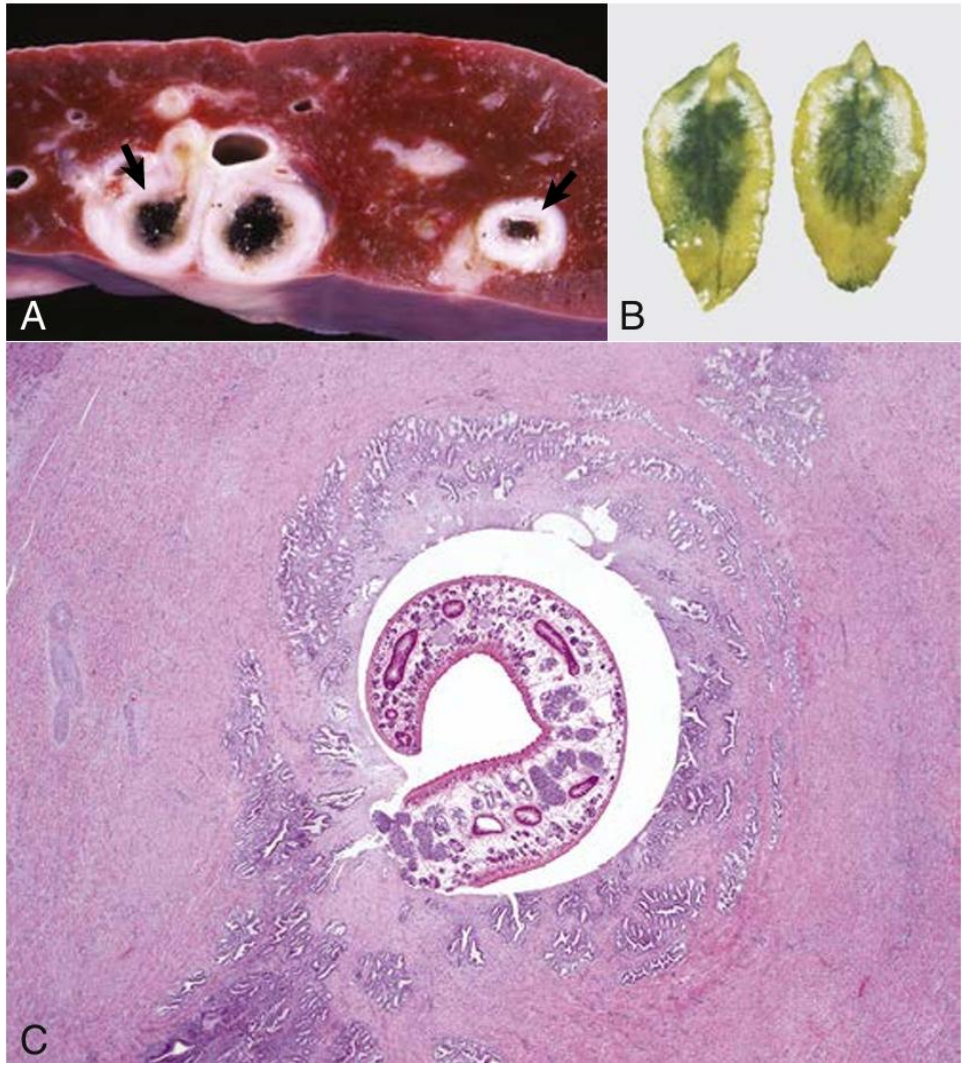
-Discrete and coalescing white-to gray foci of hepatic necrosis at random



https://davisthompsonfoundation.org/image-detail/

Multispecies Hepatic Infectious Diseases

- Fasciola hepatica: parasitic cholangitis and fibrosis
- Trematode (liver fluke) infecting cattle, sheep, goats, and other ruminants
- Life cycle involves aquatic snails as intermediate hosts
- Transmission via ingestion of metacercariae on contaminated vegetation



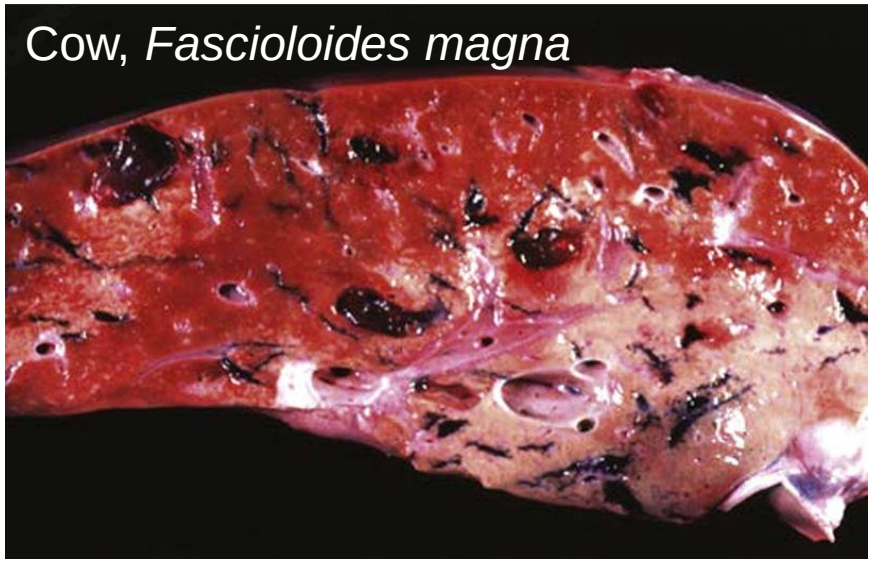
Fasciola hepatica: Pathogenesis

Acute phase

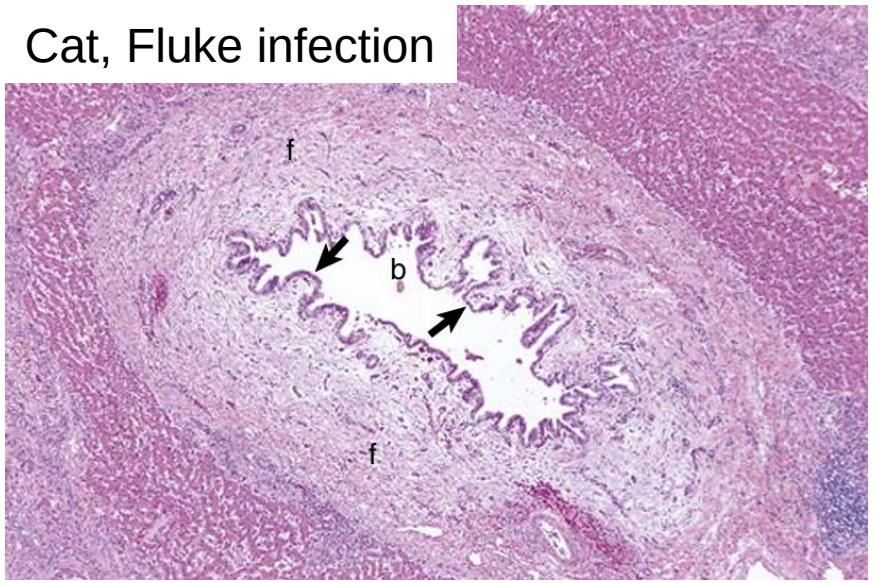
- Immature flukes migrate from intestines → liver capsule → parenchyma
- Extensive necrosis, hemorrhage, fibrin, and perihepatic adhesions
- In severe cases, hepatic rupture and sudden death (esp. in sheep)

Chronic phase

- Adult flukes reside in bile ducts
- Causes biliary hyperplasia, cholangitis, and periductal fibrosis
- Chronic cholestasis, weight loss, and poor productivity



Cat, Fluke infection



Fasciola hepatica: Complications and Co-infections

- **Bacillary Hemoglobinuria**: Clostridium haemolyticum toxin activation in necrotic liver
- **Synergy with Clostridial diseases in ruminants**
- Risk of hepatic abscessation

Multispecies Hepatic Infectious Diseases

• Clostridium hemolyticum: Bacillary hemoglobinuria in ruminants, **high mortality (within 1-2 days)**

-aka “Red water disease”

-lacks hemoglobinuria

-local hepatic necrosis induced by alpha toxin at the early stage

-Spore ingestion → small intestine → M cells/macrophages → portal vein → liver → **liver injury by flukes** → hepatic necrosis → local hypoxia → proliferation of vegetative form → toxin production

-Intravascular hemolysis (hemoglobinuria)

-hepatic necrosis (coagulative necrosis)

-endothelial damage (vasculitis)





Multispecies Hepatic Infectious Diseases

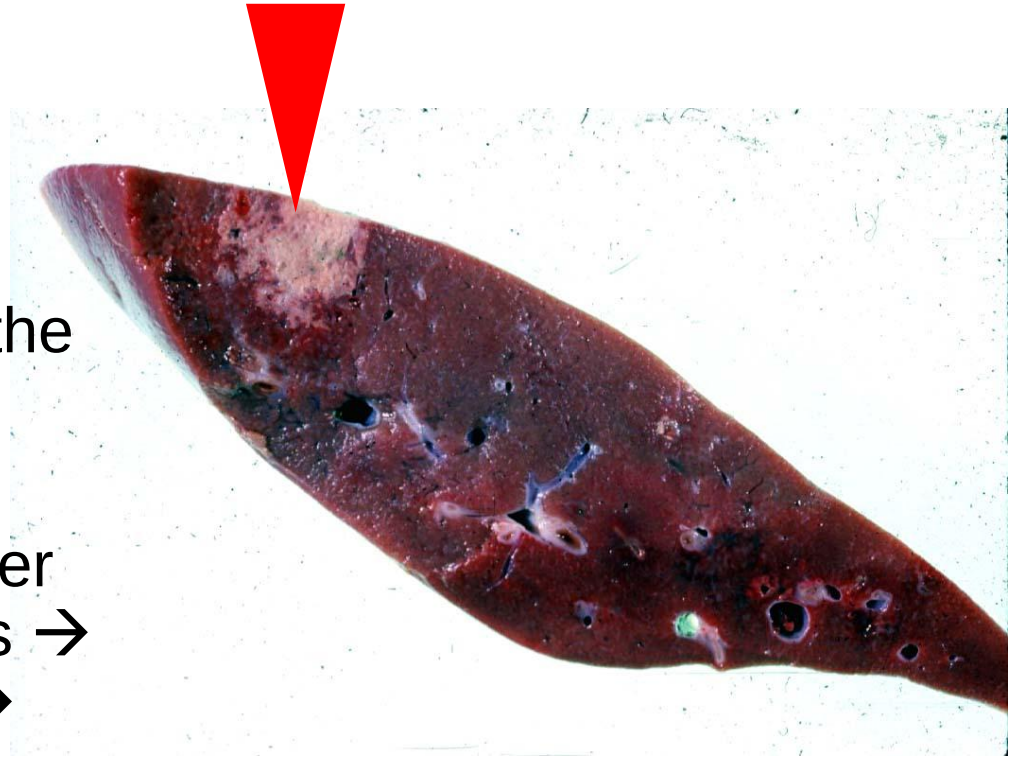
- Clostridium novyi: infectious necrotic hepatitis in ruminants (Cattle > sheep and deer)

  -aka “Black disease”

  -lacks hemoglobinuria

  -local hepatic necrosis induced by alpha toxin at the early stage

  -Ingestion → small intestine → enterocytes/M cells/macrophages → portal vein → liver → Kupffer cells → **liver injury by flukes** → hepatic necrosis → local hypoxia → proliferation of vegetative form → toxin production → hepatic necrosis



Infectious Canine Hepatitis: Overview

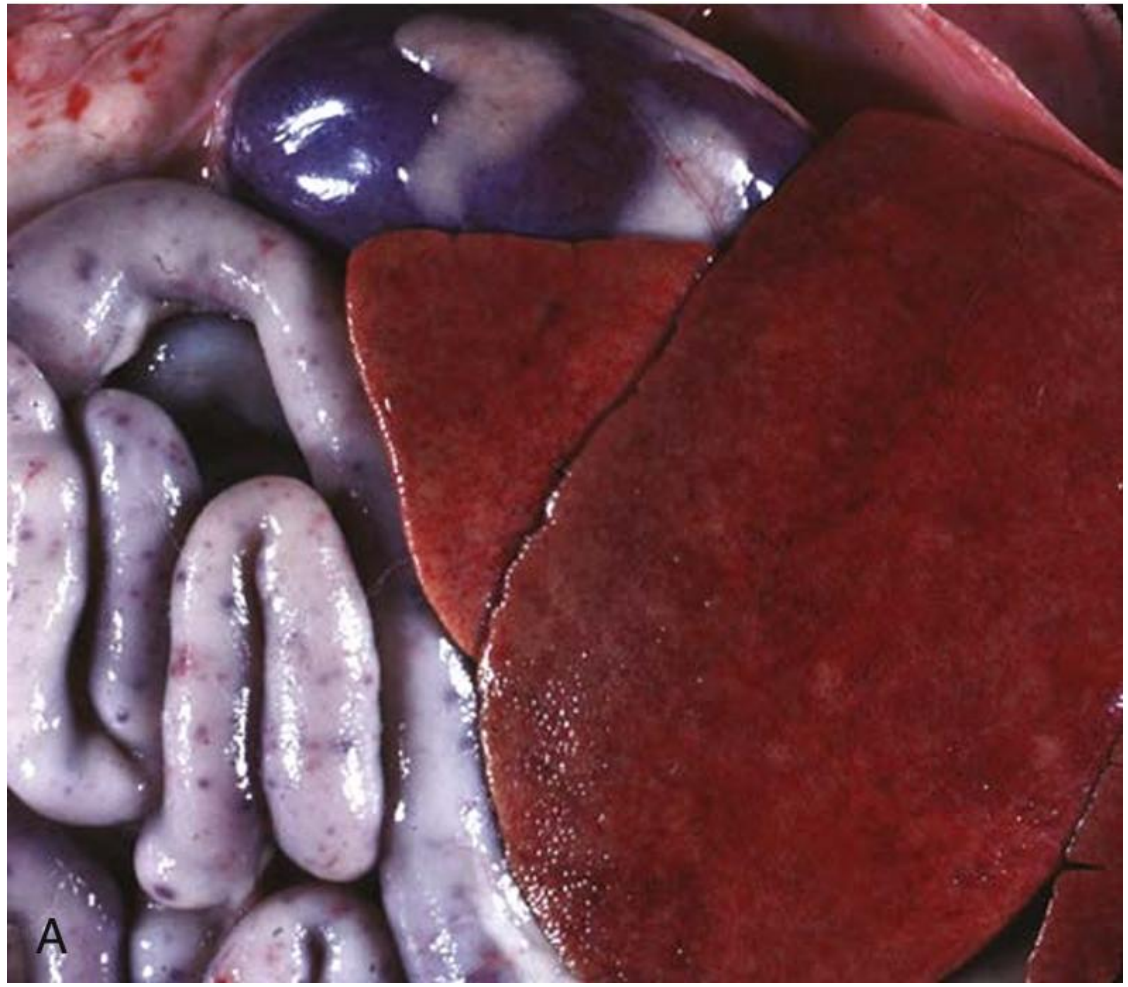
- Caused by Canine Adenovirus Type 1 (CAV-1)
- Affects liver, kidneys, eyes, and vascular endothelium
- Highly contagious viral disease of dogs and wild canids
- Transmission via urine, feces, and saliva
- Virus enters via oronasal route and replicates in tonsils

Pathogenesis

- Viremia follows initial replication in lymphoid tissues
- Virus targets hepatocytes and endothelial cells
- Hepatic necrosis and widespread vasculitis
- Localizes in kidneys and eyes

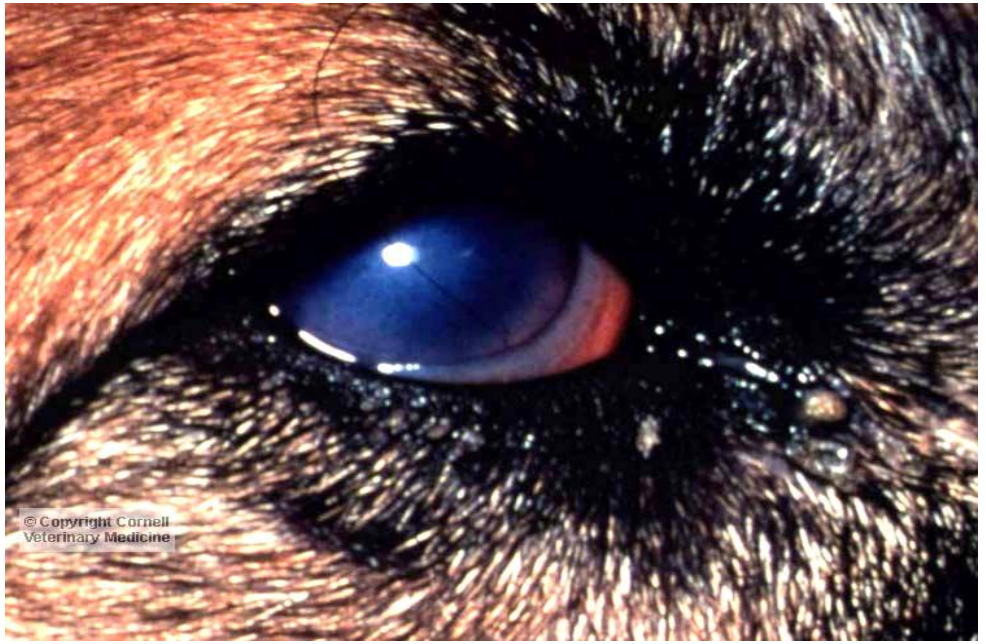
Infectious Canine Hepatitis: Clinical signs

- Asymptomatic, usually not fatal (particularly > 2yo)
- Fever, vomiting, abdominal pain
- Icterus (not severe), hepatomegaly
- Conjunctivitis, serous discharge from the eyes and nose, leukopenia, DIC
- Petechiae or ecchymoses due to DIC
- Death can occur peracutely in severe cases



