INTRODUCTION TO HISTOPATHOLOGY
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1. HISTOPATHOLOGY UNCHANGED IN THE LAST 150 YEARS

The technique of histopathology began around the time of the discovery of “cells” and when the Germ Theory of Disease was still just a theory.

Medical science has progressed remarkably in the last 150 years Ψ cloning genes, manipulating the genetic code, inhibiting receptors. We are diagnosing disorders by repositioning atoms in a magnetic field, then letting them resonate and interpreting the image patterns this creates. And now we are placing pieces of genes and proteins on computer chips and analyzing these arrays for patterns that we will relate to specific medical and pathologic conditions. These are powerful techniques that allow us to look at many data points and associate the patterns with clinical disease. Yet we are still taking 3-5 Φ thick slices of tissue, staining them with plant dyes and looking at them through a light microscope; a 19th century technology!

“WHY”?

1. **Highly efficient Technique** - lots of information, acquired rapidly at low cost. Because of the cost issues in veterinary medicine, this technique will continue to be the first line of diagnosis or the confirmatory technique for some time to come.

2. **Extensive historical database** correlated with older as well as current medical technology that is still growing. We are now enhancing routine “H&E histopathology” by the ability to label proteins with highly specific antibodies and amplifying genes in situ so that we can not only determine what proteins and genes are present but their specific location within the tissues and sometimes which cellular organelles.

3. **Initially it was the primary basis for disease diagnosis**; it stills provides reliable confirmation of the diagnosis made by other clinical modalities. Although we probably have described the histopathology of most disease entities in humans, it is still the primary basis for disease characterization in exotic species and will have a central role in transgenic animal biology. It provides rapid identification of such emerging diseases as West Nile Virus, SARS, monkey pox avian influenza
“Why should we still do histopathology”?

“Prognosis at a price”

B. LESIONS AND PATTERNS IMPLY MECHANISMS AND PATHOGENESIS

1. We have integrated these with current concepts as medicine has moved to the biochemical, molecular and genetic levels of organization.

2. Very important in discovery and safety assessment for drugs and chemicals

   Histopathology is at the beginning of toxicity assessment guiding, directing the path of toxicity mechanisms

   New molecular techniques now permit in situ studies of gene expression so it too is evolving into a more dynamic tool beyond the simple “H&E slide” such as in vivo pathogenesis and mechanistic studies.

   With the expansion of transgenic animal biology, histopathology will be the bridge to associating genetic abnormalities with clinical disease expression.

C. GOALS OF THIS LECTURE

1. Learn some guidelines for how to “do” histopathology

2. Clarify the terms and definitions used by pathologists to facilitate communication

3. Reinforce your confidence to look at the histopathology of some organs;

D. APPROACH

1. Look at a spectrum of changes and processes in some different tissues
   a. Put guidelines into practice
   b. See examples of lesions and pathologic processes - enhances conceptual understanding of disease mechanisms
   c. See deductive logic that leads from observation through description to interpretation and diagnosis at the microscopic level

2. Look at a few “Cases” where we correlate gross or clinical appearance with histopathology
Histopathology is both science and art; a learned skill that requires practice. Pattern recognition coupled with understanding mechanisms is a powerful tool for a medical scientist but there is no magic. Its “visual pattern recognition”, not “rocket science”.

It can be learned by anybody with a desire to learn it. If you have some diligence, patience and the time, you can become proficient. Be patient with yourself. Give yourself time to learn. Don’t get discouraged. Keep at it. I’m sure we all remember when it took > 1 hr to spay a cat. Most experienced surgeons can do this in 15-20 minutes. Histopathology is much the same. Like any professional skill, the more you practice, the better you get. An understanding of the concepts, terminology, power and limitations of histopathology have value for all veterinarians engaged in biomedical science. “De-mystification” of histopathology makes it more accessible to all.

