Goals of the Talk

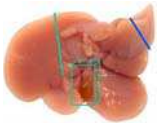
1. Provide brief background of toxicologic pathology of certain organ systems
2. Compare/contrast toxicologic pathology and lab animal diseases of each system
3. Discuss briefly drug-induced conditions that mimic common lab animal diseases
4. Compare/contrast histopathology between drug-induced and naturally occurring disease

Organ Systems to be Discussed

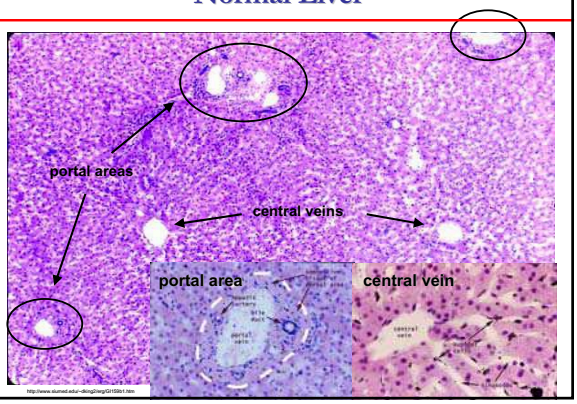
1. Liver
2. Pancreas
3. Respiratory Tract
4. Integumentary System

The Liver

- Adverse drug reactions less common than skin and gastrointestinal tract
  - Not predicted by animal studies; either allergic or non-allergic idiosyncratic in nature
- Hepatic toxicity is a challenge to contemporary hepatology in humans:
  - Apparently safe drugs occasionally produce severe adverse reactions in liver, e.g. aspirin
  - Hepatic drug reactions very difficult to diagnose b/c drug-induced injuries clinically mimic most hepatobiliary disease
  - Hepatic toxicity a common reason for termination of development of a new drug



Normal Liver

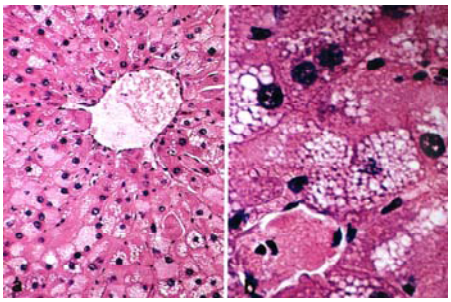


Toxicologic Pathology: Liver, Overview

- Hepatitis (Inflammation)
- Hepatic Necrosis
- Cellular changes associated with toxins
  - Hepatic fatty change (steatosis)
  - Hepatocellular hypertrophy & hyperplasia
  - Clear cell change
    - → Characterized by presence of clear cytoplasm & accumulation of glycogen in liver
  - Peroxisomal proliferation, associated with hepatic carcinoma in rodents

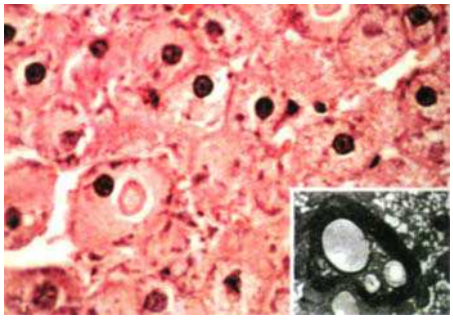
Steatosis

Imidazole antifungal agent



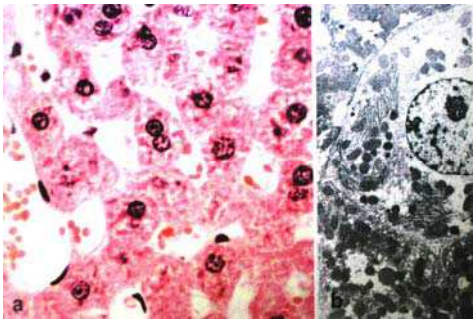
Hepatocellular Hypertrophy

Phenobarbitone



Peroxisomal Proliferation

Clofibrate



Lab Animal Liver Diseases

Rodents

- Tyzzer's Disease
- Mouse Hepatitis Virus infection
- Pseudotuberculosis
- Helicobacter infection
- Salmonellosis
- Hepatic cysticercosis
- Others