Infectious Canine Hepatitis: Clinical signs

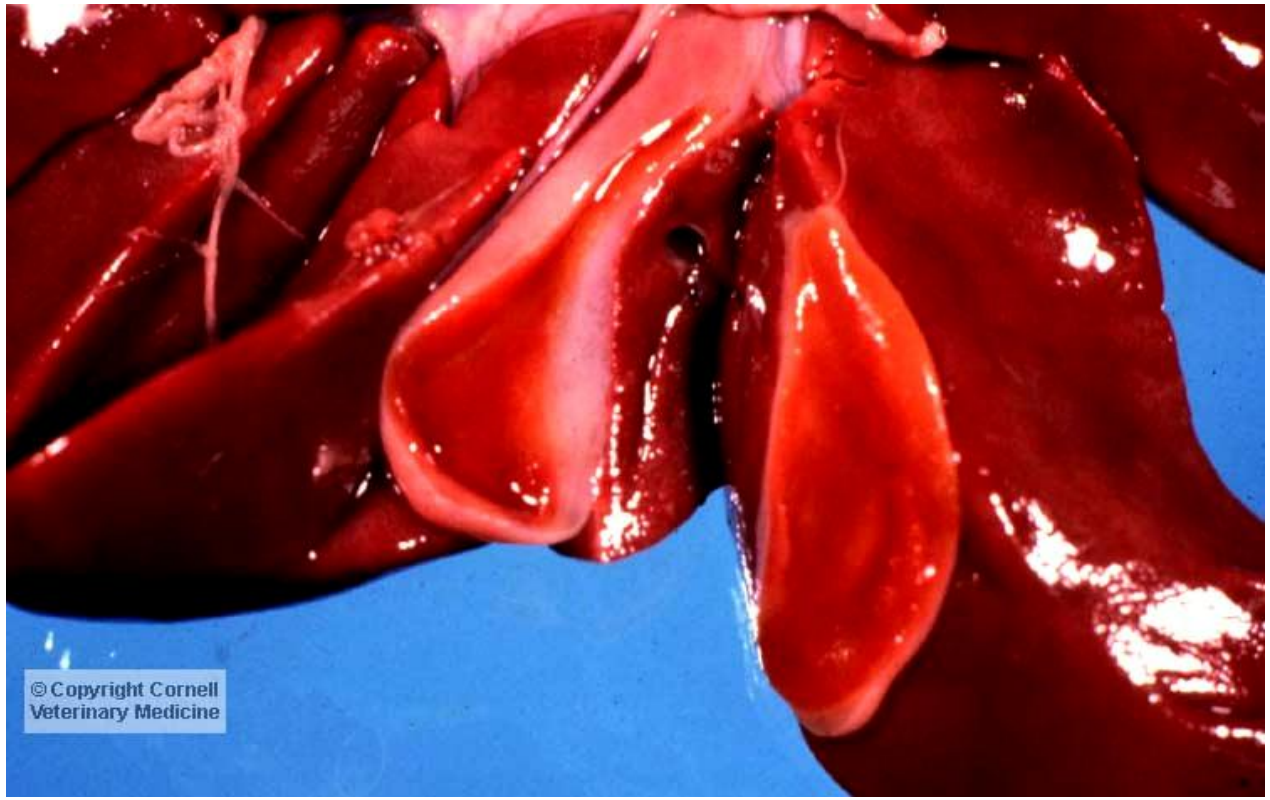
- 'Blue eye': corneal edema due to immune complex deposition
- Corneal opacity (edema)
- At recovery stage: 7-10 days after infection
- Immune complex uveitis → arthus type hypersensitivity → degeneration of corneal endothelium → **corneal edema** → blue eyes
- Viruses can be shed in urine for months
- Chronic nephritis and proteinuria possible



Dog, young. Eye, cornea. **Acute corneal edema.** Diffuse cloudiness

Infectious Canine Hepatitis: Gross

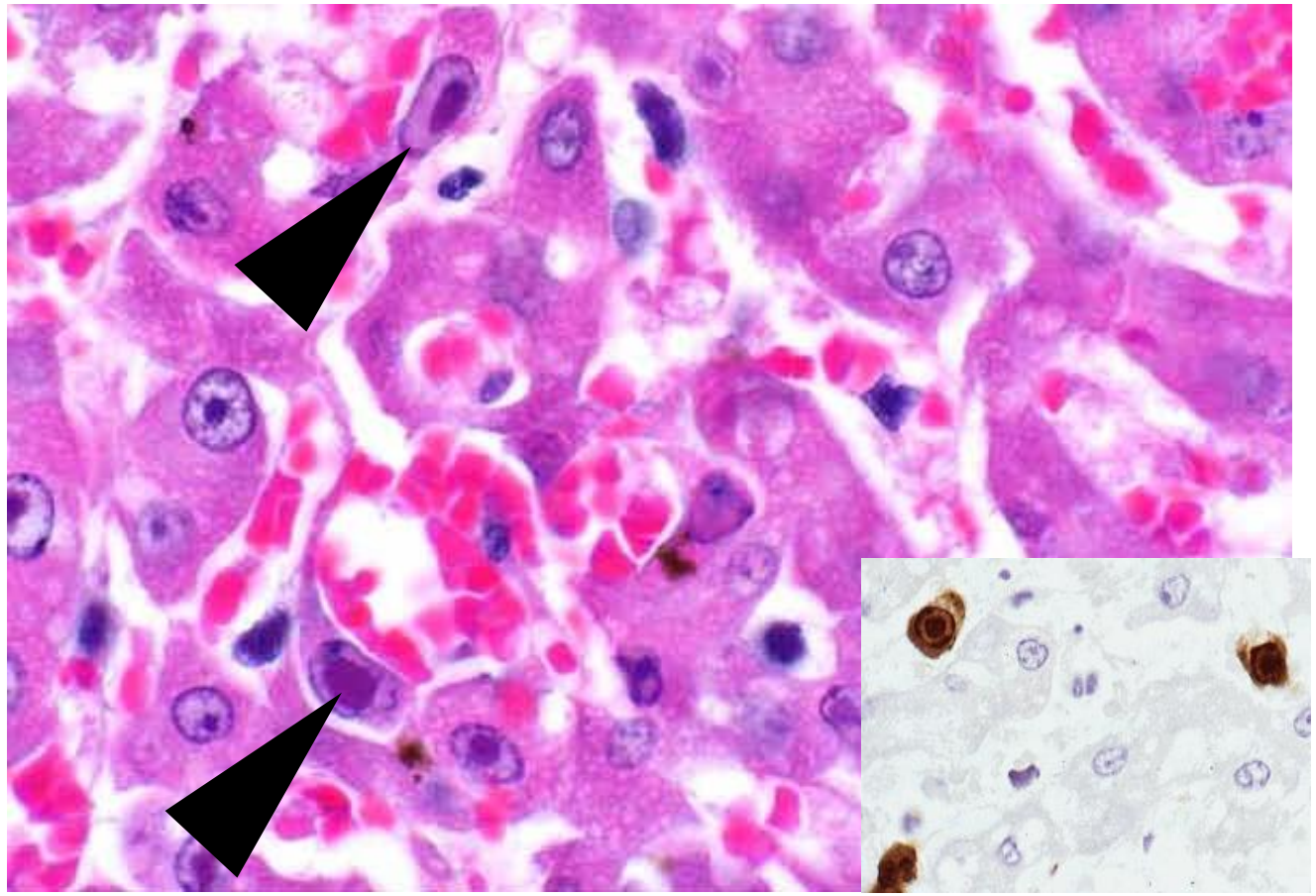
- Hemorrhages (petechia) in various organs and tissues (serosa, stomach)
- Enlargement of liver with fibrin strand, multiple pale necrotic foci
- Clear fluid in body cavities,
- Edema of gallbladder, cornea opacity



Dog, adult. **Severe diffuse edema of the gall bladder wall. Infectious canine hepatitis.** Thickened with edema.

Infectious Canine Hepatitis: Microscopic

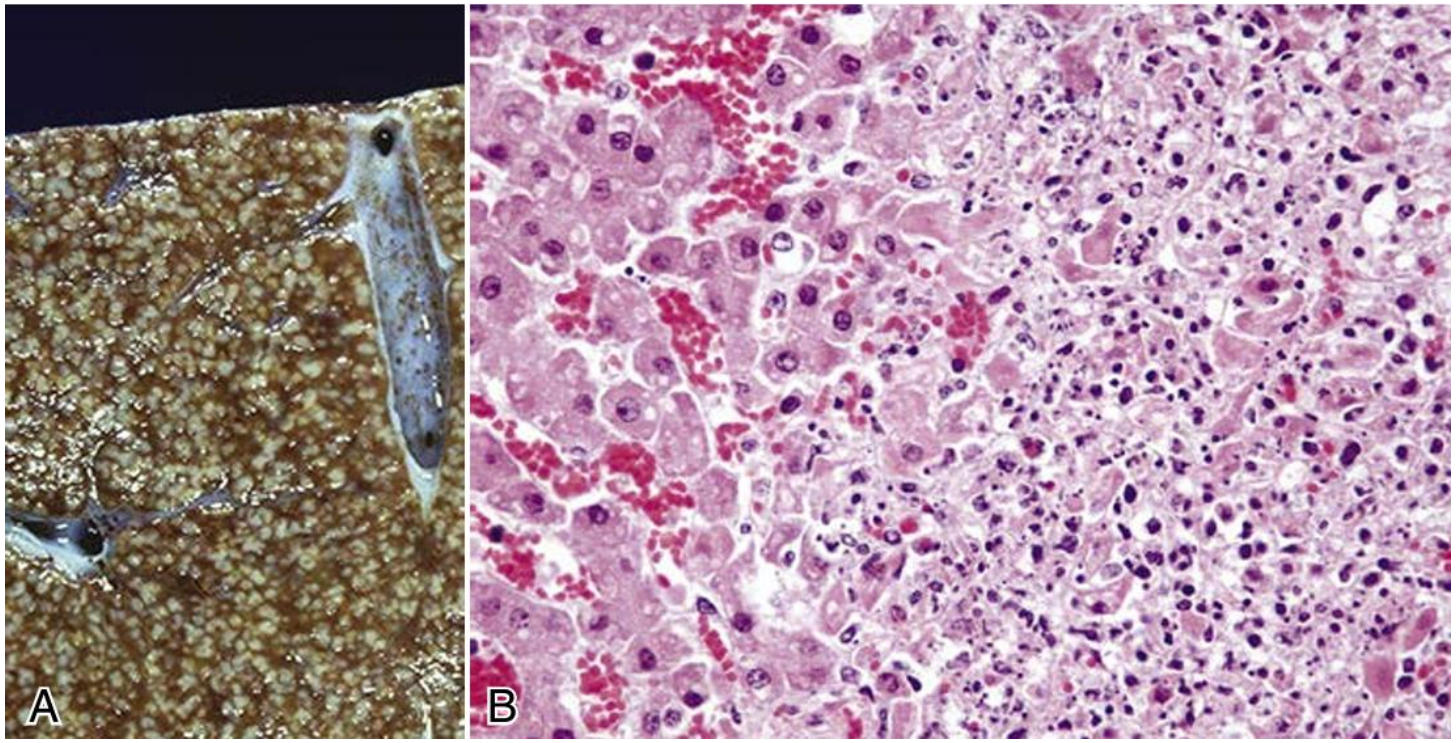
- Focal liver necrosis
  - Random necrosis or
  - Widespread centrilobular necrosis
- Ischemic necrosis (not due to virus)
- Large amphophilic intranuclear inclusions
  - in hepatocytes, Kupffer cells, and endothelial cells



ICH, liver, focal necrosis & amphophilic viral IB

Tyzzer’s disease

- Caused by *Clostridium piliforme*
- Gram-negative, spore-forming, <u>obligate intracellular bacterium</u>
- Affects young, immunocompromised animals (especially foals)
- • Sudden death, anorexia, diarrhea, icterus

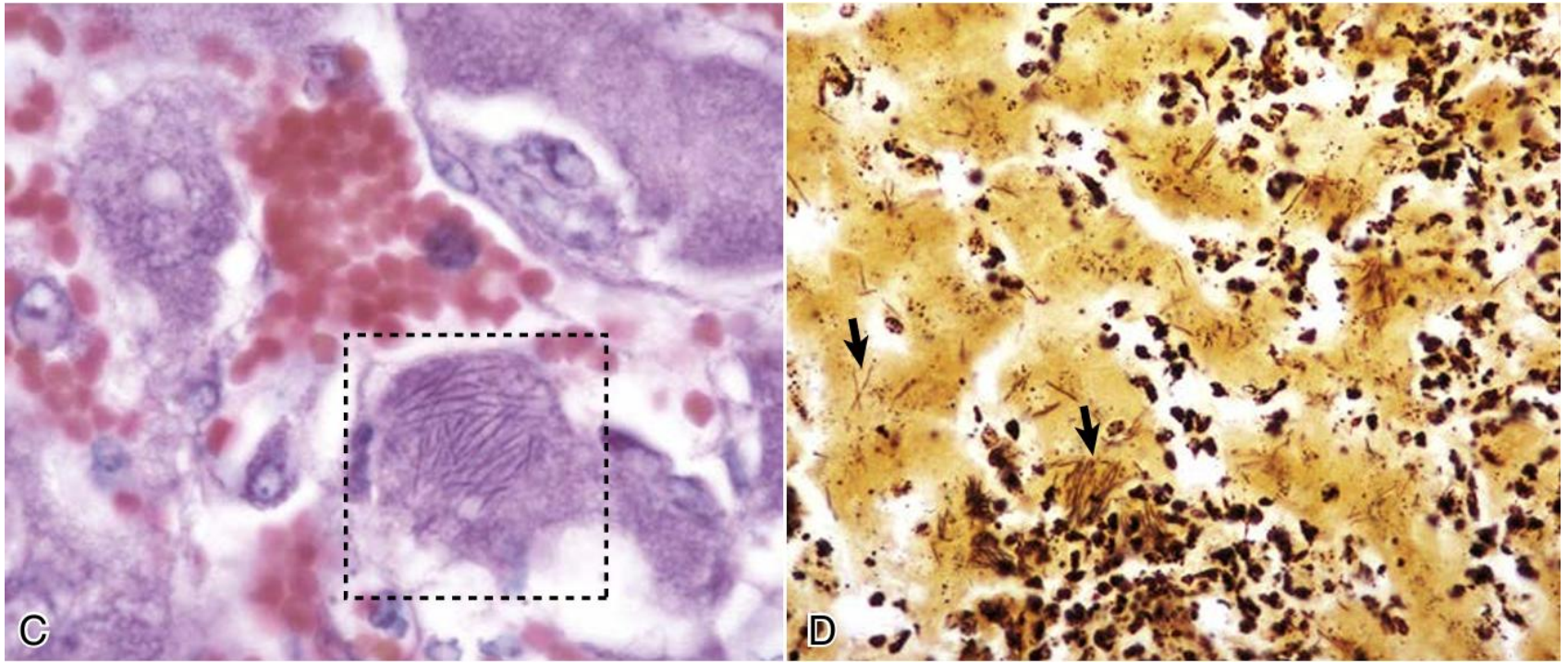


Pathogenesis

- Infection via ingestion of spores
- Translocation from intestine → portal vein → liver → infect hepatocytes → necrosis
- May also affect enterocytes and myocardial cells

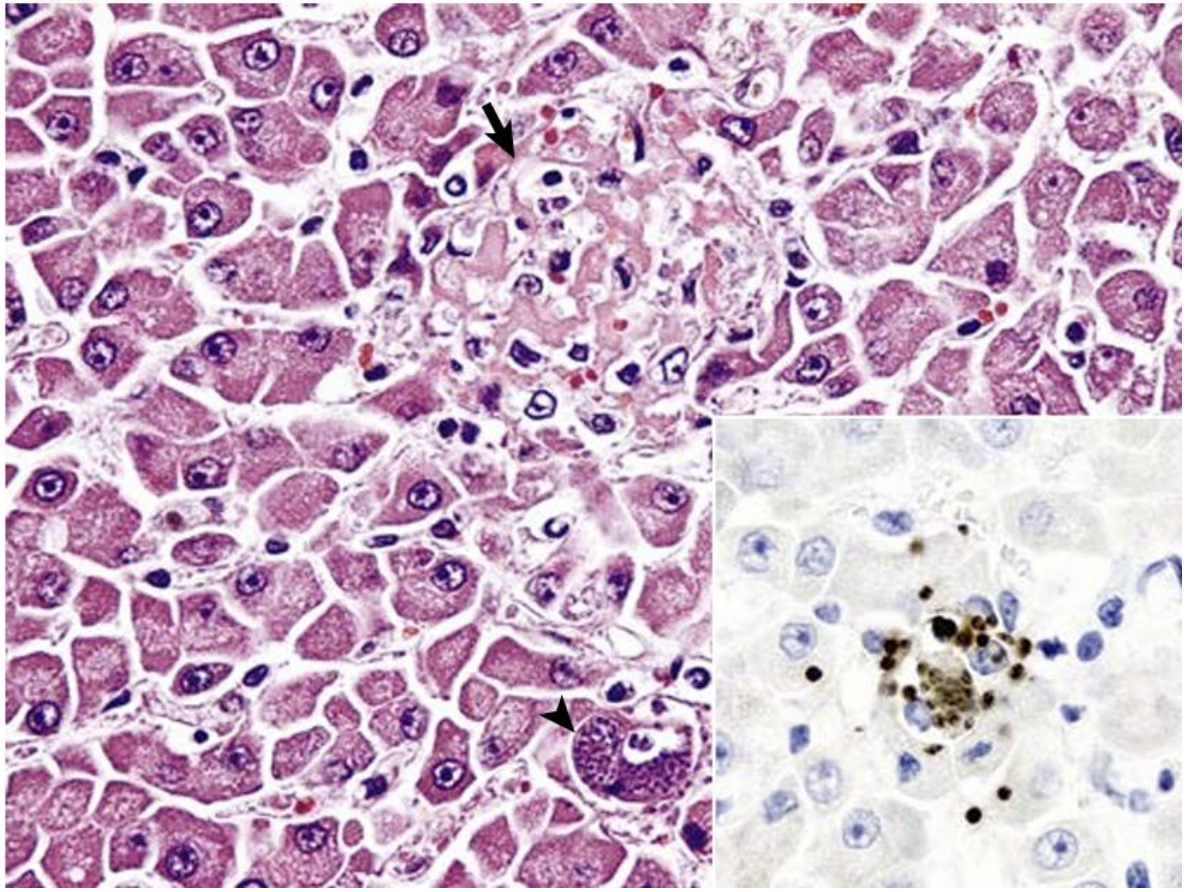
Tyzzer’s disease: Microscopic

- Random, multifocal hepatic necrosis
- Intracytoplasmic filamentous bacteria
- Detected with silver stains (e.g., Warthin-Starry, Steiner)