**APPROACH TO HISTOPATHOLOGIC INTERPRETATION**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>“Is it normal or abnormal?”</th>
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<tr>
<td></td>
<td>Normal</td>
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<th>Step 2</th>
<th>“You’re done”</th>
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<td>“What’s the abnormal part?”</td>
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<th>Step 3</th>
<th>“Describe it”</th>
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<td>“What structural subunits are affected?”</td>
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<th>Step 4</th>
<th>“Interpret a process”</th>
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<td>Morphologic Dx</td>
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<th>Step 5</th>
<th>“Make a diagnosis”</th>
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<td>Etiologic Dx</td>
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<td>Name a Specific Disease</td>
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**Supplemental Data**

- **Clinician dependent**
  1. Signalment
  2. History
  3. Clinical Data
THE ELEMENTS OF A HISTOPATHOLOGIC DESCRIPTION

A. **Location** of Lesions

Which organ, tissue or anatomic subunit is affected?
- Kidney, cortex, proximal tubules
- Liver, central lobules
- Lung, terminal bronchioles

*Fixing the precise anatomic location of the lesion sets the frame of reference so the reader knows exactly where the lesion is*

B. **Distribution** of Lesions = The pattern of spatial arrangement of the lesions within the frame of reference

- **Focal**
- Multifocal
- Multifocal to coalescing
- Multifocal widespread
- Military – “thousands”, to numerous to count
- Segmental
- Symmetrical; bilateral
- Diffuse
C. Something **Added** - “The tissue contains something not normally present”

*Cells* - normal, inflammatory, neoplastic

*Substances* - fluid, air, pigments  
  (melanin, hemoglobin), stroma  
*Agents* - microbial agents,  
  foreign bodies

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D. Something **Missing** - “The tissue looks different with normal elements gone”

*Cells* - atrophy, hypoplasia, necrosis

*Substances* - fluid, air, stroma

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E. Something **Altered** - “The normal tissue components are present but not normal”

*Degeneration*  
*Dysplasia*  
*Metaplasia*  
*Neoplasia*
**INTERPRETATION OF HISTOPATHOLOGIC LESIONS**

A. **Degeneration and Necrosis** = “Cells Altered or Missing”

- Swollen, distorted or eosinophilic
- Lysed or ruptured, nuclear debris
- Coagulation vs liquefaction, caseous
- Necrosis vs apoptosis

* Necrosis often incites inflammation

B. **Inflammation** = “Normal reactive cells added to the tissue”

- Neutrophilic or suppurative (purulent)
- Eosinophilic
- Lymphoplasmacytic (nonsuppurative)
- Histiocytic or granulomatous
- Pyogranulomatous

C. **Disturbances of Growth** = “Abnormal growth and/or arrangements of cells”
Normal cells = hyperplasia

∴ in normal cells = hypoplasia or atrophy

Hobbits

[ or addition in abnormal cells = neoplasia. Benign vs malignant

D. Characteristics of Neoplasia

1. Rate of growth – a dynamic process difficult to measure in a slide

2. Mitoses – a dynamic process but it can be roughly estimated by a mitotic index

3. **Differentiation** = the extent of resemblance to normal tissue or cells
   *Well differentiated*
   = fully developed normal cells and architecture

Normal adult perianal gland
**Poorly differentiated**
= abnormal immature undeveloped appearing cells and architecture; not recognizable yet as normal structure

4. **Anaplasia** = lack of differentiation. Primitive At an early stage of development. Pleomorphic, hyper chromatic nuclei. Large nuclei/ prominent nucleoli Bizarre, large cells; Disoriented Many mitotic figures

5. **Invasion** = “Cells where they shouldn’t be locally” = Infiltration of abnormal cells into the surrounding tissue Stimulate host reaction; desmoplasia, inflammation, necrosis
6. **Metastasis**  “Cells where they shouldn’t be far away”

= Localization of abnormal cells in sites distant from the tumor

Lymph nodes, 1st capillary bed. Lymphatic vs vascular

<table>
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<th>Characteristics of Benign and Malignant Neoplasia</th>
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<td><strong>Benign Tumors</strong></td>
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<td>Growth</td>
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<td>Mitoses</td>
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<td>Differentiation</td>
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<td>Anaplasia</td>
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<td>Invasion</td>
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<td>Metastasis</td>
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E. **Disturbances of Circulation** = “*Fluid where it shouldn’t be*”

*Edema* - extravascular fluid; interstitium between cells and structures.
*Look for dilated lymphatics.*

*Congestion* - excess *INTRAVASCULAR* blood; engorged capillaries/venules

*Hemorrhage* - *EXTRAVASCULAR* blood.

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**FORMULATING A MORPHOLOGIC DIAGNOSIS**

*MORPHOLOGIC DIAGNOSIS* = A phrase or 1-line summary of the primary or most important pathologic processes present in the tissue. It should always include a distribution of the lesions.