Nonhuman Primates

- Herpes B Virus infection
- Simian Varicella Virus infection
- Fatty Liver Syndrome
- Vitamin D deficiency
- Protozoal Merocysts
- Athesmiasis
- Cirrhosis
- Others

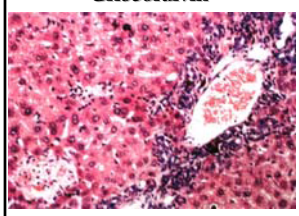
Inflammation/Hepatitis

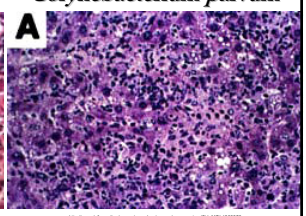
- Characterized by small aggregates of acute/chronic inflammatory cells grouped around small zones of necrotic or degenerate eosinophilic hepatocytes.
- Granulomas can be caused by particulate forms of a drug or metabolite precipitating in liver:
- **Hepatitis** – characterized by scattered foci of hepatocellular necrosis, vascular dilatation, hemorrhage, intranuclear inclusions

http://www.vetmed.wsu.edu/courses_vm5460/content_links/DiDo/Cat%20Case%204/chronic_hepatitis.htm

Drug-Induced Inflammation/Hepatitis

Griseofulvin ***Corynebacterium parvum***

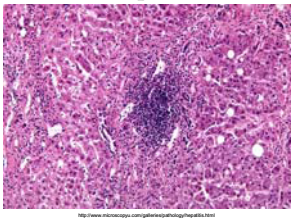




http://www.informatics.jax.org/searches/accession_report.cgi?id=MGI:1860200

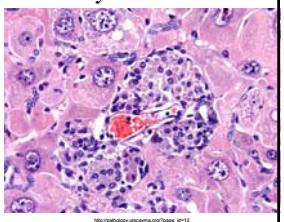
Naturally Occurring
Inflammation/Hepatitis

Mouse Hepatitis Virus



http://www.microscopyu.com/galleries/pathology/hepatitis.html

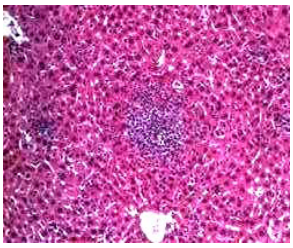
Mycobacteria



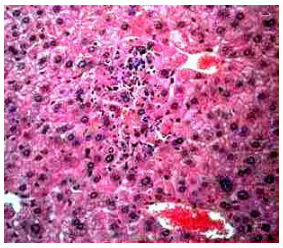
http://pathology.utacvma.org/?page_id=12

Naturally Occurring
Inflammation/Hepatitis

Salmonellosis

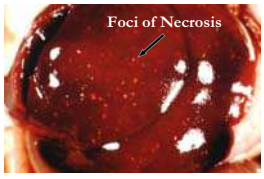


Helicobacter infection



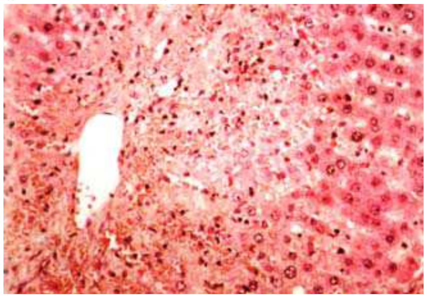
Hepatic Necrosis

- Occurs spontaneously in lab animals, but can be caused by high doses of therapeutic agents
  - Result of indirect mechanisms e.g. tissue anoxia, biliary stasis, disturbance of blood supply
- Types of Necrosis:
  - Focal, Centrilobular, Periportal,
  - Single cell necrosis (apoptosis)



