"All rats are not created equal"

- **Wistar**: The original outbred albino laboratory rat. Commonly used in Europe. Relatively small, long lived.
- **Sprague-Dawley** (Crl:CD®BR & Hsd:Sprague Dawley®SD®): Derived from Wistar stock around 1930; rapid weight gain, early sexual maturity, large.
- **F344**: Commonly used by the NIH. Small and long lived.

Choose your animal model well

- Use industry standard diagnostic criteria
- In toxicologic pathology, most hyperplasias are considered pre-neoplastic; criteria for diagnosis of hyperplasia vs adenoma is often based on size or expansile growth
- When an uncommon finding occurs in a treated animal, knowledge of spontaneous background findings in the same strain of rat and/or good historical data is essential for interpretation and assessment
REFERENCES

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Cardiovascular System

Cardiomyopathy

- Spontaneous, idiopathic, degenerative
- Incidence, severity, and age of onset affected by diet & stress.
- Males > females
- SD – early lesions by 3 months of age
- Gross: pale or tan streaks
- Micro: mononuclear infiltrates or inflammation, myofiber degeneration & necrosis, fibrosis
Atrial Thrombosis
- Dilated auricle
- Organised thrombus
- +/- emboli in other tissues

Endocardial Hyperplasia / Schwannoma
- Endocardial spindle cell proliferation
- May infiltrate myocardium & bulge into the ventricular lumen
- Size & extent of lesion dictates hyperplasia vs schwannoma

Polyarteritis
- Gross: nodular arterial thickening
- Micro: segmental fibrinoid necrosis of muscular arteries with fibrosis, mixed cell inflammation, +/- stenosis & thrombosis
- Common in mesentery, heart base, testes, epididymides
- Wistar > F344 or SD
Respiratory System

Alveolar Histiocytosis
- Prevalence: seen occasionally in young animals, but very common in older rats
- Cause unknown, not infectious or contagious
- White to pale tan 1-3mm areas on the pleural surface
- Clusters of foamy macrophages in alveoli and terminal airways

Digestive System & Liver
Malocclusion

- Incisors grow throughout life
- Malocclusion prevents normal wear
- Can interfere with food intake and cause weight loss
- Low incidence
- Occurs more often when rats are fed powdered diets, not pelleted food

Stomach Erosion / Ulceration

- Gross: red or black areas on the nonglandular or glandular mucosa
- Histo: necrosis / loss of epithelium with inflammation, granulation tissue
- Multifactorial; related to stress, irritating test articles, or powdered diets

Normal Liver

- Occasional mitotic figures & multinucleate hepatocytes are normal, increased numbers indicate pathology
- "Streamlining" - blood from different segments of GI tract concentrates in different liver lobes; toxins with segmental absorption may cause lesions in only one lobe; must examine multiple lobes.
Foci of Cellular Alteration

- Common in old rats
- Distinct areas in which hepatocytes differ in size & staining quality from surrounding hepatocytes, usu no compression
- Basophilic, eosinophilic, clear, vacuolated, or mixed
- Significance is somewhat controversial
- Increased incidence, esp basophilic foci, can be considered pre-neoplastic

Hepatocellular Adenoma / Carcinoma

- Adenoma:
  - Larger than one liver lobule, expansile
  - Loss of normal architecture
- Carcinoma:
  - Loss of normal architecture; trabecular pattern with irregular cords is most common
  - Cells can be fairly normal to pleomorphic
  - Invasive growth, mets

Bile Duct Hyperplasia

- Common; 20-50% incidence in older rats
- Not considered preneoplastic; bile duct neoplasms are rare
- No gross lesions
- Micro: proliferation of well-differentiated bile ductules, +/- fibrosis
Liver Lobe Torsion
- Acute: hemorrhagic coagulative necrosis +/- neutrophilic inflammation
- Chronic: fibrosis, variable necrosis & neutrophilic inflammation
- May occur in any lobe; usually the papillary process of the caudate lobe

Hepatodiaphragmatic nodule
- Nodule on anterior surface associated with small diaphragmatic hernia
- Microscopically normal hepatic tissue
- F344 > SD
- Differentiate from hepatic neoplasia

Pancreatic Lobular Atrophy
- No gross lesions
- Micro: atrophy / loss of acini with retained ducts, mononuclear inflammation, +/- fibrosis
- Common finding; increases with age
Urogenital System

Chronic Progressive Nephropathy (CPN)
- Most important disease of rat kidney
- Incidence & severity higher in males
- Common cause of early death on carcinogenicity studies
- Cause unknown; progressive: causes renal malfunction or renal failure

Chronic Progressive Nephropathy (CPN)
- Incidence varies with strain; SD may have early lesions by 3 months of age
- Calorie & protein restriction lowers incidence & severity
- Difficult to distinguish from drug-related effects in toxicity or carcinogenicity studies
Chronic Progressive Nephropathy (CPN)