- Kidney, multifocal, fibrinopurulent glomerulonephritis
- Intestine, diffuse, granulomatous enteritis
- Liver, multifocal, widespread, massive, hepatocellular necrosis and hemorrhage
- Lung, diffuse, proliferative and exudative interstitial pneumonia
- Heart, multifocal widespread myocardial degeneration with proliferation
- Pancreas, focal coagulation necrosis with suppurative inflammation

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**FORMULATING AN ETIOLOGIC DIAGNOSIS**

*ETIOLOGIC DIAGNOSIS* = A phrase denoting both a pathologic process AND cause. Often it = naming a specific disease entity.

** This is the most desirable result of the histopathologic examination

1. See the specific disease agent
2. Usually requires supplemental data i.e. signalment, history, clinical data
Morphologic Dx          Etiologic Dx

Kidney, multifocal fibrinopurulent glomerulonephritis
Intestine, diffuse granulomatous enteritis
Liver, multifocal widespread hepatocellular necrosis & hemorrhage
Lung, diffuse exudative and proliferative interstitial pneumonia
Heart, multifocal widespread Myodegeneration w/ proliferation
Pancreas, focal coagulation necrosis with suppurative inflammation

Embolic nephritis
Intestinal histoplasmosis
Hepatosis dietetica, clay-pigeon poisoning, gossypol toxicity
Pulmonary toxoplasmosis
Nutritional cardiomyopathy
Vit E/Se def, white muscle disease
Acute pancreatitis

I. KIDNEY
Architectural Organization

A. Glomeruli
B. Tubules
C. Interstitium
D. Vasculature
1. **Glomerular Lesions**
   a. Inflammation ([glomerulonephritis](#))
      1) Exudative GN ~ septic embolism in a pig. The Bowman’ space is
distended with fibrin, hemorrhage and pyknotic cellular debris which
likely is dead neutrophils.

      2) Membranous GN in a dog with CRF - glomerular thickening/sclerosis.
This dog has segmentally thickened mesangium and hyperplastic parietal
epithelium lining the wall of the Bowman’s capsule

      3) Membranoproliferative GN in a dog with chronic renal disease. This
image the glomerular mesangium is diffuse thickened with homogeneous
pink material that obliterates the glomerular filter. Also there is marked
hyperplasia of the parietal epithelium producing an epithelial crescent.
The combination is termed membranoproliferative and is a hallmark of
long term change.

   b. Amyloidosis - pink homogeneous fine fibrillar material fills mesangium
May also be found in the interstitium. The mouse has a glomerulus that looks very
similar to the dog with membranoproliferative disease.
Dog w/ membranoproliferative GN

Fibrin & hemorrhage

Hyperplasia

Mesangial thickening

Pig w/ exudative GN - septicemia

Dog w/ segmental exudative proliferative GN

Fibrin

Crescents

Mouse w/ Amyloidosis
2. **Tubular Lesions**
   
a. Acute tubular necrosis (ATN = “nephrosis”).
   Selective necrosis, sloughing of “selective” tubular epithelium.
   Differentiation from autolysis is determined in that nephrosis usually does not
   affect all of the tubules in a slide whereas autolysis often affects all tubules
   equally. The assessment of nephrosis in autolyzed kidneys is usually a “fool’s
   errand”.

   1) Common response to toxins, ischemia - with time the *epithelium*
      *regenerates* - look for evidence of young, proliferating cells and mitotic
      figures. In acute necrosis, the remaining viable epithelial cells flattened
      out and “slide over” to cover the basement membrane in a process called
      “**Restitution**”

   2) Ethylene glycol toxicity - many oxalate crystals in tubules polarize light

b. Tubular dilation, proteinuria, casts - often ~ interstitial lesions.

c. Tubular atrophy - ***easily overlooked because tubules are not there!***
Interstitial lesions

a. Inflammation - cells between the cortical and medullary tubules; = interstitial nephritis. Anything deposited in the interstitium potentially disrupts the concentration gradients and $\rightarrow$ ↓ renal function and ultimately cause Renal Failure. Like fibrosis often distorts the architecture.
4. **Vasculature** - vasculitis or its effects. *Look for geometric shaped lesions.

   a. *Cortical infarction* - wedge or triangular shaped foci in the cortex~ septic embolism. Very common. Often do not see the obstruction. Vasculitis is inflammation within the wall of the blood vessel. It may be cells or a pink smudgy deposit called **Fibrinoid necrosis**.