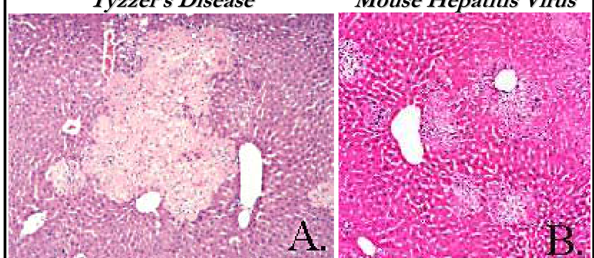
Drug-Induced Hepatic Necrosis

Experimental Antiproliferative Anticancer Drug



Naturally Occurring Hepatic Necrosis

Tyzzer's Disease ***Mouse Hepatitis Virus***



http://www.radil.missouri.edu/info/dora/mousepag/vir.htm

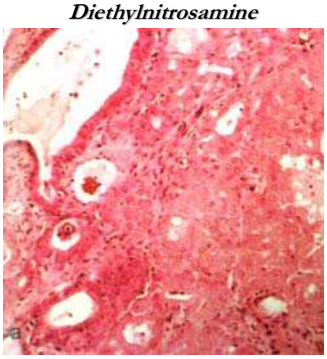
Hepatocellular Carcinoma

- Malignant tumors resembling hepatic parenchymal cells
- Occurs spontaneously in rodents with advancing age, rare among dogs and primates.
- Can develop ion response to genotoxic carcinogens
  - e.g. diethylnitrosamine, phenobarbitone
- In humans, most common primary malignant liver tumor, associated with chronic hepatitis and cirrhosis

http://www.vetmed.wsu.edu/MedSci520/images/neoplasia/n32.jpg

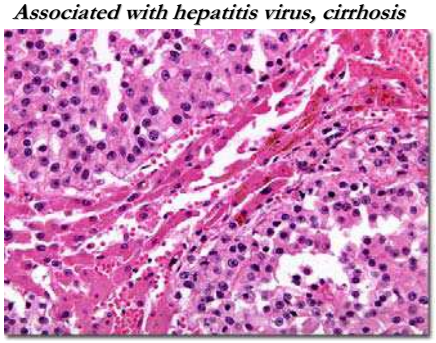
Drug-Induced Hepatocellular Carcinoma

Diethylnitrosamine



Naturally Occurring Hepatocellular Carcinoma

Associated with hepatitis virus, cirrhosis



http://www.microscopyu.com/galleries/pathology/hepatocellularcarcinoma.html

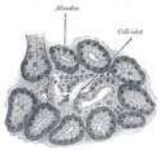
The Pancreas

Two basic anatomical patterns among lab animals:

- Mesenteric (rabbit, rat, mouse)
  - diffusely distributed in mesentery of small bowel
- Compact (hamsters, dogs, monkeys)

Drug metabolizing enzymes present in exocrine pancreatic tissue, inducible by certain chemicals

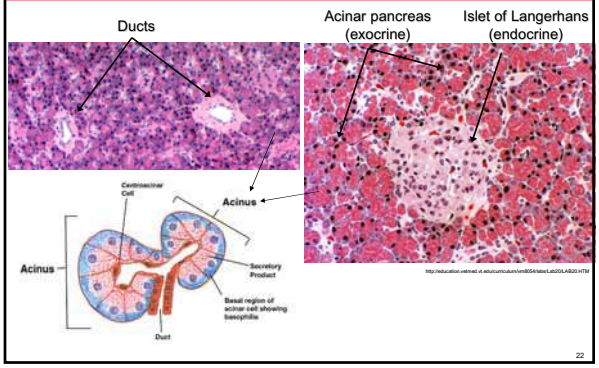
- Expression of enzymes vary among lab animal species
- Patients with chronic pancreatitis and pancreatic cancer are associated with altered immunoreactivity to these enzymes



http://commons.wikimedia.org/wiki/Image:Gray1105.png

http://www.med.upenn.edu/dbmlabb/research.html

Normal Pancreas



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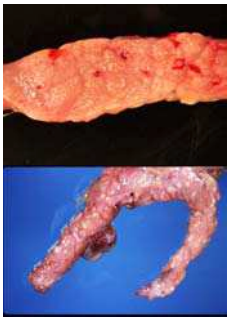
Toxicologic Pathology: Pancreas, Overview

- Pancreatitis/Inflammation
- Atrophy
- Pancreatic Necrosis
- Amyloid deposits
- Insulitis
- Duct Proliferation
- Hypertrophy, Hyperplasia, Neoplasia
  - Adenoma
  - Carcinoma