Other infectious diseases in the liver

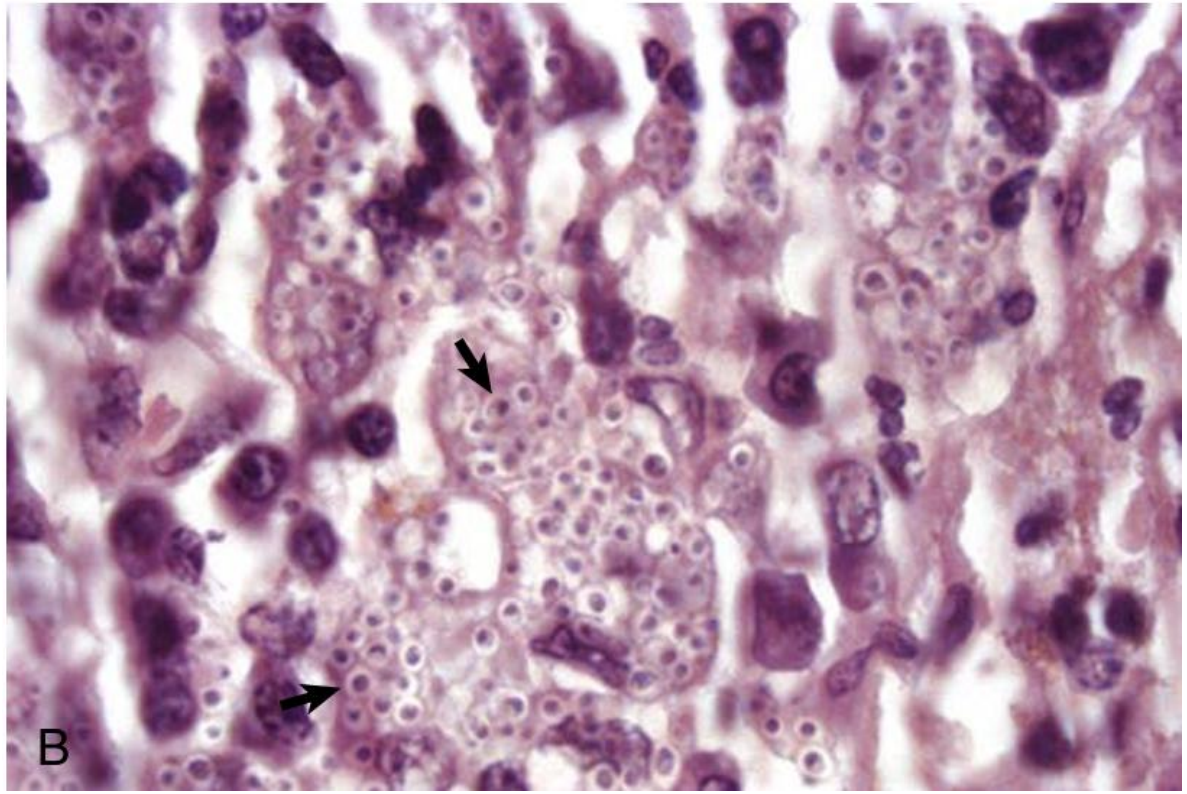
- Protozoal Liver Diseases
  - Leishmaniasis (Leishmania spp.) – Dogs
    : Granulomatous hepatitis, hepatomegaly
  - Toxoplasmosis (Toxoplasma gondii) – Sheep, goats, dogs
    : Hepatic necrosis, multifocal inflammation



Toxoplasmosis, Liver, Cat

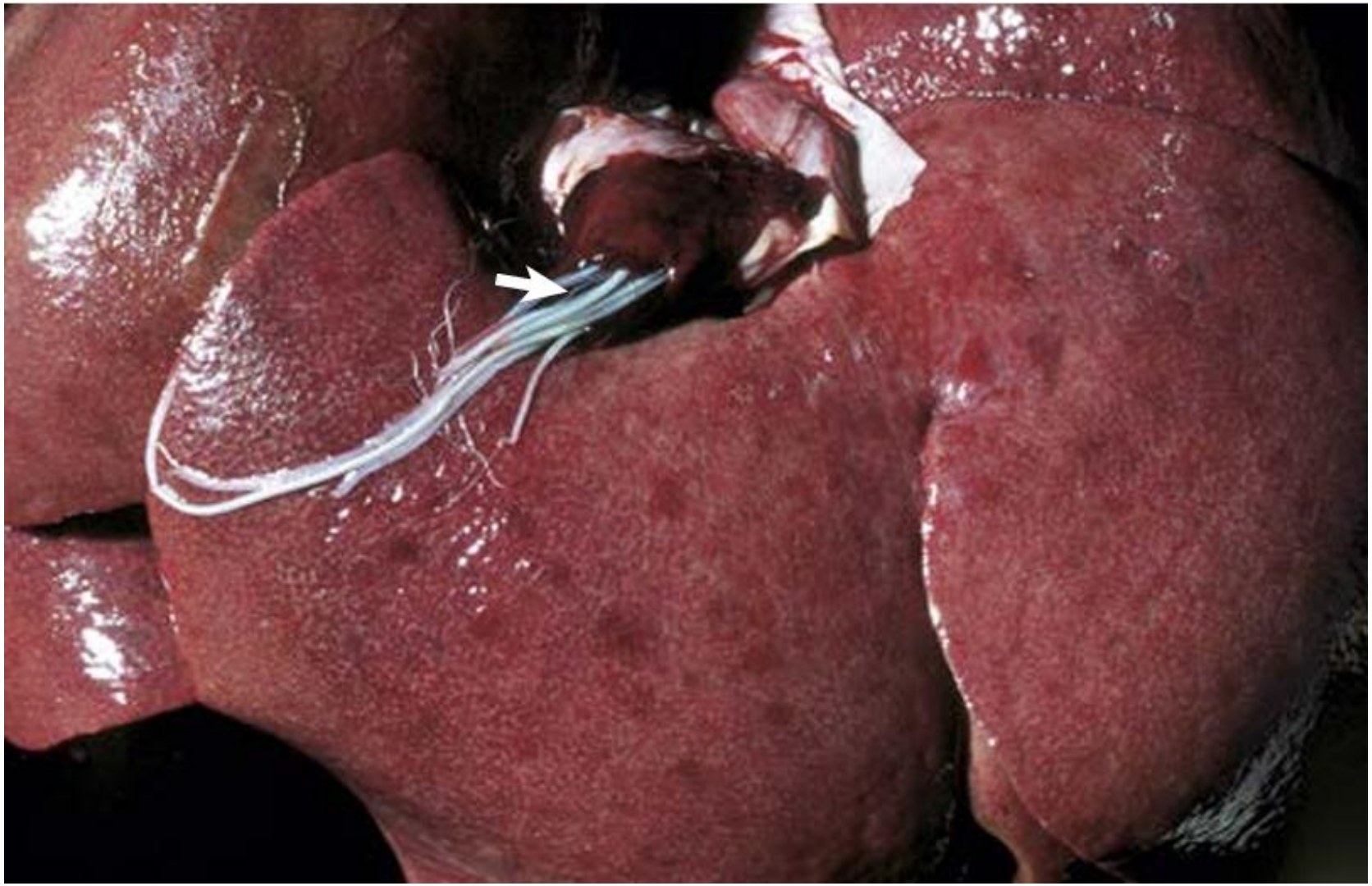
Other infectious diseases in the liver

- Fungal Liver Diseases
  - Blastomycosis (Blastomyces dermatitidis) – Dogs
    : Granulomatous hepatitis, systemic spread
  - Histoplasmosis (Histoplasma capsulatum) – Dogs, cats
    : Diffuse granulomatous hepatitis
- Others: Candidiasis, Aspergillosis – Opportunistic, rare



Histoplasmosis, Liver, Dog

Other infectious diseases in the liver



Dirofilariasis, Vena Caval syndrome, Dog

Aflatoxicosis

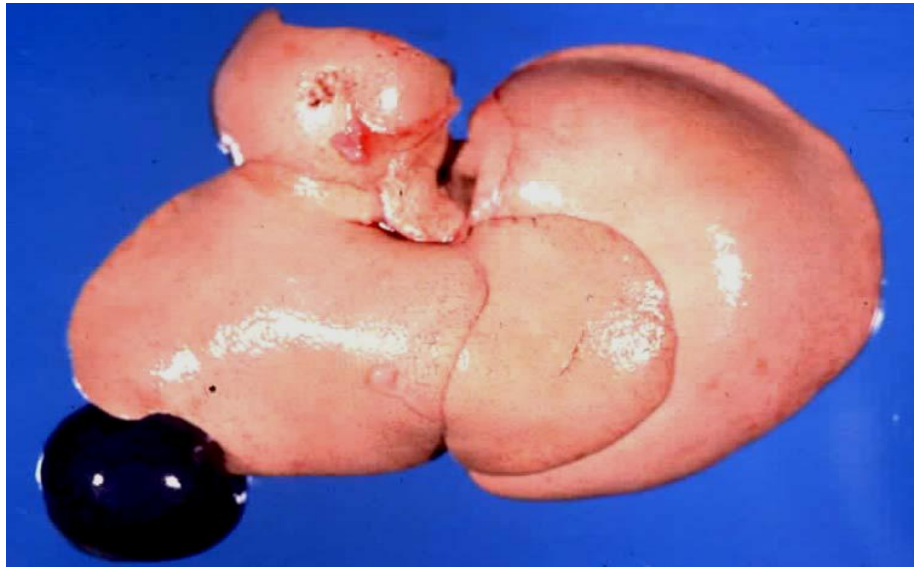
- Caused by ingestion of aflatoxins, primarily aflatoxin B1
- Produced by Aspergillus flavus and A. parasiticus
- Affects many species (sensitivity)
  - **Pig**, dog, horse, cattle > sheep, goat
  - Young > old, male > female
- Chronic: growth retardation, sensitive to other infectious diseases, hepatic failure

Pathogenesis

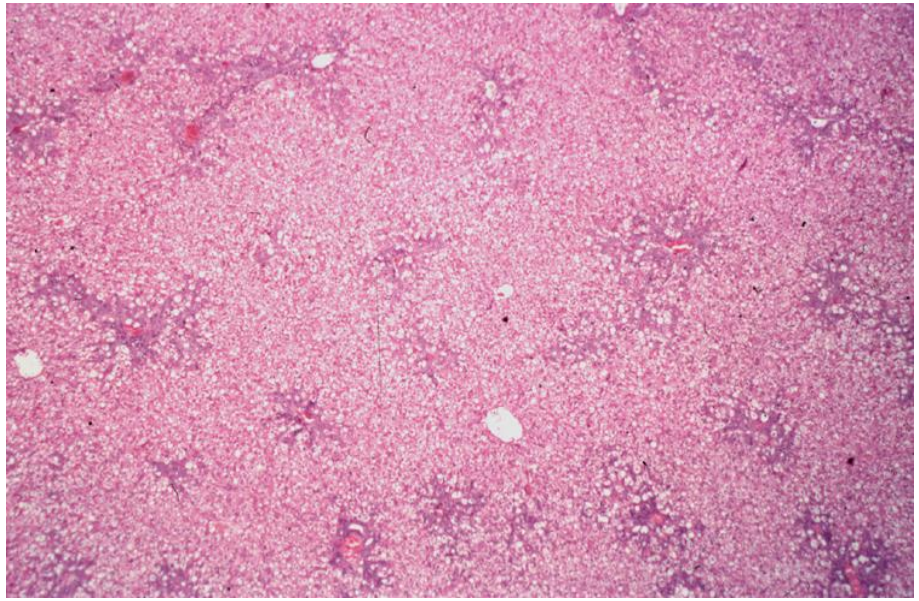
- Aflatoxin B1 → metabolized in liver to a **reactive epoxide**
- Binds DNA and proteins → hepatocellular injury
- Inhibits RNA synthesis → impaired protein production
- Leads to oxidative stress and cell death

Aflatoxicosis: Gross and microscopic

- Liver: pale, enlarged, friable (acute), fibrotic (chronic)
- Histology: hepatocellular necrosis, bile duct proliferation
- Megalocytosis, fatty change, and fibrosis
- Can progress to cirrhosis, **hepatocellular carcinoma or cholangiocarcinoma**



Woodchuck. Liver. **Early hepatic lipidosis. Acute Aflatoxicosis.** Liver swollen and pale with fat in each and every cord cell in excess.

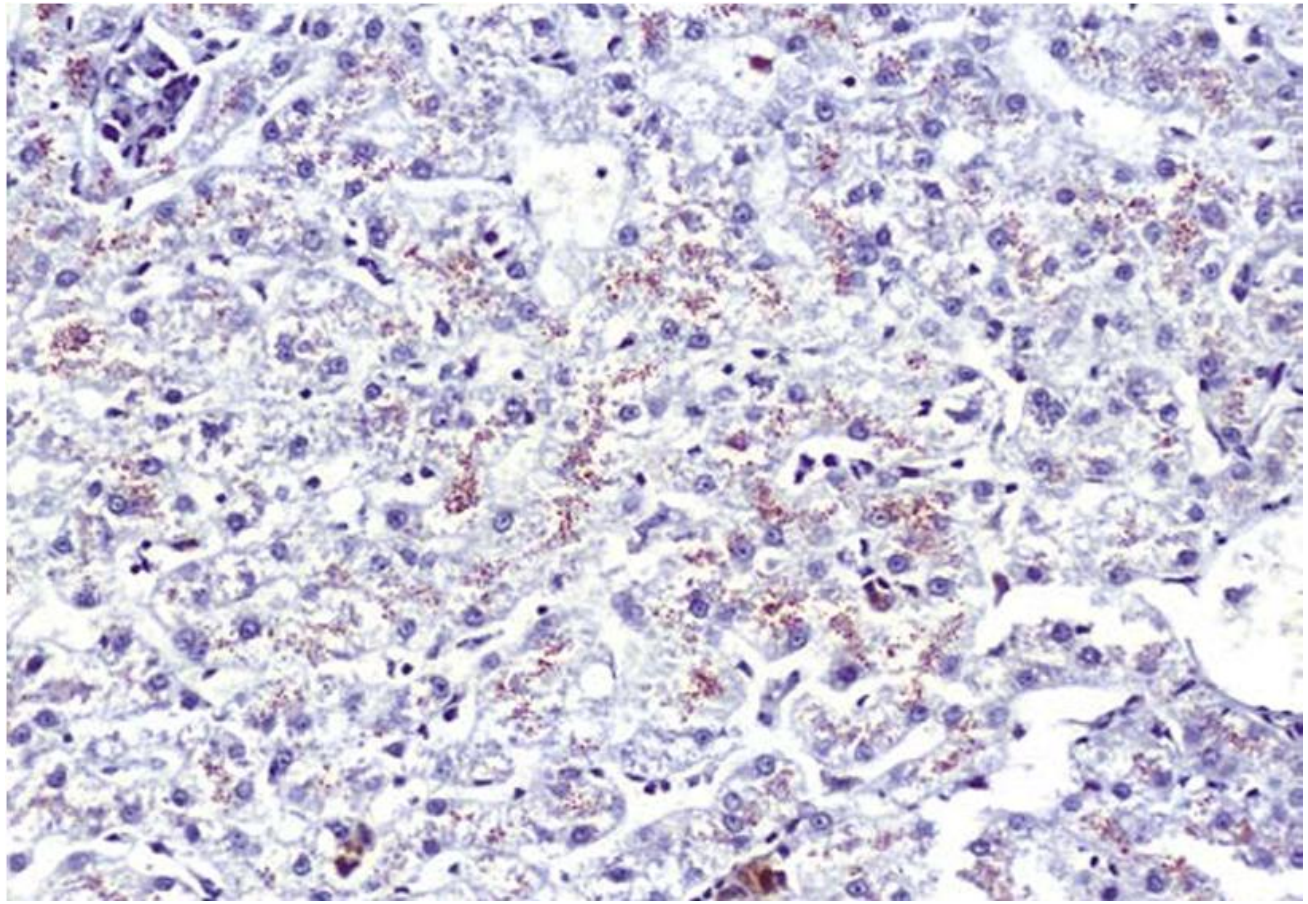


Woodchuck. Liver. **Peripheral hepatic necrosis and bile duct proliferation. Aflatoxicosis**

Metabolic & Storage diseases

Copper-Associated Chronic Hepatitis

- Genetic or acquired
- Bedlington terrier, Dobermans, Labrador retrievers, Skye terriers, West Highland white terriers, and Dalmatians

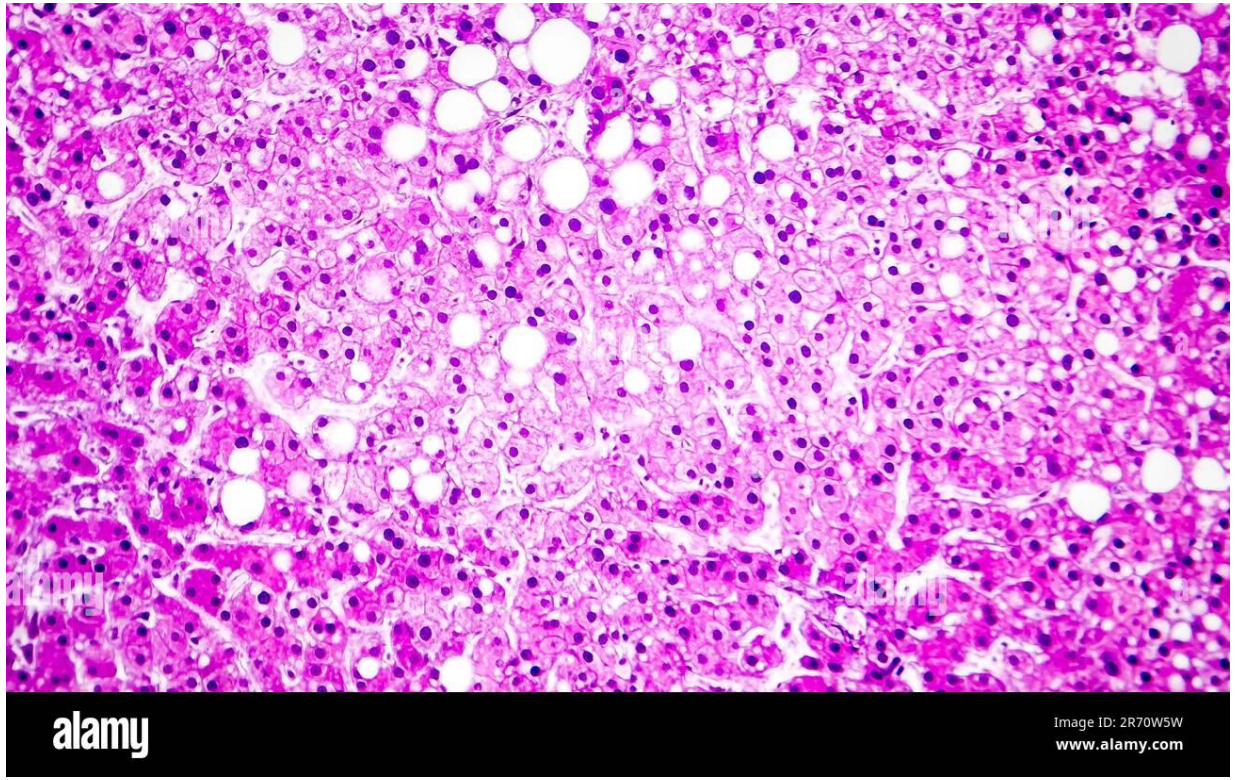


Hepatic Copper, Liver, Dog.