5. **Pyelonephritis** = inflammation centered on the renal pelvis or medulla

   a. Look for necrosis, suppurative inflammation (tubular and interstitial) deep in the medulla. Most is ascending but descending can occur. Bacterial infection is a common cause
6. **Neoplasms** - “domestic” or “imported” (primary or metastatic)
Primary renal neoplasia well reported but uncommon. Obliterative infiltrations of atypical cells that do not belong.

**CASE NO. 1**

**Mouse Kidney w/ Lymphoma**

**3 mo old Sprague-Dawley rat treated w/ 25mg/kg methylprednisolone PO for 6 wks**

Std protocol to induce *Pneumocystis* pneumonia

Rat became weak, lost wt, sacrificed

**Postmortem:** multifocal random 1mm white nodules in the kidneys
II. LIVER
Architectural Organization

- **Lobules** - contain sinusoids and hepatocytes, Kupfer cells
- **Portal triads** - contain bile ducts, arterioles, venules, lymphatics
- **Capsule**
DISTURBANCES OF CIRCULATION

1. Congestion - excess blood in sinusoids or vessels. Stasis in the liver often ~ RT sided heart failure and occasionally shock

2. “Hemorrhage” often accompanies necrosis in lobules. Patterns of lesions in lobules distinctive for different diseases. Lesions may be:
   
   1) Centrilobular
   2) Midzonal
   3) Periportal
   4) Massive = entire lobule affected
This liver from a pig w/ hepatosis dietetica has massive necrosis meaning the entire lobule is affected. The hepatocytes are gone and blood is pooling where the cells once were. The same pattern is seen in cocklebur toxicity, coal tar pitch poisoning and gossypol toxicity.

3. **Hydropic degeneration/Lipidosis** - clear swollen cells squeeze sinusoids closed. Common response to many insults. Distribution ~ pathogenesis; multifocal vs diffuse

Hepatic Lipidosis in a dog with diabetes mellitus, Cushing’s Disease and Idiopathic feline hepatic lipidosis, and diabetes mellitus are common diseases with lipidosis.
4. **Necrosis** - Swollen, eosinophilic cytoplasm, faded nuclei with karyorrhexis and pyknosis. Distribution ~ pathogenesis; focal, multifocal vs diffuse. “Multifocal implies an embolic shower” i.e. septicemic or infectious disease. Diffuse may ~ toxic or metabolic disease

5. **Inflammation = Hepatitis.** May be acute or chronic or mixed. The elements of chronicity: 1. *Fibrosis* 2. *Plasma cells* 3. *Proliferation or regeneration*

Chronic cholangiohepatitis in a cat - inflammation, fibrosis, nodular regeneration, biliary hyperplasia
Nodular regeneration and “cirrhosis” = “architectural reorganization of the liver”. Often the end stage of chronic insult from a variety of causes i.e. hepatitis, toxic hepatopathy, immune-mediated and metabolic disease with/without fibrosis.

In the dog w/ chronic hepatitis and nodular regeneration you can see a distinct nodularity to the liver tissue. The horse w/ chronic aflatoxicosis has extensive replacement of the liver tissue with fibrous connective tissue.

7. **Atrophy** - loss of functional hepatic parenchyma. If severe enough you will see liver failure. If diffuse and symmetrical, difficult to appreciate. Especially microscopically. Liver wt may be a good objective measure of the loss of hepatic parenchyma, especially in lab animals. If atrophy is severe enough, you may see the signs of liver failure such as icterus, bleeding ~ lack of clotting factors.
8. Neoplasms - Unusual or atypical cells in any location. Always consider “domestic” tumor first, then “imported” tumors. Primary liver tumors are common i.e. bile duct tumors, hepatocellular tumors. The liver is also a common location of metastases such as HSA and LSA.

Canine liver with portal infiltration by LSA

9. Parasites - easily recognized as something REALLY strange that does not belong there. *Capillaria hepatica*

Case 2

40 wk old New Zealand White Rabbit
Depressed appetite, ?, wt gain and mild hyperbilirubinemia
Postmortem: multifocal uniform symmetrically arranged white nodules in the liver
Hepatic Coccidiosis

Weanling rat depressed with ruffled hair coat was removed from study and sacrificed.