- Gross: Shrunken, pale, and irregularly-shaped kidneys; surface pitted +/- small cysts
- Micro: Basement membrane thickening, ectatic tubules, protein casts, interstitial inflammation, fibrosis, tubular degeneration / regeneration, glomerular crescents, glomerulosclerosis

CPN related lesions

- Tubular hyperplasia
- Soft tissue mineralization (stomach, lung, blood vessels)
- Fibrous osteodystrophy

Renal Mineralization

- Distribution can be random or zonal
- Basement membranes, tubules, interstitium, pelvis
- Background finding, significance?
- Females > males
- F344 > SD & Wistar
Hyaline Droplets

- Protein resorption droplets in lysosomes of the tubule epithelium
- $\alpha_2\mu$ globulin in male rats (normal in P2 segment of PCT, more extensive with protein overload)
- Lysozyme in animals with histiocytic sarcoma

Nephroblastoma

- Multilobular tumor, usually at one pole of the kidney
- Composed of primitive embryonal blastema with tubular and glomeruloid structures

Renal Mesenchymal Tumor

- Arise near corticomedullary junction
- Composed of mesenchymal cells with differentiation into muscle, nervous tissue, cartilage or bone
- May entrap epithelial elements
- Rat specific
Genitourinary Inflammation
- Nonspecific chronic ongoing inflammation
- Common in old rats, esp males
- Caused by bacteria, but bacteria are rarely seen
- +/- calculi, epithelial hyperplasia
- May involve secondary sex glands (prostate, seminal vesicles)

Transitional Cell Papilloma / Carcinoma
- May arise within hyperplastic lesions due to chronic inflammation
- Complex branching fibrovascular core
- May see deep growth of epithelial nests; do not confuse this with infiltrative growth
- Transitional cell carcinomas have atypia & pleomorphism
- True invasive growth is rare

Testicular Atrophy (Hypospermatogenesis)
- Primary aging change or secondary to polyarteritis
- Also around interstitial cell tumors
- Multinucleated spermatids can occur in association or independently
Sperm Granuloma
- Foreign body reaction to extravasated sperm
- Not uncommon in older rats

Interstitial Cell Tumor
- Very common in F344 (~90% at 2 yrs), uncommon in SD & Wistar (<5%)
- Expansile mass of foamy polygonal cells, +/- hemorrhage, necrosis.
- Hyperplasia progresses to ICT
- Hyperplasia < 3 tubules diameter < ICT
- Nearly always benign

Ovarian Cysts
- Intraovarian
  - Follicular
  - Luteal
  - Glandular
- Paraovarian
  - Bursa
Teratoma
- Tumor of germ cell origin, usually in ovary or testes
- 2 or more germ cell layers present
- Neural tissue & epithelium often most prominent
- May also see muscle, fat or other tissues.

Endometrial Stromal Polyp
- Polypoid mass of endometrial stroma
- Very common; F334 > SD
- May undergo torsion / infarction
- Atypia & invasive growth $\rightarrow$ sarcoma

Endocrine System
Pituitary Hyperplasia

- Nonexpansile (distinguish from adenoma)
- Very common
- Cannot determine cell of origin without IHC

Pituitary Adenoma
Pituitary Carcinoma

- Expansile mass in pars distalis +/- hemorrhage
- Often compresses ventral brain
- Usually sharply demarcated (some diagnose carcinoma if infiltrative growth)
- Very common in SD (~80% in females, 60% in males). Slightly less common in F344 & Wistar.
- Nearly all are prolactin + with IHC

Islet Fibrosis / Pigmentation

- Idiopathic
- Occurs sporadically
- Affected islets are admixed with normal islets in the same section
Islet Cell Hyperplasia
Islet Cell Adenoma / Carcinoma
- Criteria is not clear cut, continuum of diagnoses
- Size, compression, cellular and nuclear atypia
- Carcinomas may be well encapsulated +/- evidence of breaking through the capsule
- Rarely metastasize

Adrenocortical Cystic Degeneration
- Aging change in rats
- Females > males
- SD > F344 & Wistar
- Affected adrenal glands are enlarged, soft, dark red, and mass-like
- Cell vacuolation & loss; dilated, cystic spaces that contain blood +/- thrombi.

Pheochromocytoma
- Males > females
- F344 > SD > Wistar
- Discrete expansile clusters of basophilic medullary cells +/- atypia
- If no compression, may be medullary hyperplasia
- Malignant if capsular invasion or mets
C-Cell Hyperplasia
Adenoma / Carcinoma

- Expansile mass of well-differentiated C-cells
- If >5 avg follicles in diam → adenoma
- Carcinoma: invasive with atypia, mitoses, or mets (lungs), +/- hemorrhage, mineralization or necrosis
- Incidence low (<5%), but still more common than follicular tumors

Lymphoreticular & Hematopoietic Systems

Thymic Atrophy / Involution

- Normal, age-related process – 100% incidence in old rats
- Identifying and collecting thymus in aged rats is difficult due to small size
- Microscopically, lymphocyte population is decreased, epithelial cells are more prominent and may form cysts.
Mononuclear Cell (LGL) Leukemia