- The red-brown copper-containing granules
- Copper is not readily visible with hematoxylin and eosin (H&E) staining
- Special stains (Rhodanine stain)

Bovine Fatty Liver Syndrome & Ketosis

- Affects high-producing dairy cows during transition period
- Overweight animal in late gestation
- Trigger: Negative energy balance postpartum → adipose mobilization (adipose tissue to liver)
- Pathogenesis: Hepatic free fatty acids overload → Triglyceride accumulation
- Gross: Enlarged, yellow, friable liver
- Microscopic: Vacuolar degeneration (lipid-filled hepatocytes)
- Associated with ketosis, poor fertility, and immunosuppression

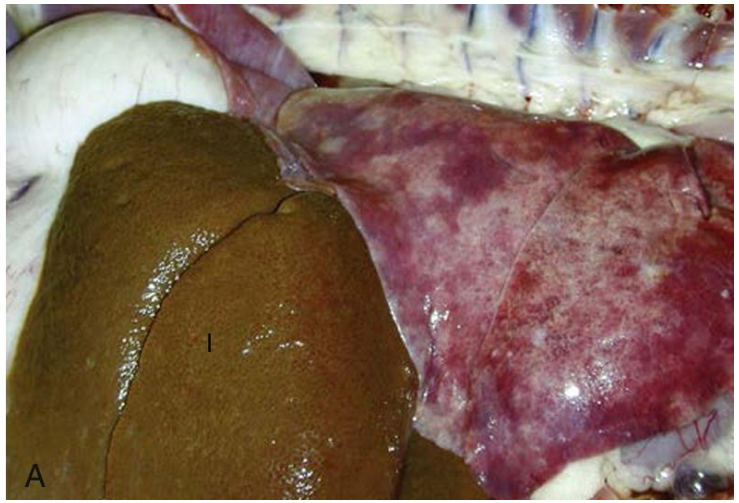


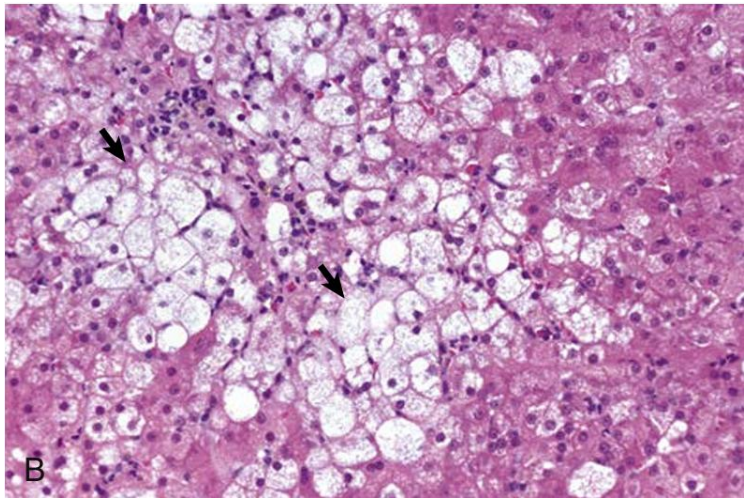
Steroid Hepatopathy

- Cause: Endogenous (Cushing's) or exogenous glucocorticoid exposure
- Pathogenesis:
  - Glucocorticoids increase glycogen synthesis in hepatocytes
  - Excess glycogen accumulates → hepatocellular swelling
- Histologic Features:
  - Vacuolated hepatocytes with PAS-positive glycogen
  - No inflammation or necrosis (non-degenerative change)
- Gross: Pale, enlarged, smooth liver
- **Common in dogs**; reversible upon withdrawal of steroids
- Diagnosis: Histopathology + PAS staining; elevated ALP

Steroid Hepatopathy

Glucocorticoid-Induced Hepatopathy, Liver, Dog.







의뢰하신 간 조직의 2 단면에 대한 병리조직학적 검사 결과, 간세포의 공포화 소견이 광범위하게 관찰되었으며 공포의 크기나 양상을 고려할 때 간세포에 과도한 glycogen이 침착되어 유발된 것으로 사료됩니다. glycogen침착의 경우, 과도한 외인성 glucocorticoid 또는 내인성 glucocorticoid(Cushing's disease), 당뇨 등의 glucose 조절의 이상 등 병적 상태일 때 관찰될 수 있습니다. 또한, 간혹 식후 등 다양한 생리학적 원인에 의해서도 유발될 수 있는데, 본 예의 경우에는 병변의 양상이 광범위하고 정도가 심하므로 정상 생리학적 소인에 의해 발생했을 가능성은 다소 낮다고 사료됩니다.
의뢰하신 조직 상에서 종양성 병변이나 심한 염증성 병변은 관찰되지 않았습니다.

Neoplasia and Hyperplasia

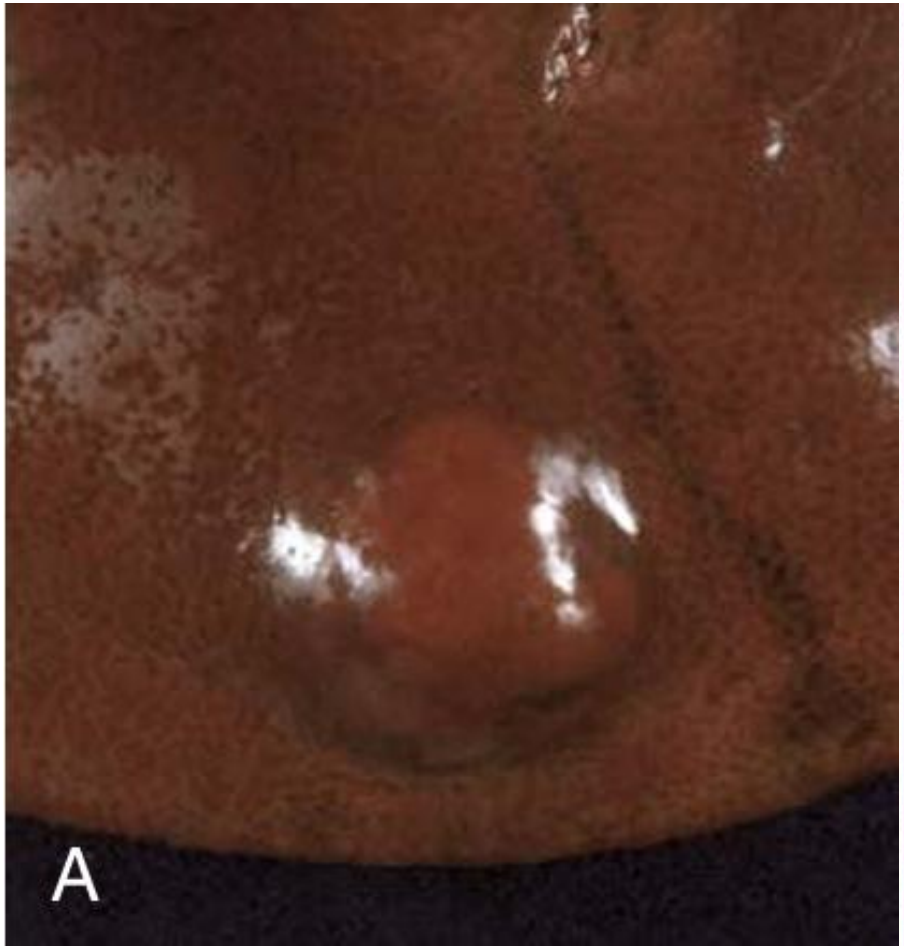
Neoplasia and Hyperplasia

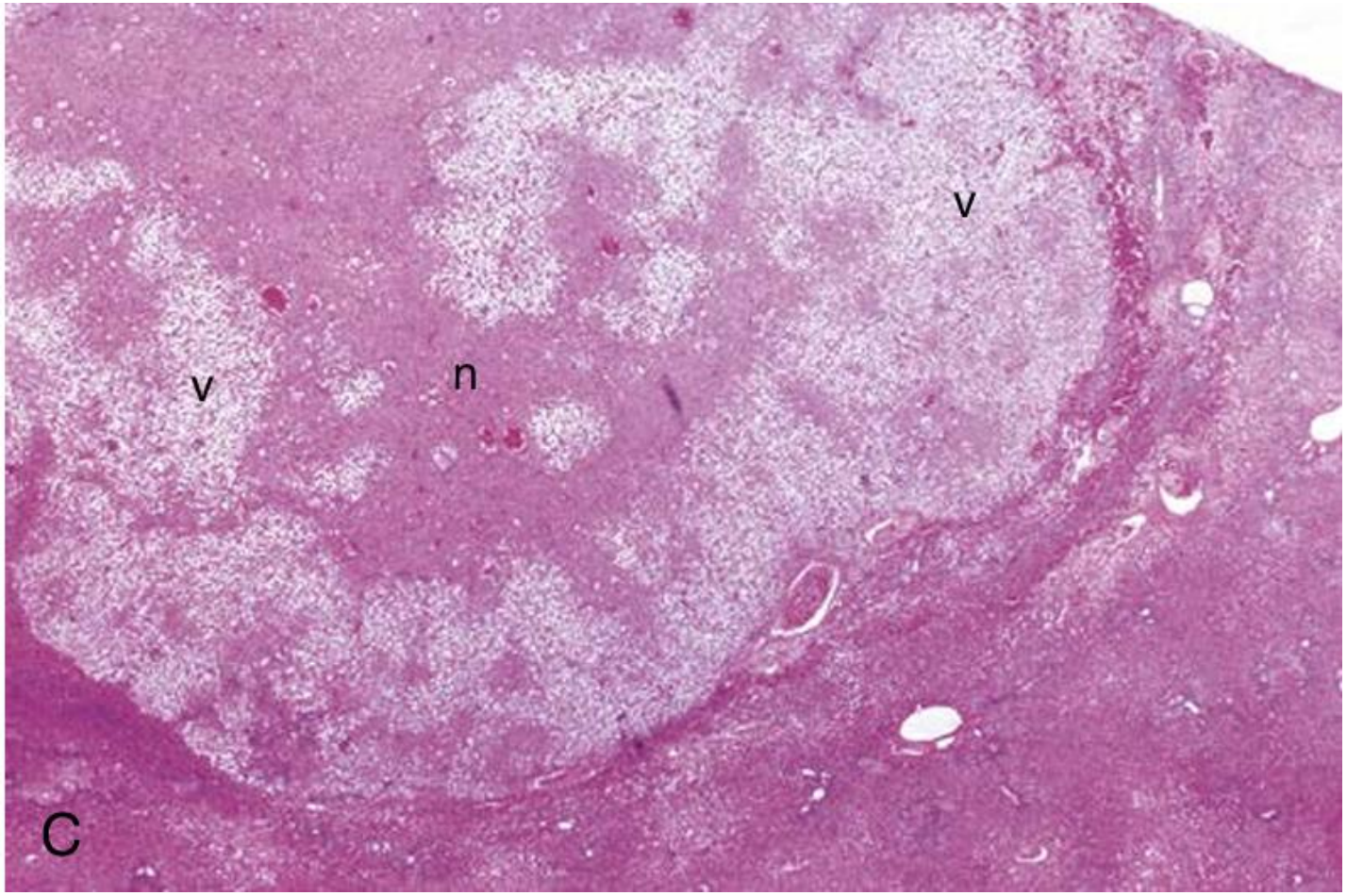
- Nodular hyperplasia: age-related, benign
- Hepatocellular adenoma or carcinoma
- Cholangiocellular carcinoma: arises from bile duct epithelium

Table 8.3 Differentiation of Nodular Lesions in the Liver

Lesion	Species Affected	Gross Appearance	Histologic Appearance
Nodular hyperplasia	Mainly older dogs, occasionally cats	Often multiple Friable Well-demarcated Compressive Adjacent liver is normal	Contains all elements of normal lobule Fewer portal tracts and central veins than normal liver Hepatocytes often vacuolated Not encapsulated
Regenerative nodules	Mainly dogs, not age-related	Multiple Rest of liver is abnormal (fibrotic)	Arise in an injured liver, most often with severe fibrosis Lack lobular organization Usually only contain a single portal tract or isolated vessels
Hepatocellular adenoma	All species	Usually single Often unencapsulated Compressive Red-brown Adjacent liver is normal	Loss of lobular architecture No or few portal tracts or central veins Well-differentiated hepatocytes Plates 2 or 3 cells thick
Hepatocellular carcinoma	All species	Usually single Can be large (can involve entire lobe) Intrahepatic metastases may be present Friable White-gray to yellow-brown Subdivided by fibrous bands	Loss of lobular architecture No or few portal tracts or central veins Irregular plates >3 cells thick Hepatocytes can be bizarre Invasion at margins
Cholangiocellular adenoma	Most common in cats	Discrete Firm Gray-white Can be cystic Compressive	Well-differentiated biliary epithelium forming tubules Can be cystic Well-developed fibrous stroma
Cholangiocellular carcinoma	All species	Large single mass or multiple nodules Often central depression (umbilicated) Gray-tan Unencapsulated Often see metastasis in other tissues	Well-differentiated, have tubular or acinar arrangement Poorly differentiated, have solid masses of cells Abundant fibrous stroma Multiple sites of invasion at margins