Postmortem: Miliary 1mm well demarcated white foci in the liver.

Case 3

Cystic biliary hyperplasia

Eimeria stiedae
Rat liver w/ Tyzzer’s Disease

Focus of hepatic necrosis w/ suppurative inflammation

Basophilic filamentous rod-shaped bacteria within hepatocytes at the edge of the lesions
III. LUNG
Architectural Organization

A. Airways - bronchi, bronchioles
B. Alveoli
C. Alveolar septae
D. Interstitium - perivascular and peribronchiolar

1. Inflammation = “Pneumonia”. Can be divided into 2 patterns that often relate to pathogenesis.

   a. Pneumonia centered on airways = “Bronchopneumonia”
   Pneumonia with an aerogenous pathogenesis.
   Pattern is that of multifocal intensified inflammation highlighting airways
   Look for loss of epithelium, necrosis. Character of the reaction ~ pathogenesis
   Look for causes - infectious agents - viral inclusions, bacteria, fungi, parasites
   * Exudate within the wall of the airway vs pulmonary clearance of alveolar inflammation. Look for local reaction by airway. Airways may become completely necrotic and obstructed with sloughed cells, suppurative exudates
   3. Cat with herpes virus bronchiolitis

Monkey with bronchiolitis & pneumonia
Caused by measles

Cow w/ *Archanobacterium pyogenes* bronchopneumonia

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Cat lung with herpes viral necrotizing bronchiolitis ~ feline herpes virus. The lumen is filled with sloughed, necrotic epithelium mixed w/ neutrophils, plasma. Higher power would reveal eosinophilic intranuclear inclusion typical of herpes virus. The virus has caused lysis of the cells leaving the surface of the bronchiole uncovered or ulcerated.

b. **Pneumonia centered on the air-blood barrier (alveolar septa)** = “*Interstitial pneumonia*”; also called “*Pneumonitis*”. Pneumonia with a vascular or systemic pathogenesis. Pattern is diffuse more uniformly spread throughout lung. Can be divided into 2 types:

1) **Nonexudative** - thickened alveolar septae but alveolar lumens clear

Mouse lung with PVM~ interstitial Pneumonia. Increased cellularity in the hilus

Mouse lung with K-virus ~ interstitial pneumonia Note increased cellularity in entire lung
2) **Exudative** - alveoli filled with exudate, fluid, sloughed cells

Cow with chemical pneumonitis (3 MI toxicity). The alveoli are flooded with edema fluid and neutrophils. The capillaries are congested.

3) **“Proliferative Pneumonia”** = the recovery phase following epithelial necrosis in which there is hyperplasia of tall Type II pneumocytes and remodeling into the flattened Type I cells covering the alveolar septae.

Toxoplasmosis in cats = an exudative and proliferative interstitial pneumonia. There is Type II pneumocyte hyperplasia at the same time there is epithelial necrosis and exudation of neutrophils and macrophages into the alveolar lumens. Higher magnification would reveal many toxoplasma gondii organisms within cells and free in the alveolar lumens.
Multifocal interstitial pneumonia suggests an embolic event

The image on the Lt is from an antelope with embolic mycotic pneumonia caused by *Aspergillus*. On the Rt is a rat with *Corynebacterium kutcheri*. In both cases the infection spread systemically creating the multifocal pattern in the lung.

4) “Bronchointerstitial Pneumonia” = a mixed pattern with elements of both.

Fly ash inhalation in a mouse complicated by Sendai virus infection. There are elements of both airway associated inflammation related to the inhalation of fly ash particulates as well as inflammation centered on the air blood barrier caused by infection with Sendai virus.

Metaplasia (not pictured) = the replacement of the normal cell type in a tissue by another cell type not usually found in that location. Squamous metaplasia of epithelium often ~ chronic irritation or metabolic disorder.
3. **Atelectasis** = collapse of the alveoli. The lung looks denser. Atelectasis is usually secondary to another process such as airway obstruction or compression.
* Remember atelectasis normally occurs when the chest is opened. In small animals, pathologists often “inflate” the lung at necropsy to get better fixation and improve the view of the alveoli.

This pig lung looks dense because the alveoli have collapsed squeezing the air out. The atelectasis is caused by the presence of lung worms, *Metastrongylus* sp. in small airways which obstruct airflow and induce the atelectasis.