Lab Animal Pancreatic Diseases

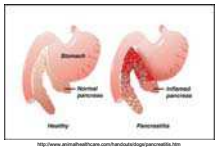
Dog (most toxicologic studies performed in dogs)

- Pancreatitis
- Pancreatic Tumors
- Insular Amyloidosis
- Multifocal Fat Necrosis
- Diabetes
- Others

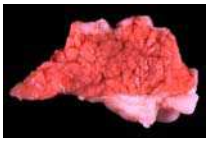


Pancreatitis

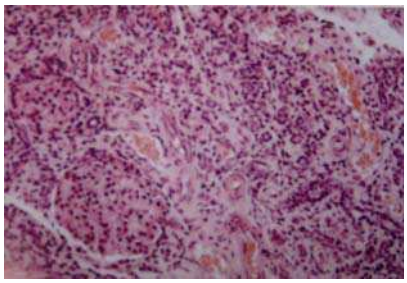
- Characterized by inflammation and pancreatic necrosis
- Pathogenesis of disease not well understood in lab animals
- Has been associated with wide range of drugs:
  - Corticosteroids, diuretics, antibiotics, antimitotics, anti-HIV, and other analgesic or anti-inflammatory agents
- Occasionally occurs spontaneously in rodents
  - Uncommon in lab dogs, more common in pet dogs



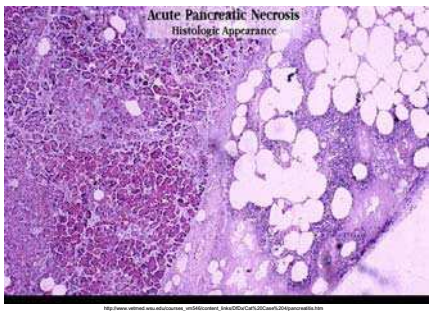
http://www.animalhealthcare.com/handouts/dogs/pancreatitis.htm


http://www.vetmed.wsu.edu/courses_vm546/content_links/DDx/Cat%20Case%204/pancreatitis.htm

Drug-Induced Pancreatitis



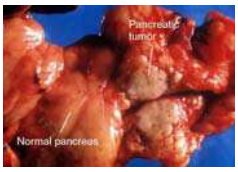
Naturally Occurring Pancreatitis



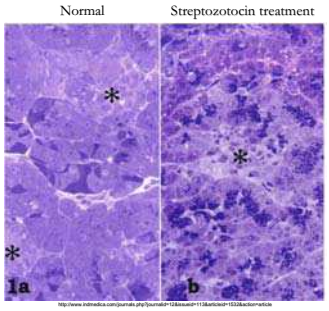
http://www.vetmed.wsu.edu/courses_vm546/content_links/DDx/Cat%20Case%204/pancreatitis.htm

Islet Cell Neoplasia

- Composed mainly of insulin-producing B cells
- Characterized by broad range of appearances such as large rounded islets, multilobulated islets, fibrosis, interspersed exocrine tissue, chronic inflammation
- Occurs spontaneously with advancing age or following administration of chemicals such as

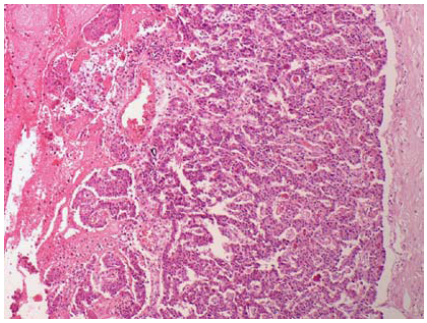


Induced Islet Cell Neoplasia



* Langerhan islets

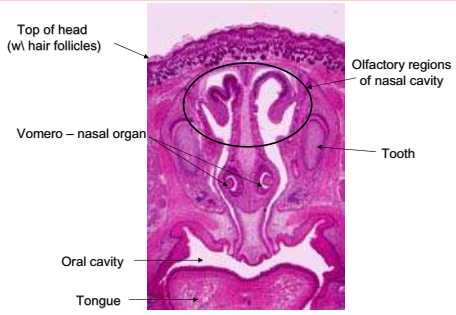
Naturally Occurring Islet Cell Neoplasia