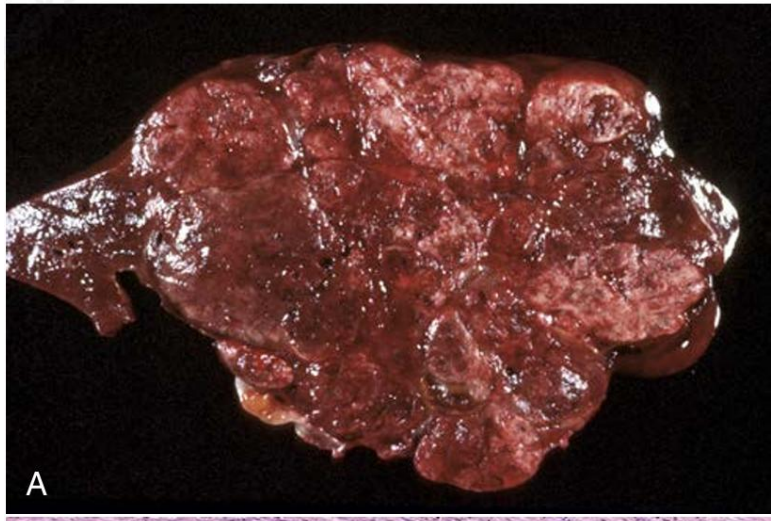
Nodular hyperplasia

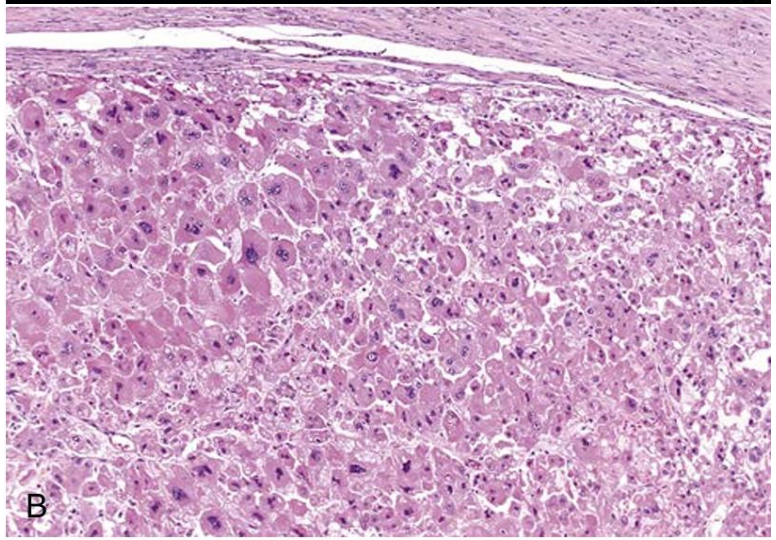


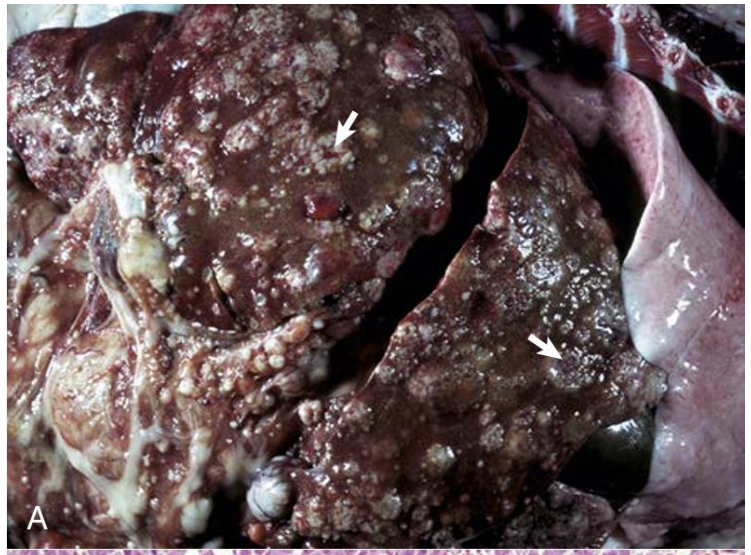


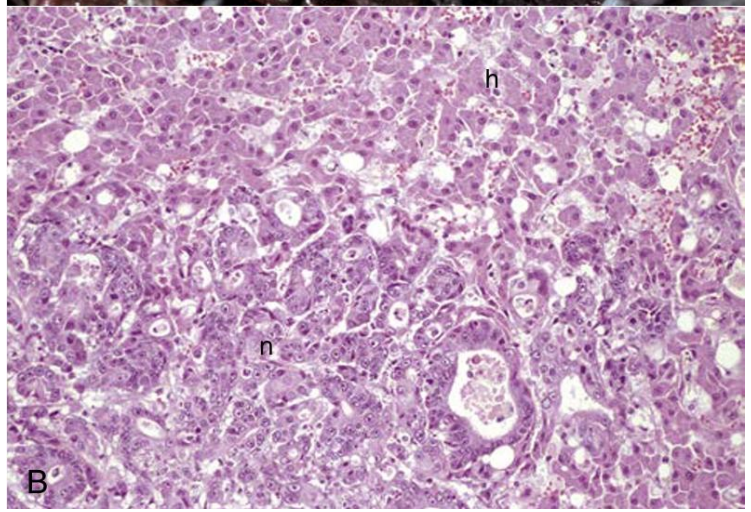
Adenoma, HCC, CholangioCA





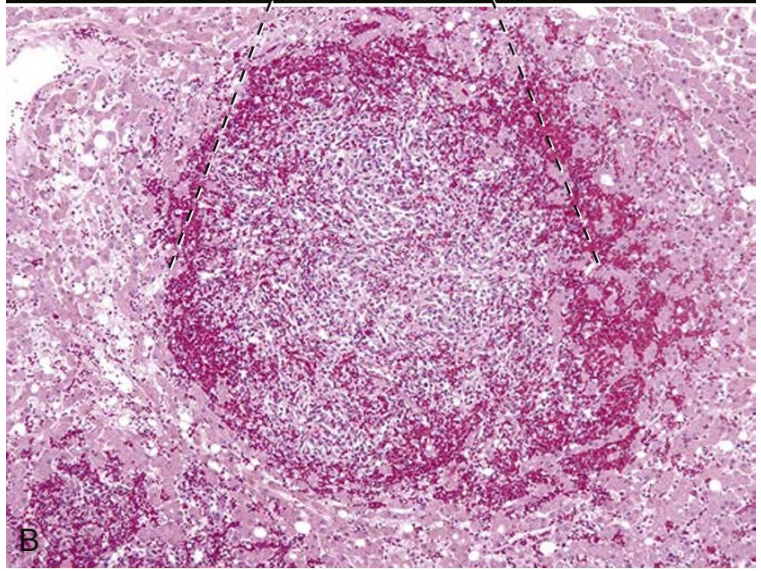


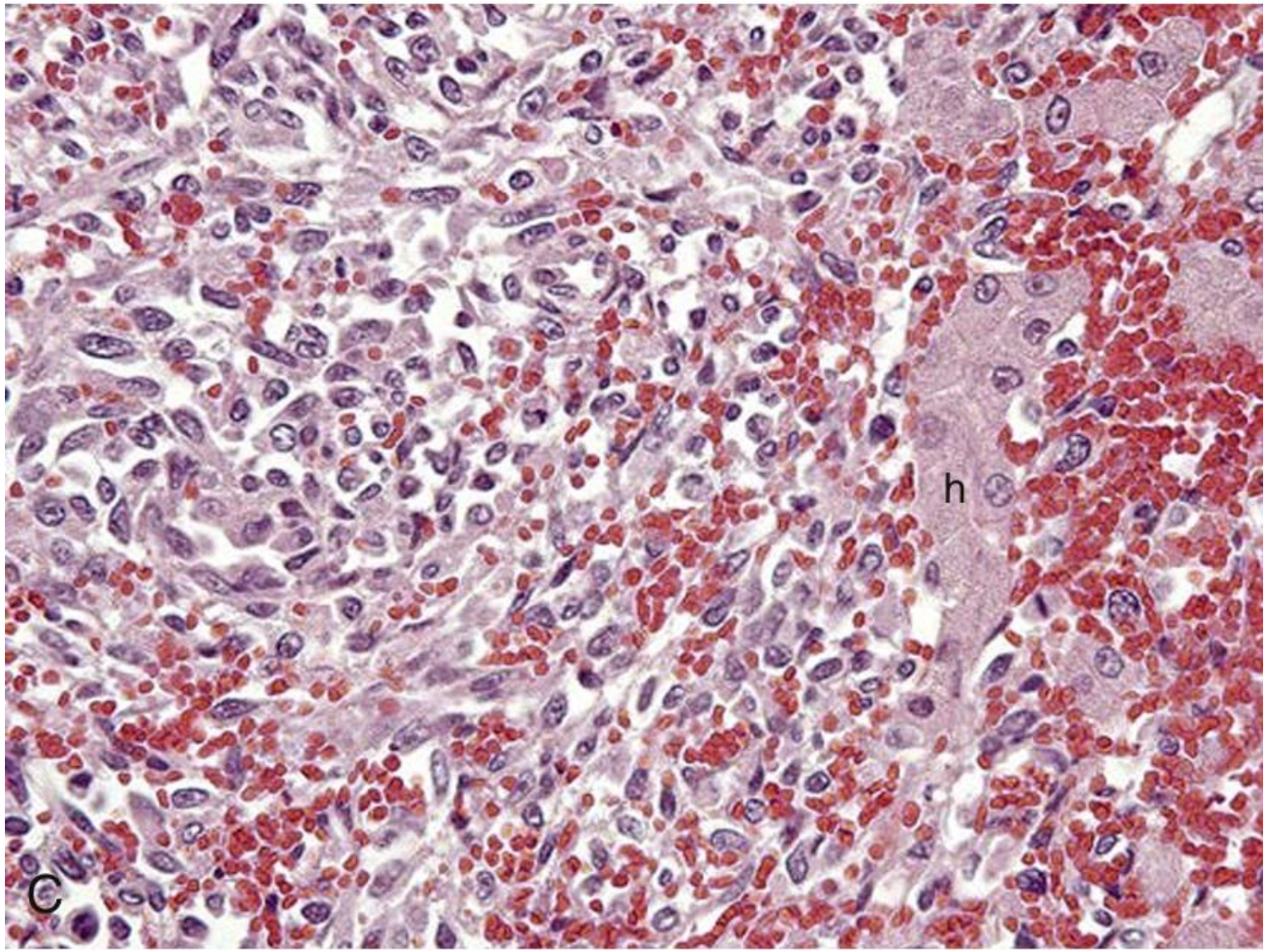




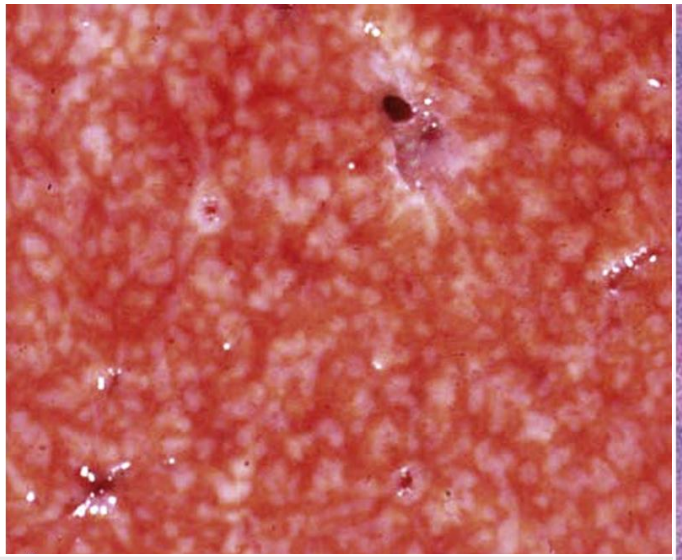
Neoplasia and Hyperplasia

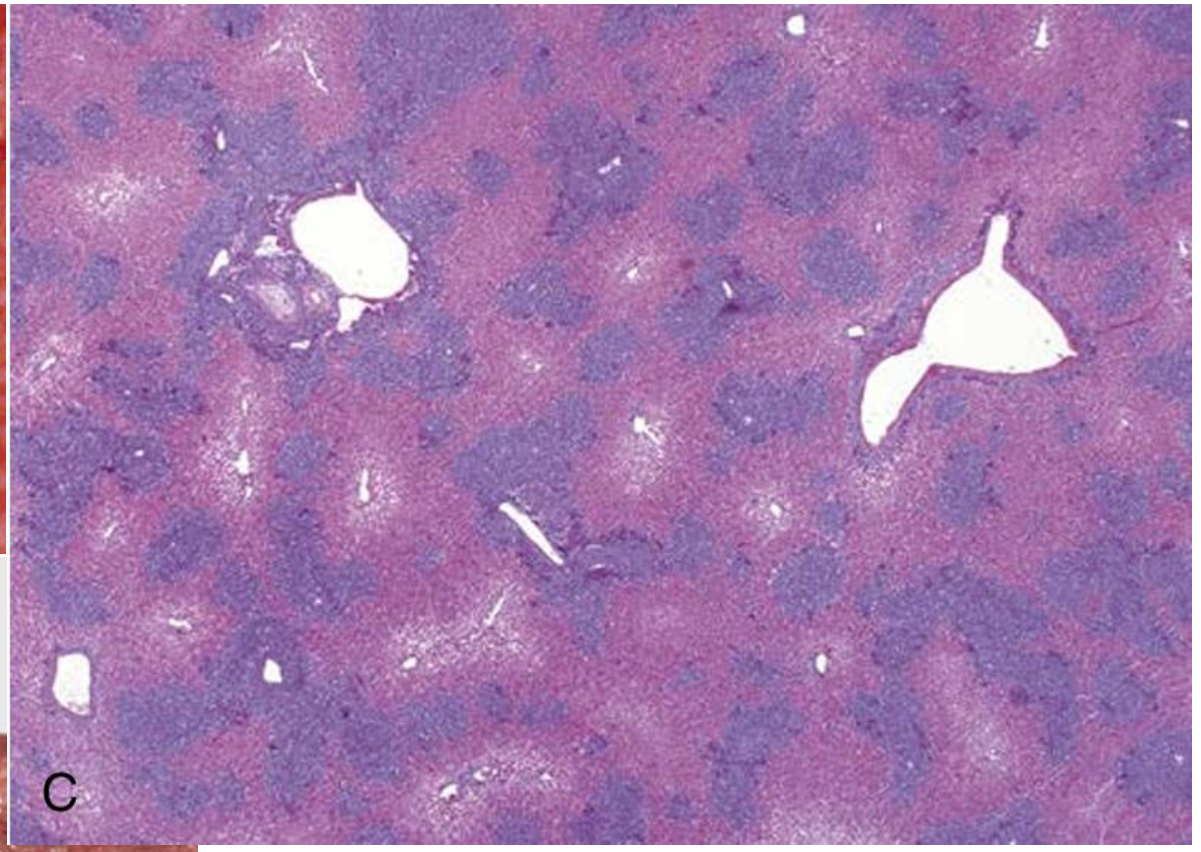


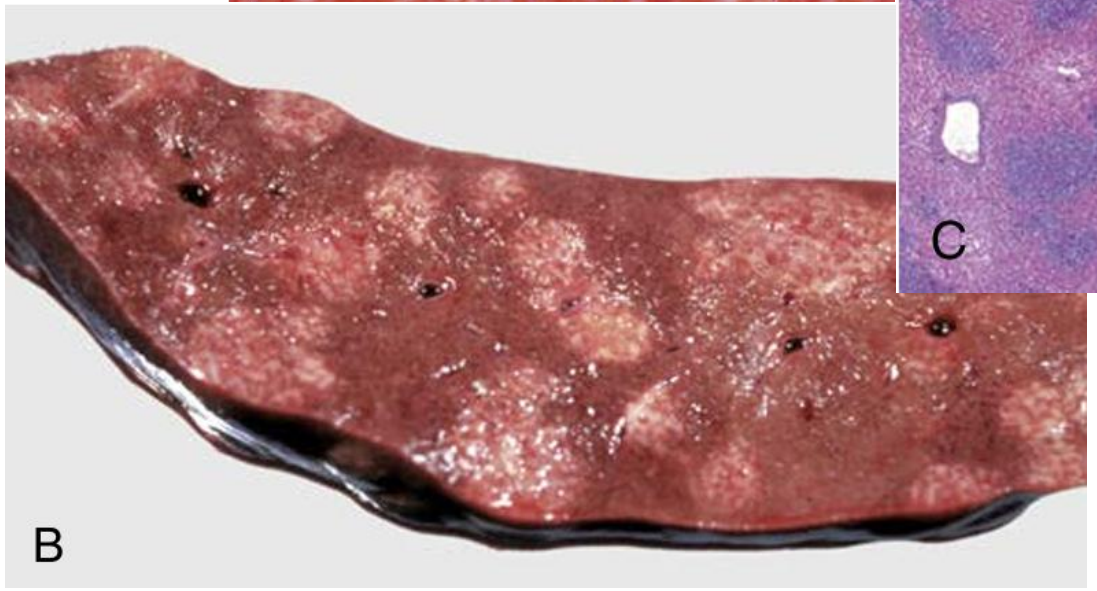




Neoplasia and Hyperplasia

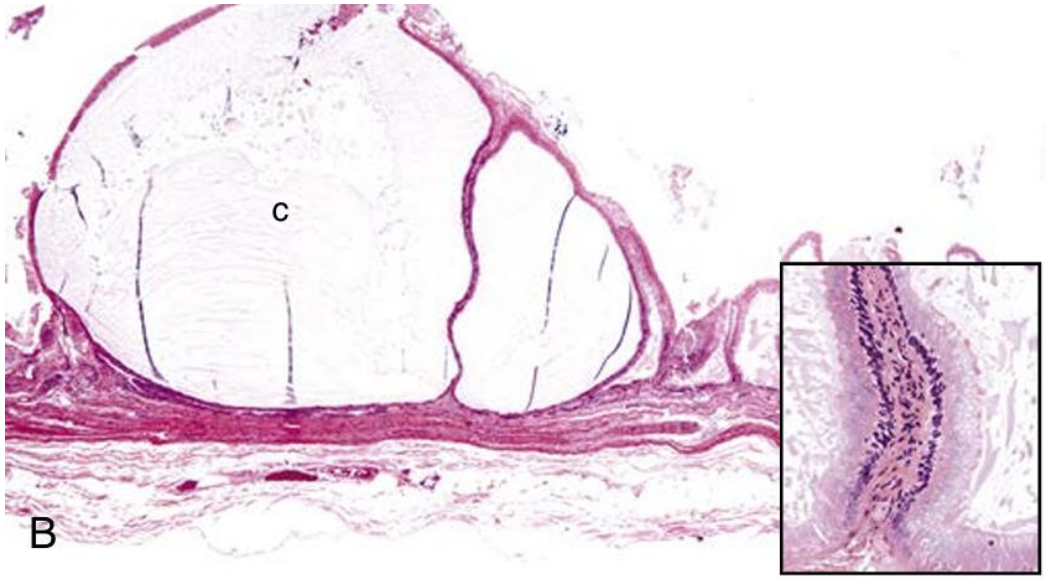






Neoplasia and Hyperplasia





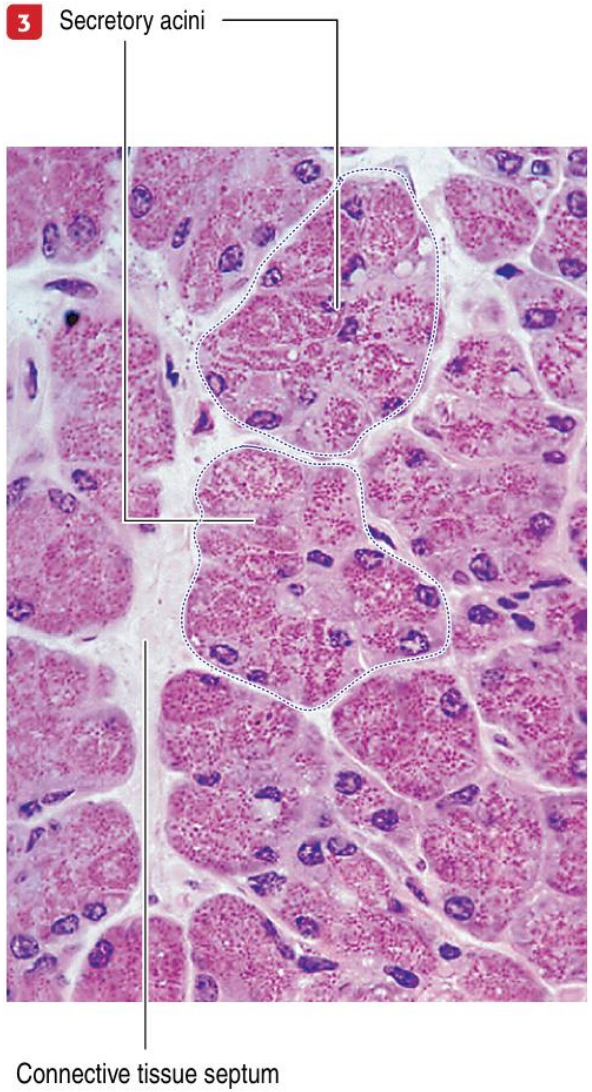
담낭에서는 gall bladder mucocele 소견이 관찰되었습니다. 본 병변은 **소형견이나 중형견에서 나이가 들며 호발**하는 소견으로, 정확한 원인은 알려져 있지 않지만, **담낭의 운동성 저하 또는 답즙 정체, 담즙의 성분 또는 점도(viscosity)등의 변화, 담낭 내부의 점액 분비선의 증식 및 기능 불량** 등으로 인하여 담낭 내에 담즙이 쌓여 확장되는 병변입니다. 주로 **cystic mucinous hyperplasia** 와 관련되어 일반적으로 무증상적으로 진행되어 보일 수 있으나 심할 경우에는 허혈성 괴사 또는 파열을 일으킬 수 있는 것으로 알려져 있습니다. 또한 의뢰하신 조직에서는 HE 염색상에서 무정형, 호산성/호염성, 갈색 /녹색의 염색성을 보이는 물질이 다량 관찰되었는데 이는 축적된 담즙으로 사료됩니다.