4. **Emphysema** = inflation of the alveoli beyond physiologic limits with destruction of septae. Look for abnormal open spaces in the lung parenchyma. Unusual in animals. Most “emphysema” in domestic animals is “interstitial emphysema” which = air where it should not be accumulating in the interstitial lymphatics, lobular septae or around vessels and airways. The emphysema seen in horses with COPD is more of a true emphysema as there is loss of alveoli and open spaces in the lung parenchyma.

The Lt image is a horse with COPD. There are open “cystic” spaces in the lung parenchyma that represent true emphysema. The Rt image is a cow with interstitial emphysema. You can see the gas or clear space is in the interstitial lymphatics in the interlobular septae.
5. **Edema** = fluid in the lung where it shouldn’t be. There are two type

1) **Alveolar edema** - flooding due to rupture of the air blood barrier. Commonly part of the exudate with pneumonia. Protein rich vs protein poor.

   In this lung you can see the alveoli are filled with a fine serofibrinous fluid laced with blood. The fluid is easily seen in this case because of the high protein content which precipitates out and is retained in the specimen preparation process. When the fluid has little protein only water exudes and this is washed out in processing so all you see is empty space. The confirmation of edema is made at gross examination when the lung is described as wet with fluid running out of the cut surface.

2) **Interstitial edema** - dilated lymphatics and spaces around vessels and airways.

   Usually protein poor. You just see clear space because there is no protein. It occurs as fluid flowing thru the lymphatics backs up before it spills over into the alveoli. Often a sign of fluid overload, or Lt sided congestive heart failure.

6. Perivascular inflammation or “vasculitis” - a sign of a systemic process simply manifesting itself in the pulmonary vessels. This is often a feature of systemic viral infection that has a tropism for the lung

7. **Neoplasms** - primary vs metastatic. The lung is a common site of metastasis. Primary or metastatic? Does the animal have a tumor somewhere else besides the lung?
The sub-gross photo of a cross section of the lung reveals the symmetrical, linear arrangement of the white nodules verifying that they are dilated ectatic bronchi filled with pus. This is consistent with bronchitis/bronchiolitis and progresses to bronchopneumonia which is consistent with the pathogenesis of chronic respiratory disease or murine respiratory mycoplasmosis caused by *Mycoplasma pulmonis*.

**Case 4**

12 mo old Sprague-Dawley w/ wt loss

Postmortem: Lung contained multifocal 5mm raised white nodules w. symmetrical distribution in the cranial lung
IV. GASTROINTESTINAL TRACT
Architectural Organization

A tubular organ system with regional segmental modifications but each segment has in common:

A. Mucosa composed of surface epithelium, glands and connective tissue
B. Submucosa - connective tissue
C. Muscular tunics - longitudinal and circumferential
D. Serosa with mesothelium

Inflammation of the mucosa = “Enteritis”. Look for abnormal inflammatory cells and signs of reaction by the body. A common process.

1. Epithelial necrosis, sloughed cells - surface and crypts
2. “Crypt abscesses” - accumulations of degenerate neutrophils in glands
3. Ulceration - look for reaction by body - congestion, hemorrhage fibrin exudation, neutrophils, edema
4. Villous collapse or atrophy
5. Epithelial regeneration - “young looking cells”
In short, use the power of histopathology = abnormal architecture

**Pitfalls to watch out for:

1. *Autolysis* - very common in the GI due to normal flora - no reaction.

2. “*Lymphoplasmacytic enteritis*” - the GI mucosa has a normal resident component of lymphocytes and plasma cells = immune response to gut antigens. How do you Dx lymphoplasmacytic inflammation in a tissue that normally has lots of lymphocytes and plasma cells? — Corroborative testimony. Look for supporting evidence of real inflammation.

**Fibrinonecrotic (pseudomembranous or diphtheritic) inflammation** = sloughed cells, fibrin, necrotic debris and inflammatory cells adhere to the ulcerated surface and form a “membrane” or layer over the surface. A common response to ulceration and necrosis and is seen in many infectious diseases.

a. Clostridial enteritis in a piglet - necrosis, hemorrhage, edema, rods
b. Parvoviral enteritis in a dog
c. *Balantidium coli* in a macaque
d. Mouse with coccidiosis ~ *Eimeria falciformis*

![Rabbit Intestine w/ Tyzzer's Disease](image)
There is diffuse congestion, hemorrhage, necrosis, fibrin, edema and gas; all the hallmarks of Clostridial infection.