Respiratory Tract

- In humans, most important lung diseases are related to tobacco smoking
  - Therapeutic agents remain relatively minor cause of pulmonary toxicity in humans
- However, drug-induced conditions are increasingly frequent in clinical settings
  - Can produce excessive effects on pulmonary function, mediate allergic reactions, precipitate thromboembolism/hemorrhage, etc.
  - Increase in number of drugs associated with parenchymal pulmonary injury e.g. anticancer drugs

Normal Nasal Cavity



http://education.vetmed.vt.edu/curriculum/vm8054/labs/Lab25/IMAGES/Trachea%20WITH%20LABELS%20SMALL.jpg

Toxicologic Pathology: Respiratory Tract, Overview

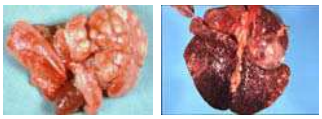
- Congestion
- Degeneration
- Inflammation
- Ulceration
- Edema
- Fibrosis
- Hemorrhage
- Neoplasia, Hyperplasia
- Emphysema
- Phospholipidosis

Lab Animal Respiratory Diseases

Rodents
- Pneumonia
- Tuberculosis
- Mycoplasmosis
- Streptococcal Disease
- Sendai Virus
- Bordetellosis
- Others

NHP
- Pneumonia
- Tuberculosis
- Herpes Virus
- Measles
- Parasites
- Simian Hemorrhagic Fever Virus
- Others

Dog
- Lung Cancer
- Histiocytosis
- Pneumonia
- Infectious Canine Hepatitis
- Others



Pulmonary Fibrosis

- Characterized by replacement of normal pulmonary structure by thickened collagenous matrix
  - Reduction in capactiy for gas exchange
- Associated with chronic lung injury from a variety of causes
- Occurs in lab animals as a response to parasite infestation, or as result of anticancer drugs i.e. bleomycin

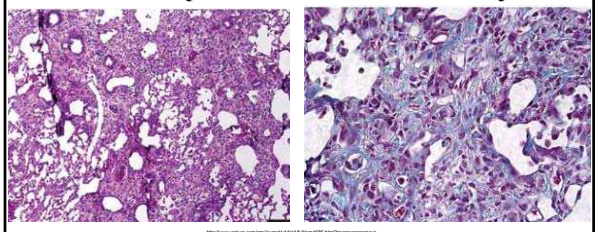
http://www.thehorse.com/ViewArticle.aspx?ID=11345&relID=32

Drug-Induced Pulmonary Fibrosis

Bleomycin

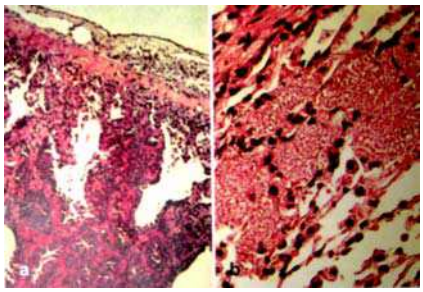
H&E staining

Trichrome staining



http://www.nature.com/nm/journal/v14/n1/full/nm1685.html?message=remove

Naturally Occurring Pulmonary Fibrosis

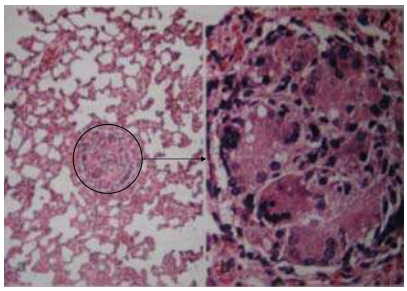


Granulomatous Inflammation

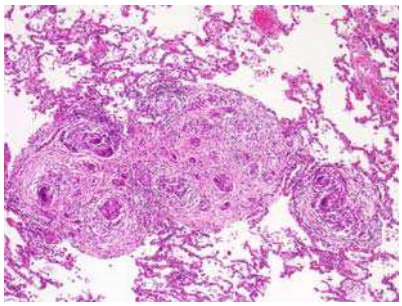
- Inflammation with granulomas develops in lab animal lungs under variety of different circumstances
  - Common cause results from aspiration of stomach contents or food particles
  - Dogs, primates more liable for parasite infestation
  - Intra-tracheal or intravaneous injection of relatively insoluble substances

http://library.med.utah.edu/WebPath/TUTORIAL/DRUG/DRUG022.html

Drug-Induced Granulomatous Inflammation



Naturally Occurring Granulomatous Inflammation

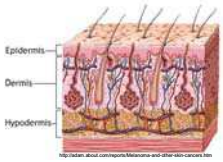


http://oac.med.jhmi.edu/pathconcepts/ShowImage.cfm?TutorialID=8&ConceptID=46&ImageID=225