Exocrine Pancreas – Structure

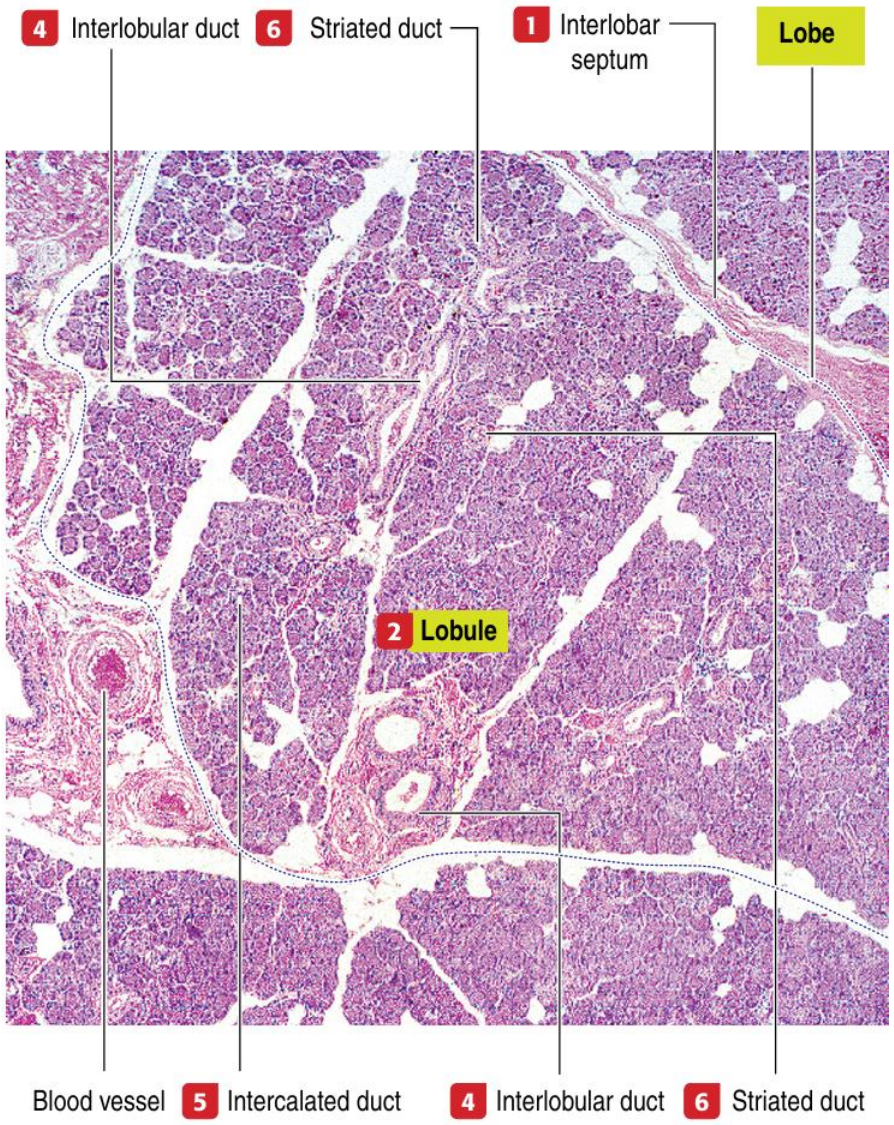
- Composed predominantly of acinar cells and ductal system

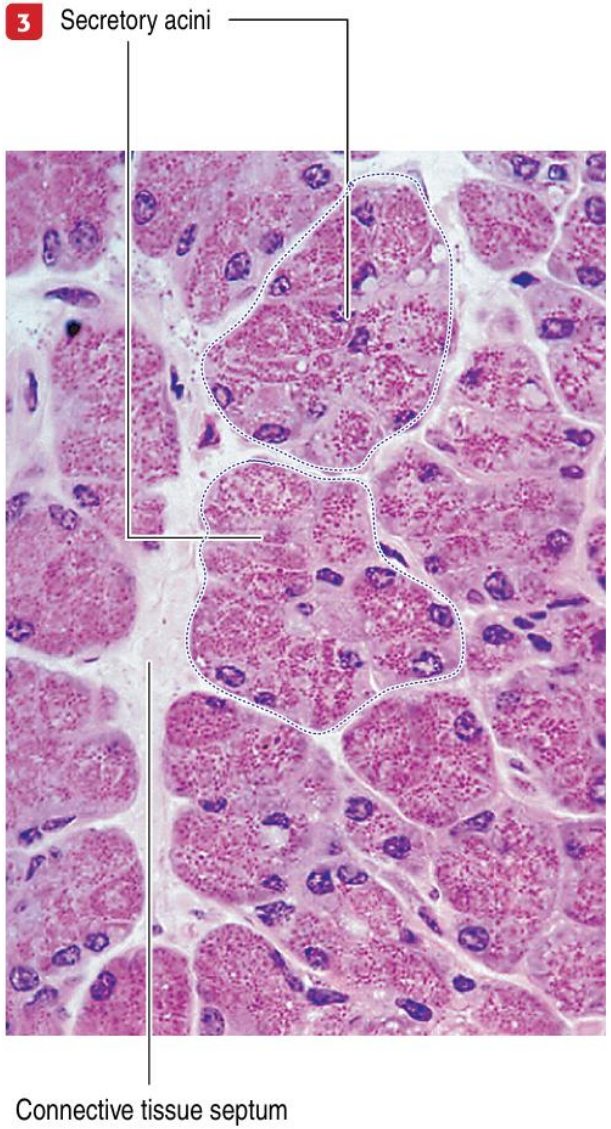
  -Basally oriented nuclei; apical cytoplasm with zymogen granules

- Acinar cells secrete zymogens (inactive digestive enzymes)
- Ductal cells secrete bicarbonate to neutralize gastric acid
- Structural hierarchy: **acini** → intercalated ducts → **intralobular ducts** → **pancreatic duct**

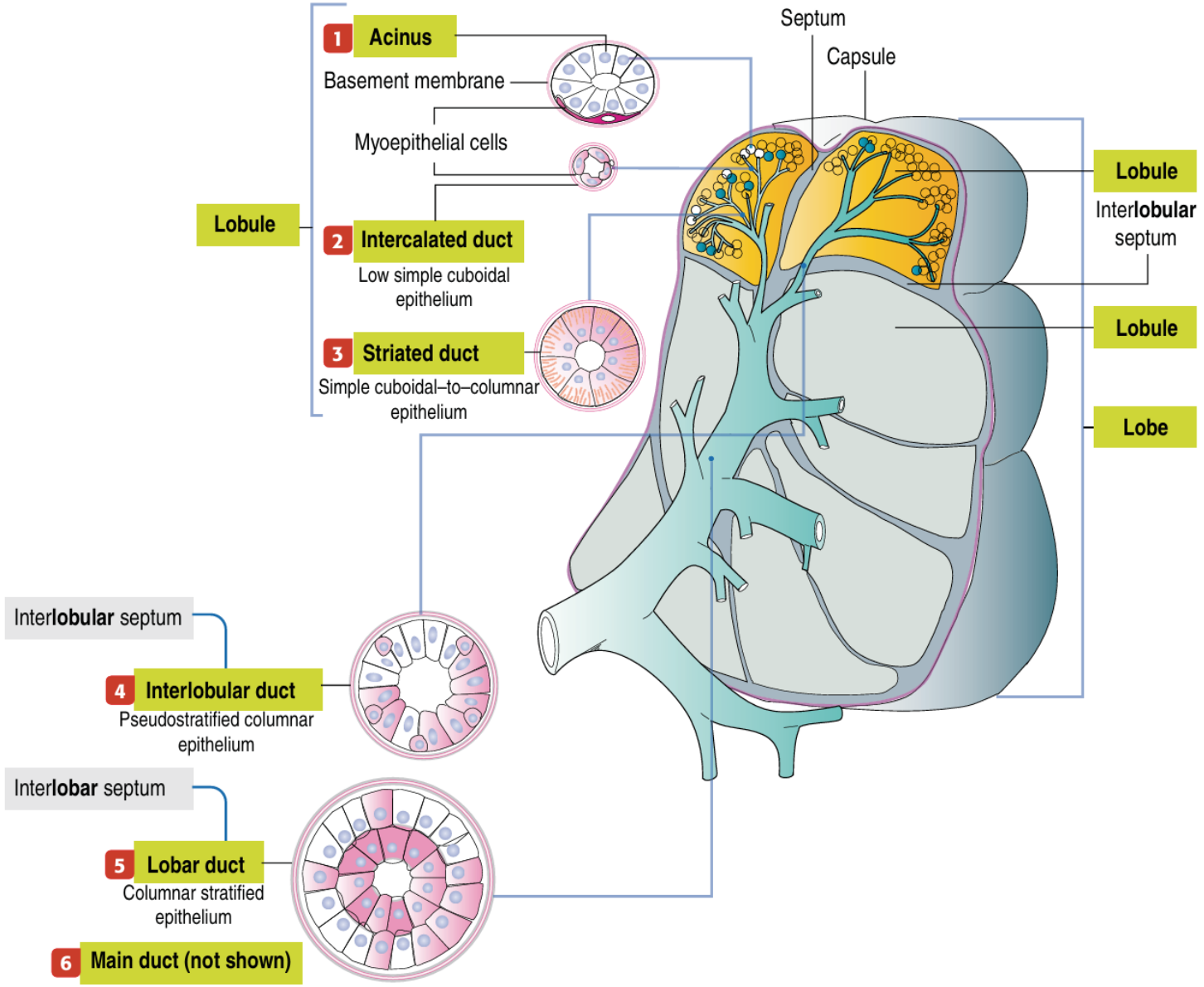


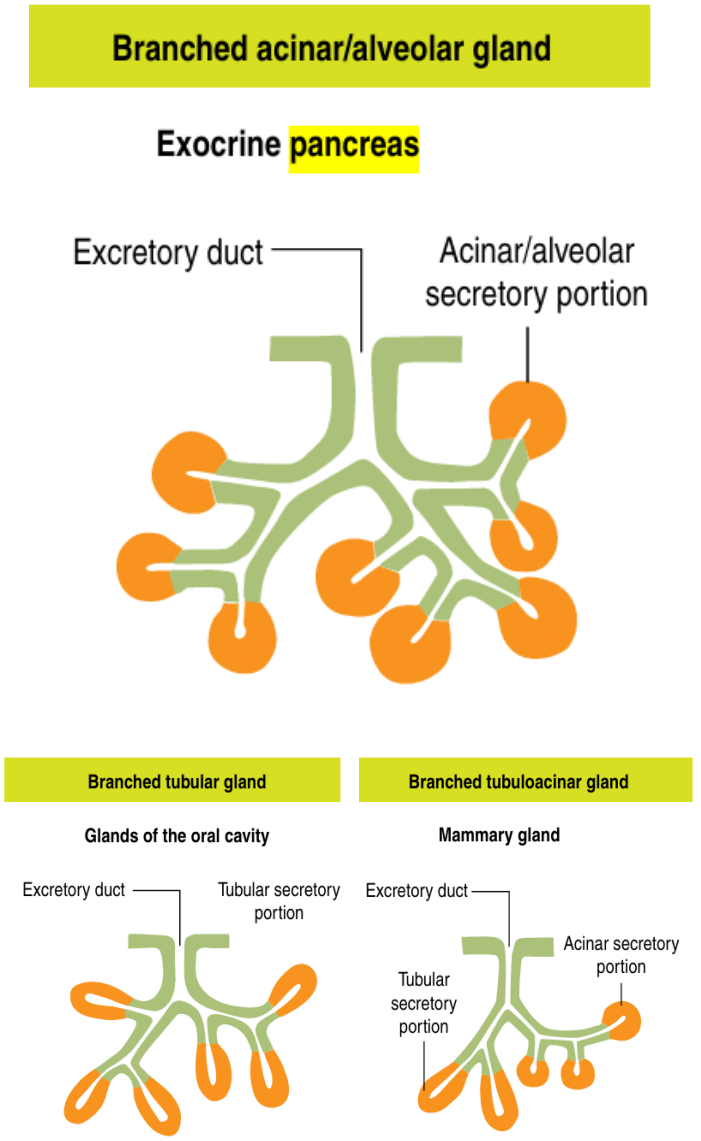
Exocrine Pancreas – Structure





Exocrine Pancreas – Structure





Functions of the Exocrine Pancreas

- Secretes digestive enzymes: trypsinogen, chymotrypsinogen, lipase, amylase
- Enzymes activated in the small intestine (e.g., trypsinogen → trypsin by enterokinase)
- Bicarbonate secretion creates alkaline environment, protecting intestinal mucosa
- Stimulated by vagus nerve, secretin, and cholecystokinin

Pathophysiology – Pancreatic Injury

Responses to Injury and Aging

- Injury leads to enzyme leakage and autodigestion → pancreatitis
- Acute pancreatitis = inflammation, necrosis
- Chronic pancreatitis = fibrosis, atrophy, exocrine pancreatic insufficiency (EPI)
- Aging: ↓ enzyme secretion, nodular hyperplasia (clinically insignificant)

Histologic Patterns

- Acute: necrotic acinar cells, edema, hemorrhage
- Chronic: loss of acini, fibrosis, lymphoplasmacytic infiltrates
- Ductal hyperplasia and fibrosis are common sequelae

Portals of Entry & Defense Mechanisms

- Portals of Entry:
  - Hematogenous
  - Ascending infections via pancreatic ducts
  - Direct extension from adjacent tissues
- Defenses:
  - Continuous flow of secretions
  - Enzymes stored as inactive zymogens
  - Intracellular inhibitors (e.g., pancreatic secretory trypsin inhibitor)

Exocrine Pancreas Disorders in Domestic Animals

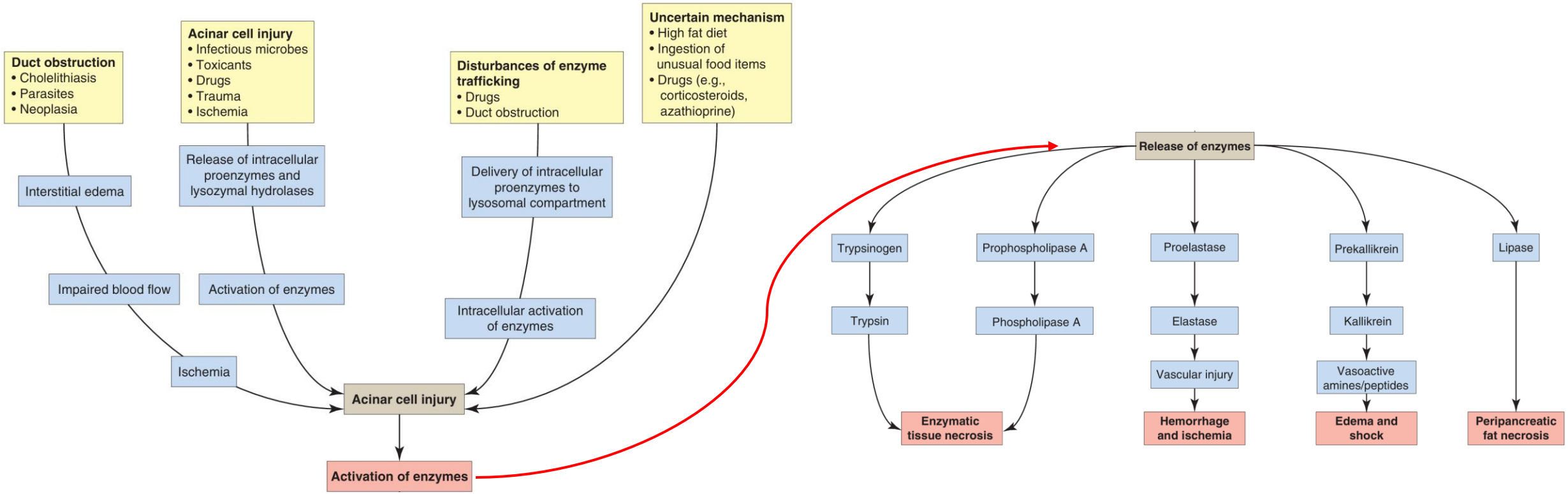
- Affected species: dogs, cats, horses
- Major conditions: pancreatitis, hyperplasia, neoplasia, parasitism
- Common clinical signs: vomiting, diarrhea, abdominal pain, EPI

Congenital and Developmental Anomalies

- Duct anomalies and ectopic pancreatic tissue
- Ectopic splenic tissue (choristoma)
- Cystic duct dilation, pseudocysts
- Usually incidental findings