There is loss of villous enterocytes with exudation of fibrin and hemorrhage. Often you can see rod shaped bacteria tangled in the fibrinonecrotic exudate. The villi are denuded of epithelium (necrosis and ulceration) and the villi are edematous and exhibit both congestion and hemorrhage.
In parvoviral infection the rapidly proliferating cells in the crypts are targeted and their death results in collapse of the villi with denudation of the surface. A fibrinonecrotic membrane forms over the surface but the overall appearance is that of no crypts, or dilated crypts with necrotic cells and flattened epithelium.

**Granulomatous enteritis** - “Space occupying inflammation” in the mucosa and submucosa that thickens the bowel wall but does not cause necrosis or a fibrinonecrotic exudate. In histoplasmosis in dogs and cats and in Johne’s Disease in ruminants, there is diffuse “space-occupying inflammation” beneath the epithelium that causes the mucosa to be thrown up into folds that resemble Morocco leather. Because there is no necrosis of epithelium, there is no fibrinonecrotic inflammation and so no pseudomembrane on the surface. In the photo to the Lt the submucosa is markedly thickened by the granulomatous inflammation. High power microscopy revealed many epithelioid macrophages filled with yeast forms of *Histoplasma*
**Epithelial hyperplasia** - often a response to epithelial necrosis; seen in the recovery or reparative phase of infection but can be a characteristic feature of some diseases.

Proliferative enteritis ~ *Lawsonia intracellularis* - crypt dilation, neutrophilic inflammation and marked epithelial hyperplasia. The organism stimulates the epithelium to proliferate at the same time it promotes inflammation. In this image you can very hyperplastic crypt epithelium but the lumens are filled with necrotic cells and neutrophils.

The colon is markedly thickened in transmissible murine colonic hyperplasia because the bacteria stimulate hyperplasia besides driving inflammation. Grossly these colons appear very thickened and opaque white because of the marked increase in the number of colonic epithelial cells.

Normal Mouse Colon          Transmissible murine colonic hyperplasia
3) **Villous “atrophy” or collapse** - If crypt epithelial proliferation stops, the villi become depleted of surface enterocytes and the villi collapse. The villi in the small intestine are shortened or nonexistent. A common feature of diseases causing crypt necrosis.

TGE in a pig with villous collapse
You can see the villi are shortened and blunted because the virus affects the crypt epithelium which keeps the villi covered. A higher magnification would reveal flattened immature villous enterocytes.

This high power view of the villus in a cat with panleukopenia caused by feline paroviral exhibits a shortened blunt villi covered by a flattened epithelium. The cat also has features of enteritis with inflammation and necrosis not visible in the image.
5) **Hydropic degeneration** of epithelial cells - nonspecific reaction to mild injury often ~ impairment of membrane ion pumps that results in fluid accumulation in the cytoplasm that appears as clear space or vacuoles.

Pig intestine with rotavirus exhibiting hydropic or vacuolar degeneration of the enterocytes primarily at the tips of the villi.
6) **Edema and lymphatic dilation** - outflow obstruction in vessels and lymphatics, vascular leakage result in accumulation of fluid in the bowel wall. Look for clear spaces in connective tissue or dilated lymphatics.

The image on the Lt is the GI of a dog with marked dilation of the central villous lacteal. It appears as clear space because it is filled with an extra cellular fluid without protein or cells. The fluid is so abundant that it markedly distends the lacteal. This lesion is typical of intestinal lymphangiectasia. The image on the Rt is that of a horse colon with acute salmonellosis. There is a pink pseudomembrane of fibrinonecrotic exudate on the surface but the submucosa is massively dilated by clear fluid that represents severe submucosal edema. In both cases the fluid (clear space) occurs where it should not normally be.
7) GI neoplasms - “atypical cells where they shouldn’t be”

This image is from a dog with intestinal LSA. The cellularity of the lamina propria and submucosa is markedly elevated, almost obliterating the architecture of the bowel wall and even extending into the muscular tunic. High power microscopy revealed atypical lymphocytes thus fulfilling the requirement for the diagnosis of atypical cells where they should not be. This can be a judgment call in some cases when the cells are confined to the lamina in much lower numbers because the lamina normal contains lymphocytes. But, normally there are no lymphocytes in the submucosa so cells in this layer of the bowel wall are highly unusual and abnormal. You must remember, however, GI LSA is most often diagnosed from endoscopic biopsies which only samples the lamina propria. So unless in early or nonuniform multifocal LSA, the diagnosis can be missed.
Case 5

Young adult baboon received a pig kidney in a transplant study. Post-op blood smear revealed malaria and the animal was sacrificed.