Intergumentary System

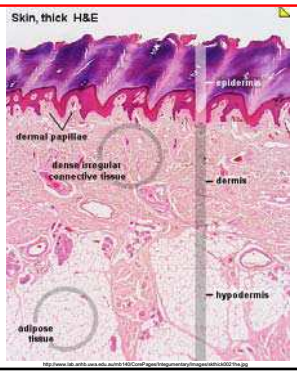
- Skin lesions among most common adverse reactions to clinical drugs
  - Non-steroidal anti-inflammatory drugs and penicilins associated with particularly high rate of adverse skin reactions
  - Incidence of skin carcinomas increases with duration of immunosuppressive therapy
- Skin may be particularly predisposed to drug hypersensitivity reactions
  - Integrated system of keratinocytes, Langerhans cells, and T lymphocytes mediates cutaneous immunosurveillance

http://vetwp.pdn.cam.ac.uk/Necropsy_of_the_Mouse/printable.php



http://adam.about.com/reports/Melanoma-and-other-skin-cancers.htm

Normal Skin Histology



http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Integumentary/Images/skthick002fna.jpg

Toxicologic Pathology: Skin, Overview

- Inflammation
  - Injection site
  - Implanted biomaterials
  - Systemic drug administration
  - Granulomas
- Hyperplasia/Neoplasia
- Necrosis
- Skin Irritancy
- Dermatitis
- Cutaneous phototoxicity
- Steatitis
- Haematopoiesis
- Hyper/Hypo pigmentation
- Elastosis
- Atrophy
- Alopecia

Lab Animal Skin Diseases

Mouse
- Mousepox
- Staphylococcus
- Mites
- Squamous cell carcinoma
- Streptococcal dermatitis
- Skin cancer
- Others

NHP
- Bacterial infections
  - Staphylococcus
- Viral infections
  - Papillomatosis, Herpes
  - SIV, Pox, etc
- Cancer
- Others

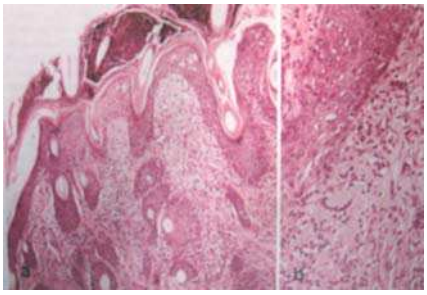
Dog
- Hyperpigmentation
- Allergies
  - Dermatitis
  - Anaphylaxis
  - Food
- Several bacterial/viral infections
- Fleas, Ticks, Mites
- Cancer
- Others

Inflammation, Dermatitis

- Can be induced by systemic drug administration, allergic reactions, phototoxicity, or implanted biomaterials
- Spontaneously occurs following loss of integrity of epidermal barrier
  - Localized infections, abrasions, minor traumas, excessive blood sampling,
- Nature and distribution of lesions allow toxicologists to make clear distinctions between intercurrent and drug-induced changes

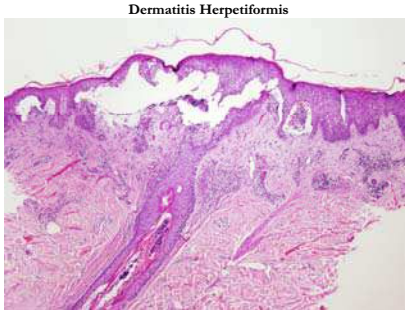
Drug-Induced Dermatitis

Anti-EGF treatment



Naturally Occurring Dermatitis

Dermatitis Herpetiformis



http://dermatology.cdlib.org/94/NYUNov2001/9.html