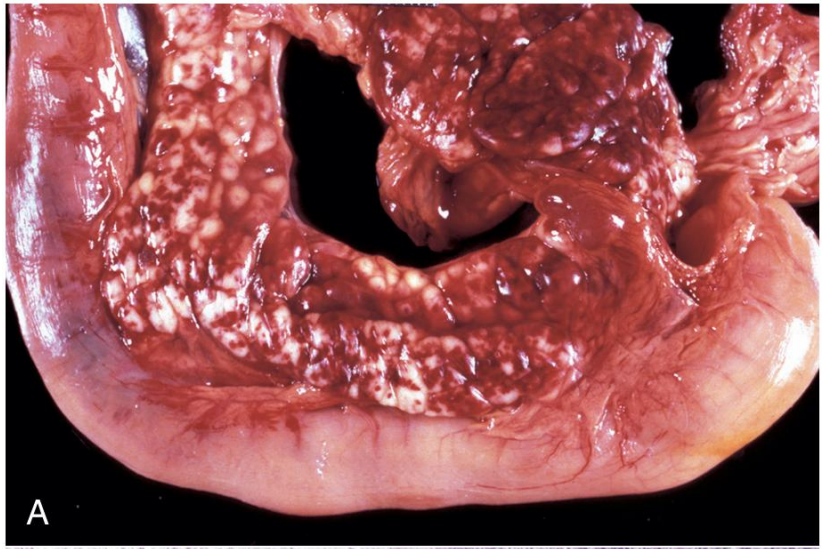
Acute Pancreatitis – Pathogenesis

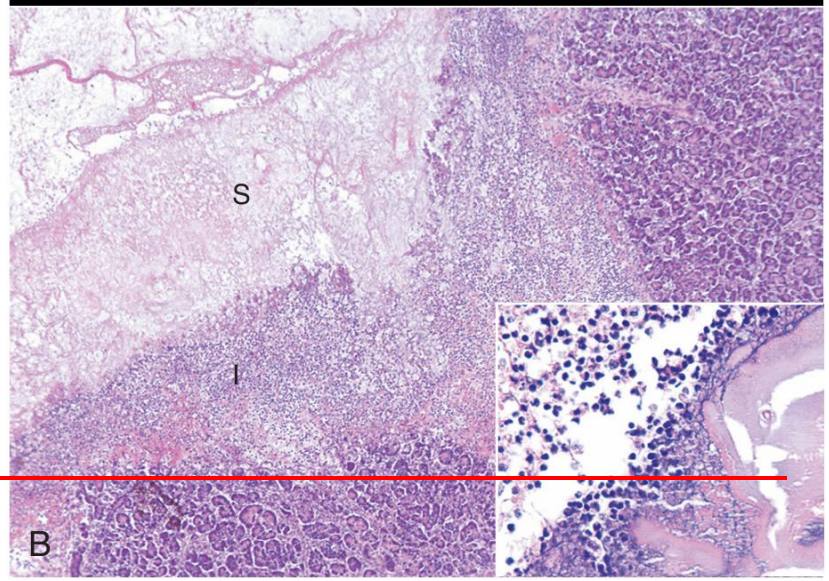
- Enzyme activation within acinar cells → autodigestion
- Causes: dietary indiscretion, trauma, toxins, parasites
- Trypsin activates elastase, phospholipase A → tissue necrosis

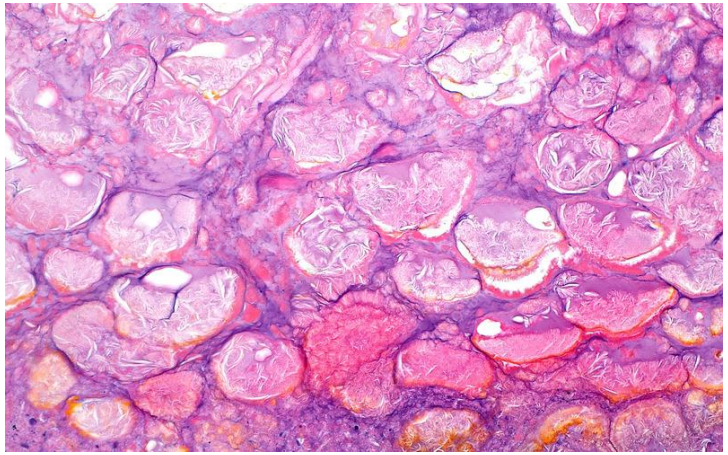


Acute Pancreatitis – Lesions

- Gross: hemorrhagic, edematous pancreas with **fat necrosis**
- Micro: necrosis, hemorrhage, neutrophilic inflammation
- Peritonitis, DIC, liver involvement common in severe cases







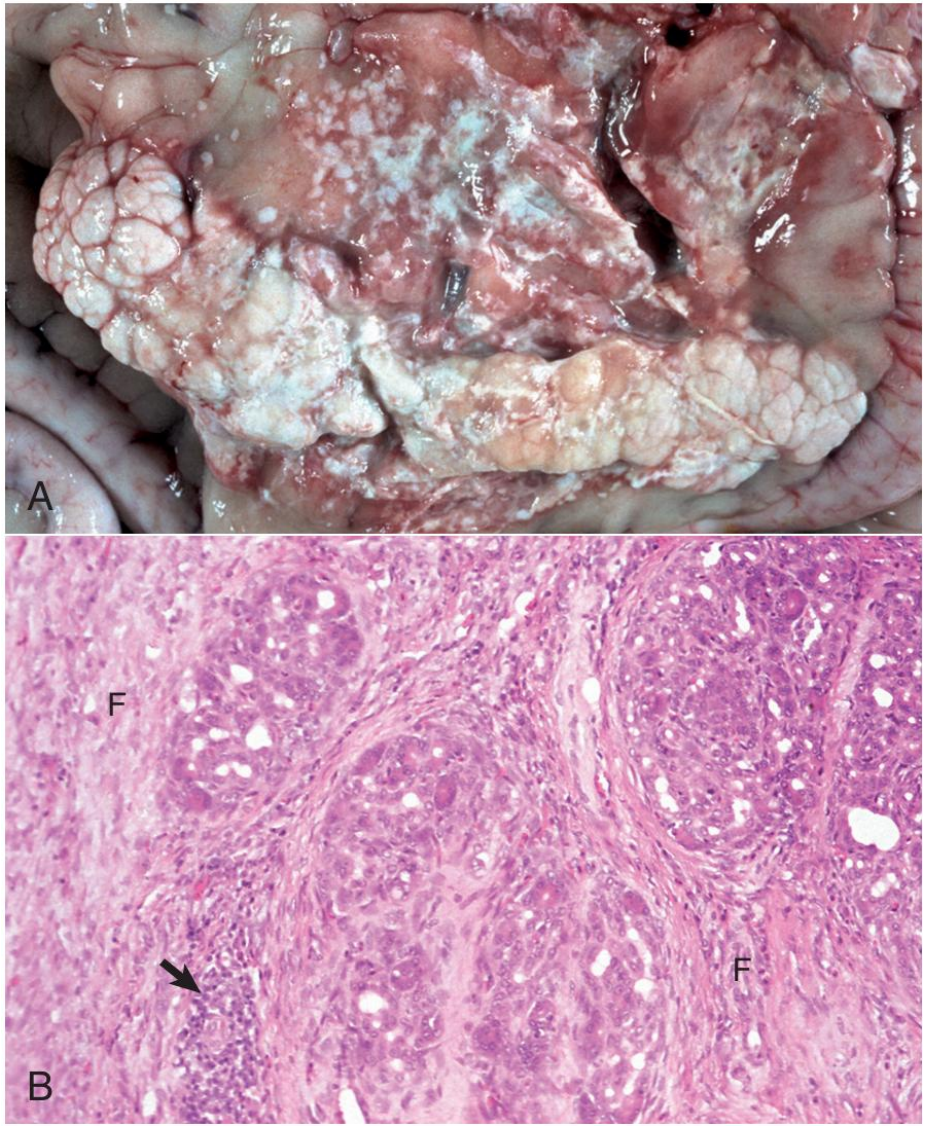
Saponification

https://www.sciencephoto.com/media/1305735/view/saponification-fat-necrosis-light-micrograph

Chronic Pancreatitis

- Causes: repeated subclinical acute episodes
- Leads to fibrosis, ductular hyperplasia, acinar atrophy
- Common in Spaniels, Boxers, Collies, and Cats
- May progress to EPI or diabetes mellitus

- Extensive fibrosis with little inflammation in **cats**
- Fibrosis of the exocrine pancreas in **sheep**: after the necrosis of exocrine pancreatic cells from zinc toxicosis

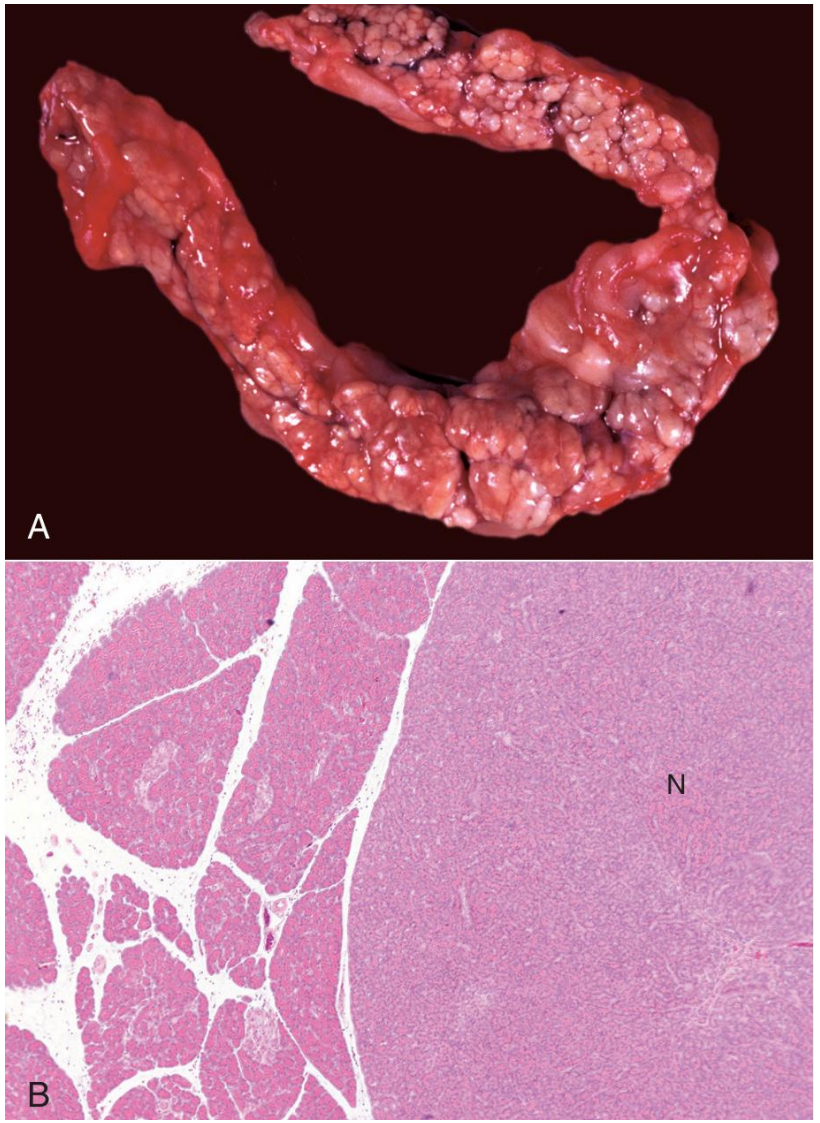


Parasitic and Infectious Pancreatitis

- Parasites: Opisthorchiidae, Dicrocoeliidae (e.g., Eurytrema)
- Mechanism: duct obstruction, inflammation, fibrosis
- Suppurative pancreatitis in cats: ascending bacterial infection
- Often coexists with cholangitis and IBD (triaditis)

Nodular Hyperplasia

- Common incidental finding in older dogs and cats
- Multiple raised, pale nodules with acinar cells
- No clinical significance unless misdiagnosed as neoplasia



Pancreatic Neoplasia

- Pancreatic adenocarcinoma: rare but aggressive

  -Pancreatic adenoma: extremely rare, reported in cats

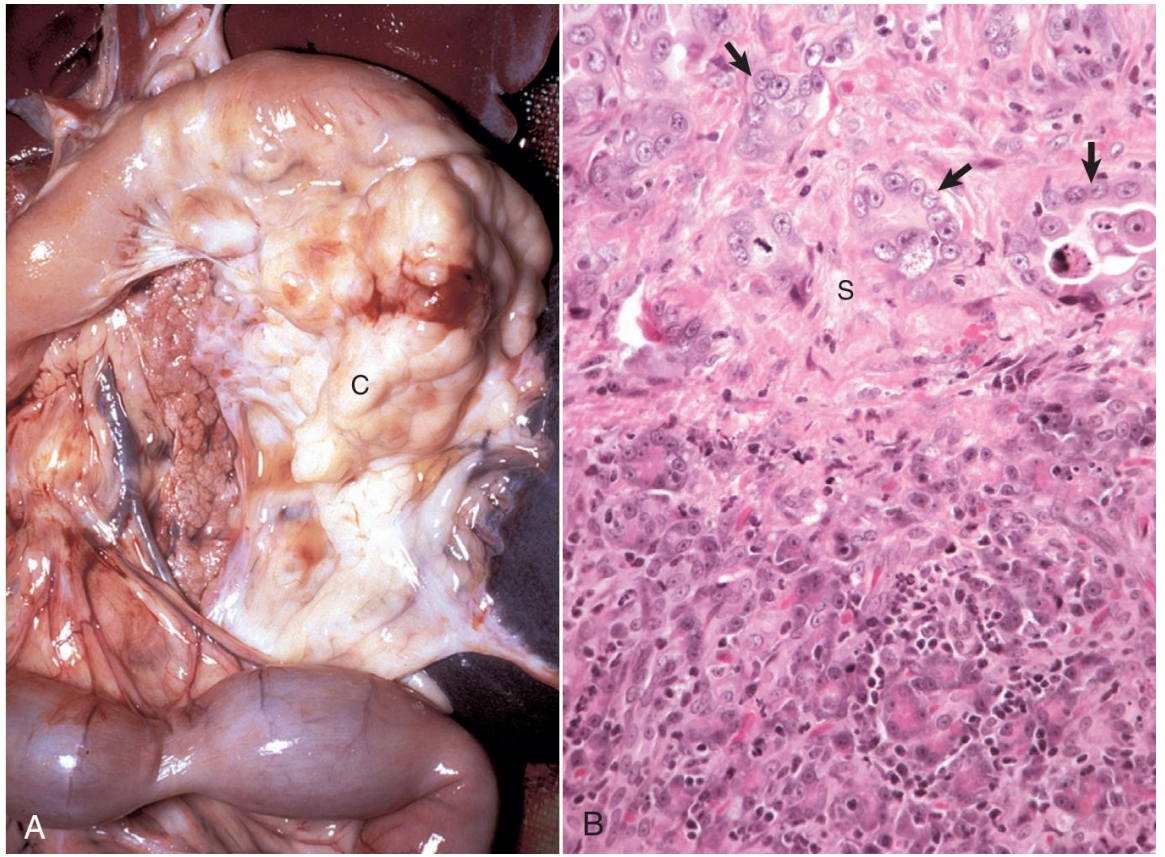
- Gross: firm, infiltrative masses with metastasis

- Micro: variable differentiation, mitotic figures, fibrosis

- Cats may show paraneoplastic alopecia

-A unique <u>cutaneous paraneoplastic syndrome</u>: **pancreatic adenocarcinoma** or **cholangiocarcinoma**.

-Grossly symmetric alopecia of the ventral trunk and limbs with a glistening appearance.



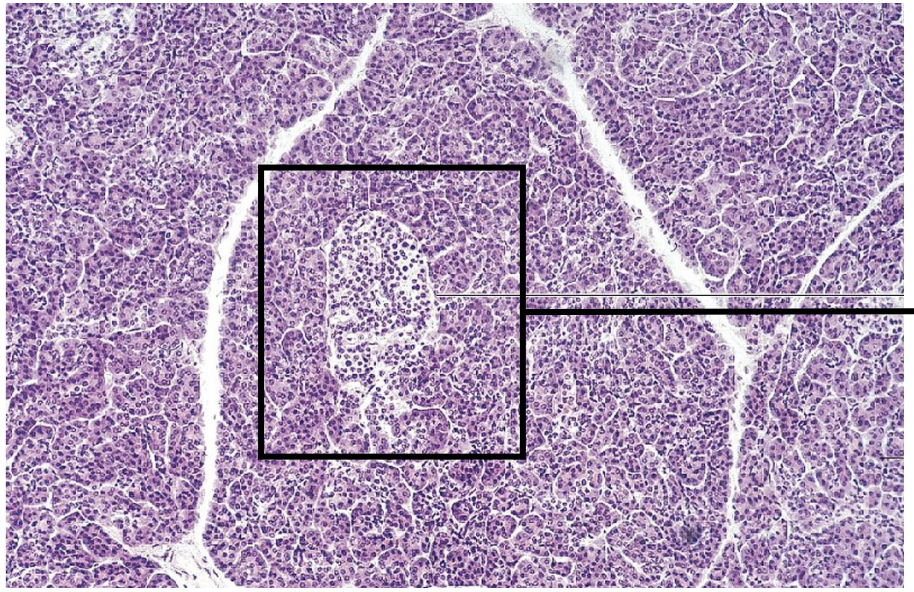
Pancreatic Endocrine tumors

- Two main types: **Insulinoma (β-cell)** and Glucagonoma (α-cell)
- Functional tumors → hormone overproduction
- Affect glucose metabolism and systemic health

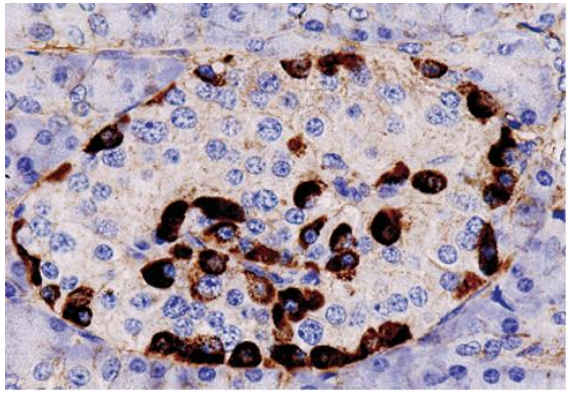
β-cell tumor (Carcinoma > adenoma)

- Functional tumor of β-cells → excessive insulin
- Most common in dogs and ferrets
- Causes recurrent hypoglycemia and neurologic signs
- Diagnosis (Whipple's Triad): symptoms + low glucose + recovery after glucose