Postmortem: The bowel was thickened and contained numerous 2-4mm tan serosal nodules in the colon.
Egg granulomas in the lamina propria with macrophages and mixed lymphocytic inflammation surrounding eggs of Schistosoma sp. The image on the Lt is a section of both the male and female adult fluke in a vein in the submucosa. The adult female lays eggs in the wall of a mesocolonic vein and they are moved through the interstitium to the surface by the inflammatory response and shed into colon and feces.
V. HEART
Architectural Organization

A. Myocardium
B. Interstitium with vessels

1) **Myocardial degeneration** - a spectrum of changes ranging from swollen fibers with loss of striations (hyaline degeneration) to shrunken, hypereosinophilic, attenuated and abnormally arranged fibers such as in cardiomyopathy. Look for responses by myofibers exhibiting irregular or nonuniform fibers; enlarged hypertrophied nuclei, widened interstitial space between fibers and fiber disarray. The presence of Anitschow cells (Caterpillar Cells) and swollen hyalinized fibers that have lost striations.

Non uniform fibers with increased cell numbers, hypertrophied nuclei, expanded interstitial space and fiber disarray or interweaving of the myofibers. The clear space is likely edema.
Anitschow (Caterpillar) cells

Nuclear rowing
2) **Myocardial necrosis** - common response to ischemia, toxins, nutritional deficiencies, metabolic disorders. Often accompanies inflammation. In acute necrosis, there may be often mineralization or the fibers may be swollen, hyalinized with coagulated sarcoplasm, a change called **Rhabdomyolysis**.
3) **Myocarditis** = inflammation in the heart. Common response to infection. Character of the exudate is key to the cause and pathogenesis.

There is mixed neutrophilic and lymphoplasmacytic inflammation in the interstitium between the cardiac myofibers. There are degenerative changes visible in the fibers but the changes are interpreted to be secondary or caused by the presence of the inflammatory cells. Unlike in the purely degenerative lesion in which there is no inflammatory component to the lesion.

This heart is from a dog with suppurative myocarditis caused by systemic bacterial infection. Although there are lymphocytes and plasma cells present, the lesion is dominated by degenerate neutrophils that secrete proteases and toxic species of O2 that destroy myofibers which exhibit degenerative changes.
Chronic suppurative myocarditis in a rat with *Corynebacterium kutcheri*

There is inflammation, necrosis, fiber degeneration, necrosis, atrophy and fibrosis.

Rat heart w/ septicemia ~ *Corynebacterium kutcheri*
Puppy with Parvoviral “myocarditis”
There is interstitial edema, fiber degeneration, lymphocytic inflammation and intranuclear inclusions. The inflammation is lymphocytic reflecting the viral nature of the infection. While the inflammatory component of the lesion is most obvious, there are degenerative changes in the myofibers caused by the virus with only the intranuclear inclusions as footprints of the virus.
This heart features lymphocytes, plasma cells and macrophages in the interstitium between the myofibers, there are numerous amastigotes of *Trypanosoma cruzi* visible within the myofibers. Many myofibers are thin and attenuated, have lost striations and are becoming atrophied.

**Neoplasms - not common**

Cat heart with infiltration of large immature and atypical lymphoid cells typical of LSA. The cells infiltrate the interstitium between myofibers but do not cause myocardial necrosis.
Case 6

3 mo old Sprague-Dawley rat in an experimental mammary carcinogenesis study was gavaged with a carcinogen @ 8 wks of age and is now losing wt

Postmortem: **Diffuse fibrinopurulent pleuritis**
Gavage accident. Punctured esophagus inoculates normal flora into mediastinum → septic effusion. 4 wks later restrictive pleuritis. *Staphylococcus aureus* cultured
Fibrinopurulent Pleural Effusion w/ Staphylococci

MF's or mesothelial cells w/ phagocytized bacteria