- Common in F344 (~25%), rare in SD & Wistar
- Monomorphic round cell infiltrates in any organ (esp. spleen, liver, lymph nodes, bone marrow)
- May not see cytoplasmic granules

Histiocytic Sarcoma

- Monomorphic histiocytic infiltrates in any organ, often with spindle cell morphology
- Multinucleate giant cells
- Low to moderate incidence
- Lysozyme & ED-1+ by IHC
- May see hyaline droplets (lysozyme) in renal tubules

Lymphoma

- Monomorphic lymphocytic infiltrates in any organ
- Low incidence
- Rarely typed, but most are reported to be B cell origin
Nervous System

Astrocytoma
Oligodendroglioma
- Expansile mass with indistinct margins, blend with surrounding neuropil
- Rare
- Oligodendrogliomas tend to have more round nuclei, clear cytoplasm

Granular Cell Tumor
- Discrete, expansile mass of polygonal cells with PAS+ cytoplasmic granules
- Uncommon, benign
- Arise in meninges
Degenerative Myelopathy

- Common in old rats (15% in SD)
- May see posterior paresis or ataxia
- Also see sciatic nerve degeneration
- Demyelination, axonal swelling & loss, Gitter cells, reactive gliosis in the ventral & lateral tracts from T4 – L4

Special Sense Organs

Retinal Degeneration

- Thinning / loss of the outer nuclear layer, rods & cones
- More common in old rats, esp albino
- Light induced retinopathy; minimize by rotating cages in animal rooms or putting a solid “roof” on the cage racks
**Corneal Dystrophy**
- Early: basophilic granules along epithelial basement membrane
- Later: mineralization plaque along basement membrane and into superficial corneal stroma

**Cataract**
- Degenerate, swollen lens fibers
- Displacement of nuclei of lens epithelium
- Common in aged rats

**Zymbal's Gland Tumors**
- External auditory sebaceous gland
- Gross: Look like abscesses, express caseous material
- Micro: proliferative sebaceous & squamous elements
- Can grow very large very quickly, may invade into brain
- Mets to lungs may occur
Integumentary System & Mammary Gland

Galactoceles
- Very common in older rats, esp females
- Gross: cysts or masses
- Micro: affected ducts and glands are dilated, filled with secretory material, +/- cellular debris & inflammatory cells
- If ruptured, inflammation is more severe and extends into adjacent tissues

Mammary Fibroadenoma
- SD > F344 & Wistar
- Females > males
- Calorie restriction decreases incidence
- Occur anywhere except head, tail, & distal extremities
- Well circumscribed, firm, lobular mass with variable amounts of mature collagen & ductular / glandular elements
Ulcerative Pododermatitis
- Variably-sized ulcers on soles of feet
- More common with wire cages & ad libitum feeding
- SD > F344 & Wistar
- Males > females
- Micro: epidermal ulceration, chronic inflammation; +/- hyperostosis of underlying bone

Auricular Chondritis
- Trauma related (ear tags, bites); may be immune-mediated reaction to Type II collagen
- Low to moderate incidence in group housed animals of certain strains
- Gross: distorted thickened pinnae
- Micro: cartilage degeneration with hemorrhage & granulomatous inflammation

Squamous Papilloma
- Exophytic, squamous epithelium overlying fibrovascular core
- Low incidence
- Non-viral
Keratoacanthoma
- Multilocular / cystic invaginations lined by squamous epithelium & filled with keratin debris
- Incidence low
- May progress to squamous cell carcinoma

Preputial / Clitoral Gland Abscess
- Specialized sebaceous glands (paired) near the base of the penis or clitoris
- Gross: abscessed glands may be mistaken for skin or mammary neoplasms
- Micro: inflammation is generally chronic and ongoing, with marked dilatation of main ducts

Preputial / Clitoral Gland Adenoma / Carcinoma
- Acinar or squamous differentiation
- Acinar tumors have brightly eosinophilic cytoplasmic granules (rats only)
- Uncommon
- Carcinoma may met to lungs
Miscellaneous & Systemic Lesions

**Chordoma**
- Multilobular tumor of primitive notochord elements (physaliferous cells)
- May have chondroid or osseous differentiation
- Uncommon, usually located along the cervical or anterior thoracic spine

**Hibernoma**
- Multilobular tumor of microvesculate round to spindloid cells
- Originate in brown fat; usually on midline (intrascapular, periaortic)
- Historically rare; recent reports of moderate incidence in SD, Wistar
- Distinctive ultrastructural appearance, positive for uncoupling protein by IHC
- Mets to lungs are not uncommon
Mesothelioma

- F344 & Wistar (3-4%), SD (<1%)
- Gross: pale tan nodules on testis, peritoneum
- Micro: complex papillary fronds of stroma covered by mesothelial cells
- All are considered malignant
- Distinguish from simple mesothelial hyperplasia

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