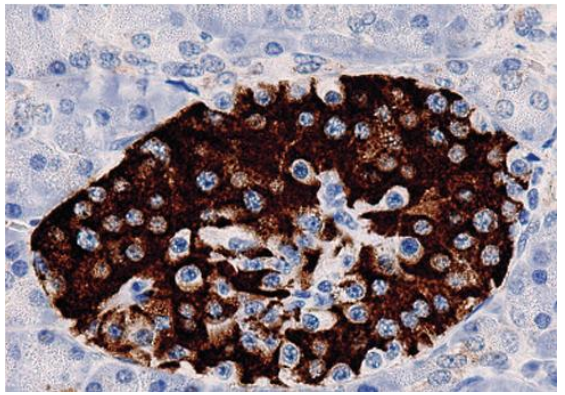
Pancreatic Endocrine tumors

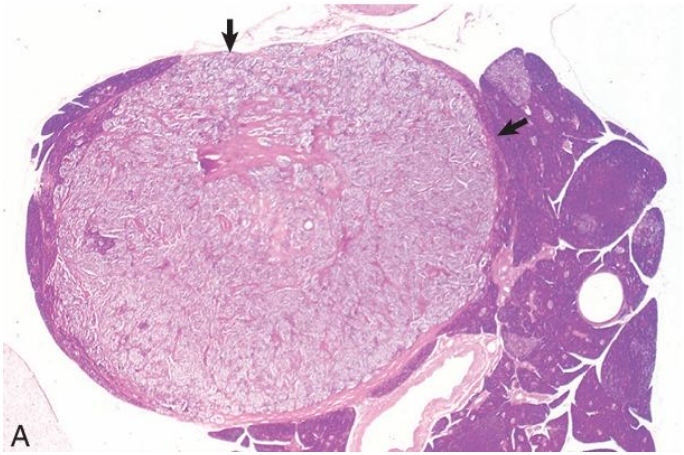


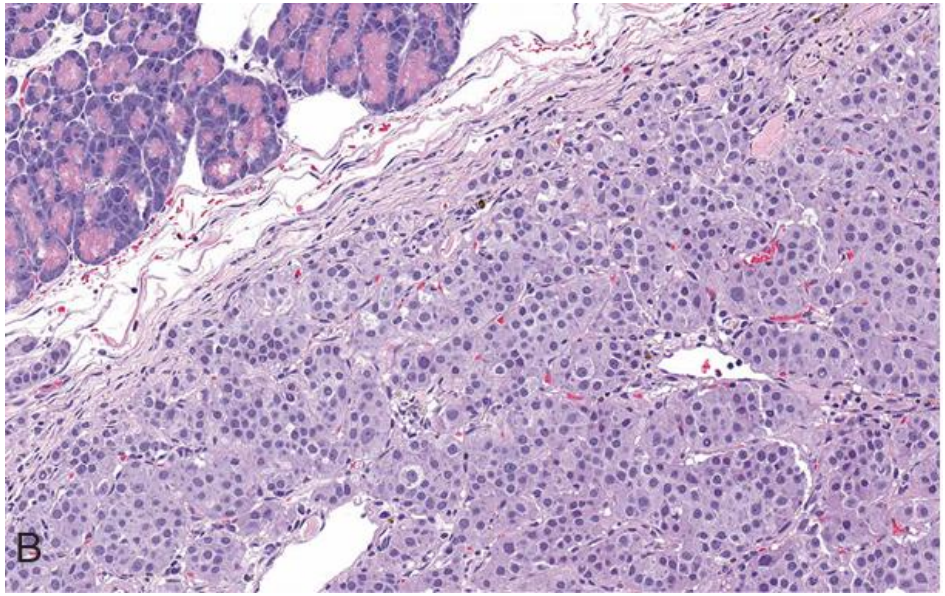
Glucagon

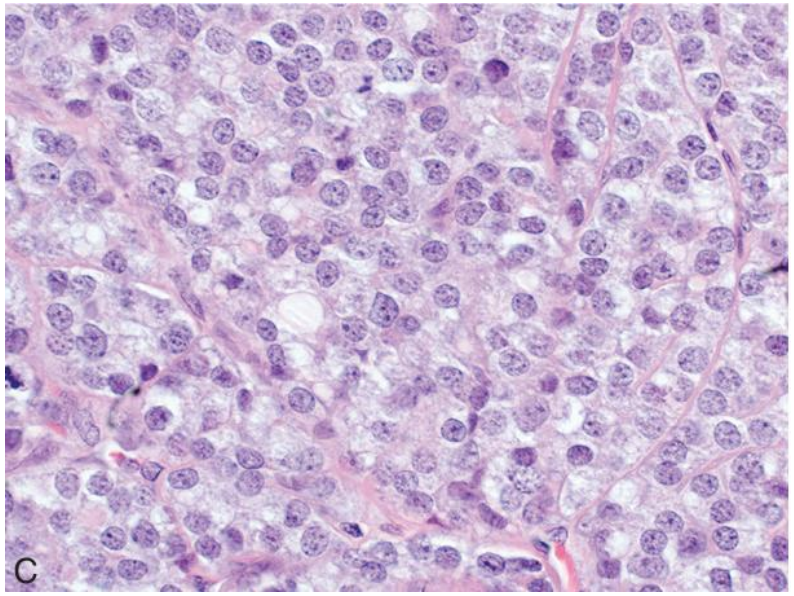


Insulin

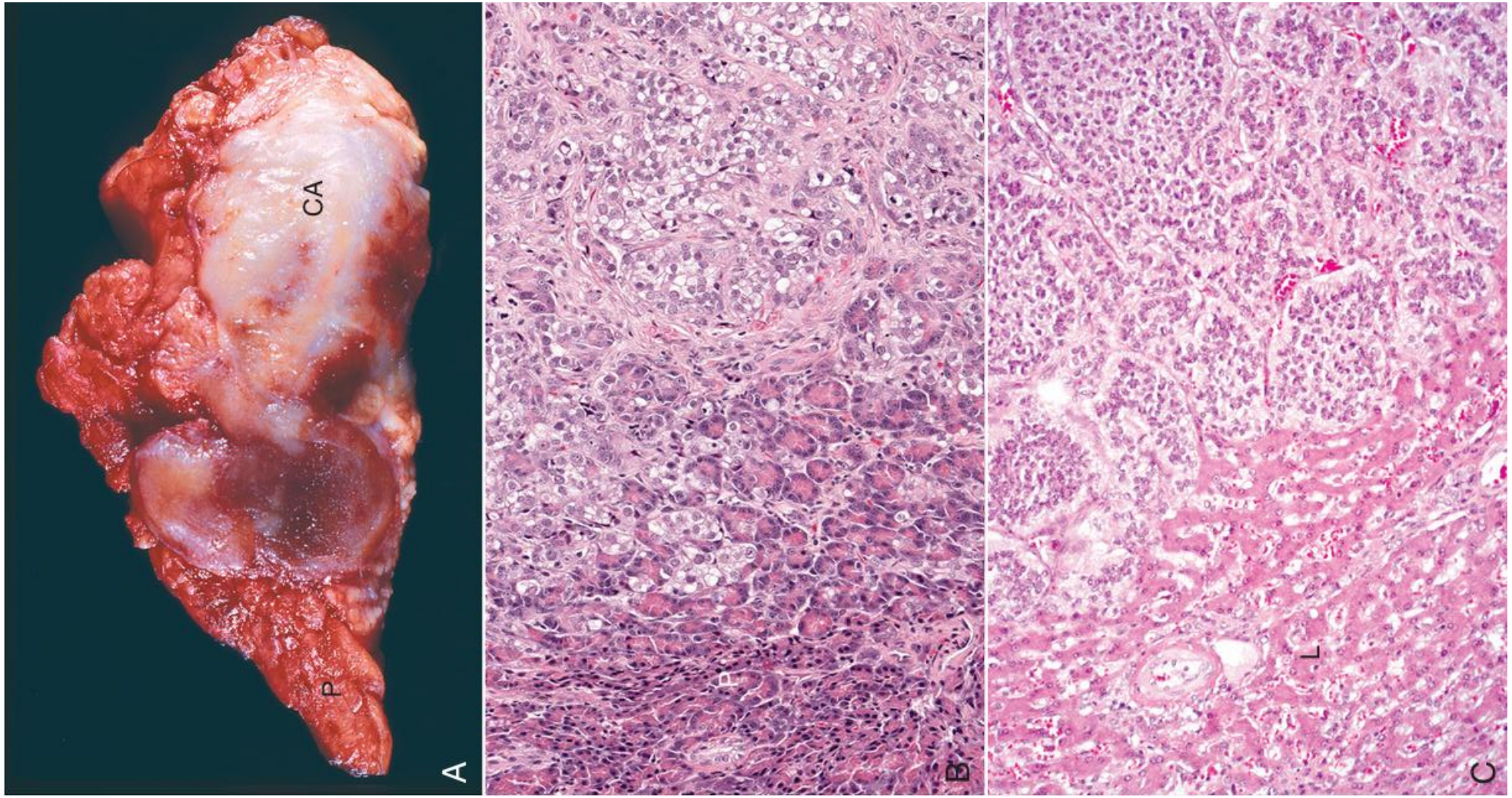








Pancreatic Endocrine tumors



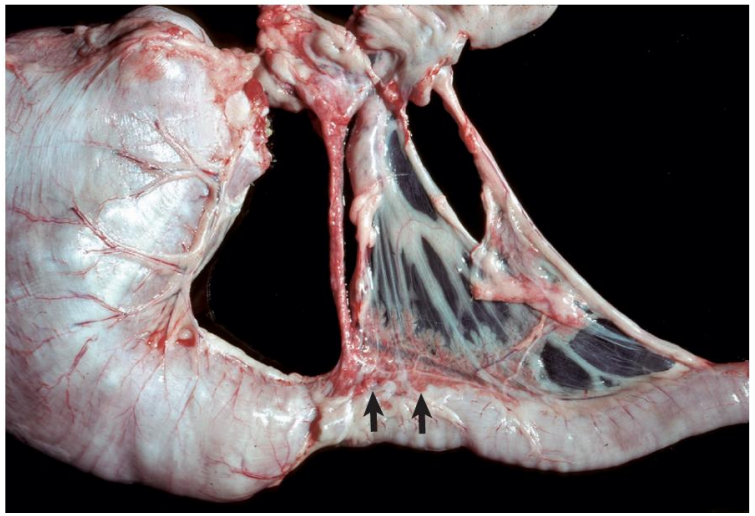
Other Conditions

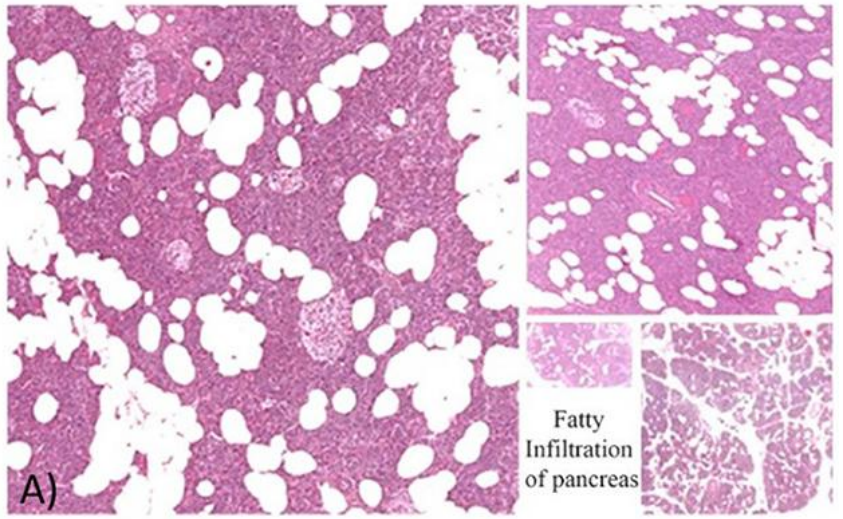
- Exocrine pancreatic atrophy (Juvenile pancreatic atrophy)

  -German Shepherd and Collies (6 to 12 months old)

  -Hypoplasia vs Atrophy

- Fat infiltration in obese cats (associated with obesity, diabetes mellitus (especially in cats), Chronic exocrine pancreatic atrophy)
- Pacinian corpuscles (mechanoreceptor): normal in feline pancreas





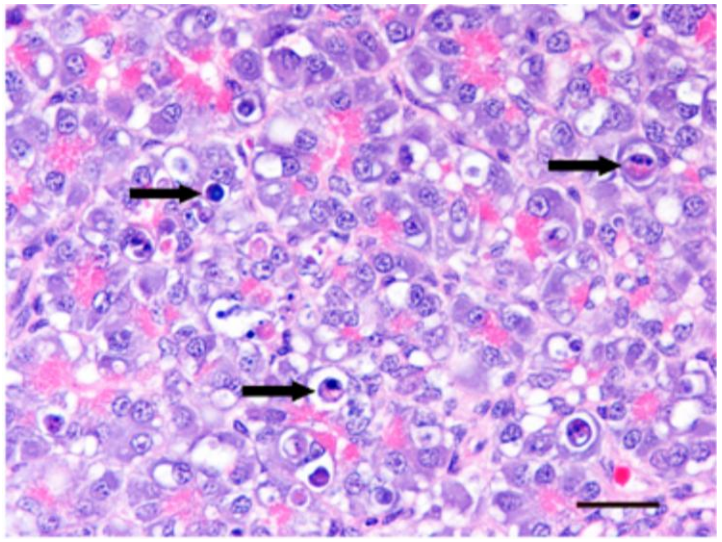
https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2023.1227188/full

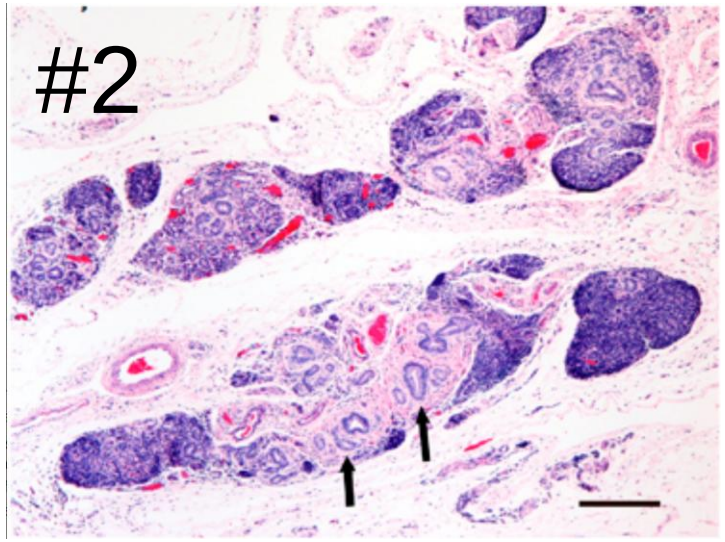


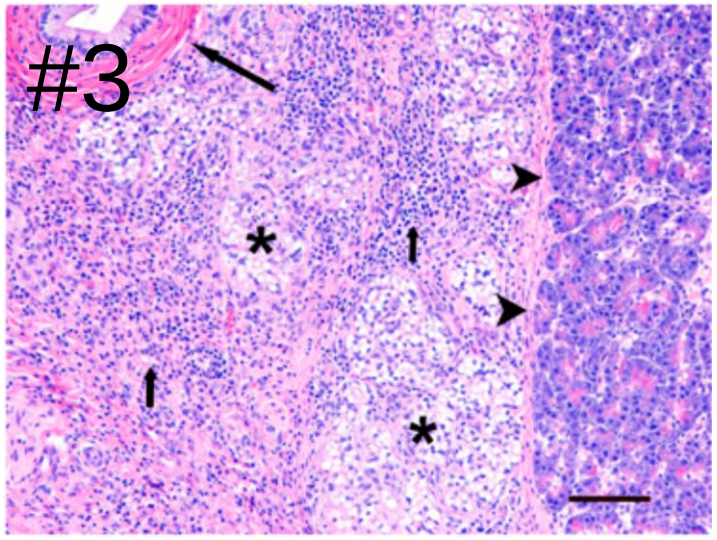
https://www.alamy.com/pacinian-corpuscle-located-in-a-cat-pancreas-it-has-a-thick-capsule-organized-in-concentric-lamellae-the-pink-central-point-is-the-nerve-fiber-image401743633.html

Juvenile pancreatic atrophy









Exocrine Pancreas Disorders in Ruminants

- Affected species: cattle, sheep, goats
- Major conditions: hypoplasia, nodular hyperplasia, pancreatolithiasis, parasites
- Most lesions are incidental; clinical disease is rare

Pancreatic Hypoplasia

- Sporadically seen in calves
- Endocrine pancreas usually normal
- Gross: pale, small pancreas; visible as white streaks in mesentery
- Histology: poorly organized acinar tissue, few zymogen granules
- Clinical: exocrine pancreatic insufficiency (EPI)

Nodular Hyperplasia

- Occasionally seen in cattle, especially older animals
- Nodules: firm, pale, with or without zymogen granules
- Micro: unencapsulated acinar aggregates, may resemble adenoma
- Clinically insignificant but can mimic neoplasia grossly

Pancreatolithiasis (Pancreatic Calculi)

- Rare in cattle, often incidental finding at slaughter
- More frequent in cattle >4 years of age
- Rarely causes duct obstruction or secondary pancreatitis

Parasitic Diseases

- Ductal parasites include flukes (Opisthorchiidae, Dicrocoeliidae)
- Eurytrema pancreaticum: most notable in ruminants
- Effects: duct obstruction, inflammation, fibrosis
- May cause segmental pancreatitis

Stromal Fat Cell Infiltration

- Infrequently reported in ruminants
- More common in obese animals
- Histologic: adipocytes within stroma, displacing acini
- No significant impact on pancreatic function

Chronic Pancreatitis in Ruminants

- Rare and usually subclinical
- Can result from parasite migration or ascending infection
- Histology: interstitial fibrosis, mononuclear inflammation
- Fibrosis may lead to parenchymal atrophy

Other Lesions and Findings

- Ectopic pancreatic tissue rarely documented
- No consistent congenital anomalies reported beyond hypoplasia
- No significant neoplasms documented in routine practice