"All rats are not created equal"

- Wistar: The original outbred albino lab rat. Common in Europe. Relatively small, long lived.
- Sprague-Dawley (Crl:CD®BR or Hsd:SD®): Derived from Wistar stock ~1930; rapid weight gain, early sexual maturity, large.
- F344: Commonly used by the NIH. Small and long lived.
How old is an old rat?

- Average lifespan ~24-36 months
- Sexual maturity at 8-14 weeks
- Estrus cycle is 4 days long; irregularities begin at 6-18 mos of age
  - Persistent estrus (vaginal cornification)
  - Repetitive pseudopregnancy (vaginal mucification)
  - Persistent anestrus - senescence

Factors that influence longevity

- Strain: F344 > Wistar > SD
- Diet: calorie, fat & protein restriction increase lifespan
- Pathogen status: SPF > conventional
- Reproductive status: retired breeders vs virgins

Choose your animal model carefully

- Use industry standard diagnostic criteria, be consistent with proliferative lesions – most hyperplasias are considered to be pre-neoplastic
- Knowledge of spontaneous ‘background’ findings is essential for interpretation and assessment
- Lab employees should NOT have pet rodents!
REFERENCES

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• The Standardized System of Nomenclature and Diagnostic Criteria: *Guides for Toxicologic Pathology - STP Website*
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Viral Diseases

Rat Parvoviruses

Three distinct antigenic groups:
• Rat Virus (RV), aka Kilham’s Rat Virus
  • Occasional clinical disease
• Toolan’s H-1 virus
  • Nonpathogenic
• Rat parvovirus (RPV-1 & RPV-2, Minute Virus (RMV))
  • Nonpathogenic
Rat Paroviruses
• Common in lab, wild, and pet rats
• Transmission: oronasal, transplacental, milk, feces, urine, fomites (persistent), common contaminant in biological products
• Replicates in dividing cells: lymphocytes, endothelium, bone marrow, hepatocytes

Rat Paroviruses
• Infertility, fetal resorption, abortion
• Immune dysfunction, cytokine stimulation, enhanced hepatocellular damage
• Gross: hemorrhage (esp peritesticular), cerebellar hypoplasia (neonates)
• Micro: hemorrhage/thrombosis, necrosis, IN inclusions
• Coronavirus
• Uncommon in lab rats, common in pet rats
• Transmission: aerosol, contact
• High morbidity, low mortality
• Harderian, salivary and lacrimal glands
• Sequelae: corneal ulcers, megaloglobus
• Immunodeficient - persistent infection

Sialodacryoadenitis virus (SDAV)
Hantavirus

- Rare in lab or pet rats; common in wild mice
- Transmission: feces, urine, saliva
- No clinical signs in rodents
- ZOONOTIC
  - Hantavirus cardiopulmonary syndrome
  - Hemorrhagic fever with renal syndrome
  - No effective antiviral treatment

Bacterial Diseases

Mycoplasma pulmonis

- Murine Respiratory Mycoplasmosis (MRM)
- Endemic in wild and pet rodents; infected animals NOT suitable for research
- Transmission: contact, aerosol, intrauterine
- Respiratory tract, middle ear, joints, endometrium
Mycoplasma pulmonis

- Bronchiolitis with bronchiectasis and lymphoid hyperplasia (cuffs) -> abscesses
- Suppurative rhinitis, otitis, arthritis, metritis
- Lymphoid hyperplasia (cell membranes are mitogenic for lymphocytes)
- Difficult to culture, fastidious, slow growing
  - PCR – acute infections
  - Serology - chronic infections
• Common in wild rodents and rabbits
• Common co-infection with *M. pulmonis*
• Transmission: contact
• Suppurative bronchopneumonia, bronchiectasis/bronchiolectasis, lymphoid cuffing
• Gram negative, Warthin-Starry positive
“Pseudotuberculosis”

- Rare in lab rats, prevalence in wild and pet rats not known
- Transmission: fecal-oral
- Persistent asymptomatic infections
- Embolic suppurative inflammation with necrosis in liver, kidney, lungs, spleen, LNs
- Gram + bacteria prominent in lesions
- Culture for definitive diagnosis
**Streptococcus pneumoniae**

- Gram + diplococcus
- Usually asymptomatic, no disease outbreaks reported in 35+ years
- Transmission: contact, aerosol, humans
- Fibrinosuppurative inflammation in young or immunosuppressed animals
- May exacerbate concurrent infections

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**Clostridium piliforme**

- Tyzzer’s Disease
- Intracellular, Gram -, silver +, filamentous, spore-forming bacilli
- Rare in lab rats, prevalence in wild and pet rats unknown
- Transmission: ingestion of infective spores from environment (up to 1 yr)
Clostridium piliforme

- Usually asymptomatic
- Disease → poor husbandry or immunosuppression
- Embolic white spots (necrosis) in liver
- Necrotizing colitis, typhlitis, (megalo)ileitis
- Organisms at periphery of lesions
Genitourinary inflammation

- Nonspecific chronic active inflammation of kidney, ureters, urinary bladder, urethra, prostate, seminal vesicles
- Caused by bacteria; rarely seen in lesions
- Common in old rats, esp males
- +/- calculi, epithelial hyperplasia

Pyelonephritis
Chronic Cystitis

Chronic Prostatitis

Preputial/Clitoral Gland Abscess

- Specialized paired sebaceous glands near the base of the penis or clitoris
- Caused by bacteria, but bacteria are rarely seen in lesions
- Gross: abscessed glands may be mistaken for skin or mammary neoplasms
- Micro: nonspecific chronic and ongoing inflammation, with marked dilation of main ducts
Fungal Diseases

Pneumocystis carinii

- Ubiquitous
- Asexual: binary fission → trophic form
- Sexual → ascus w/ 8 ascospores
- Asci inhaled, ascospores released in alveoli
- Attach to Type I pneumocytes and macrophages by fibronectin-binding integrins
- Pneumocyte necrosis, damage to alveolar basement membranes
- Type II pneumocyte hyperplasia
**Pneumocystis carinii**

- Immunosuppressed animals
- Distinctive eosinophilic, “foamy” material in distended alveoli
- Silver stains demonstrate fungi

2010: cause of “Rat Respiratory Virus”
- RRV first described in 1997
- Global distribution, 6% incidence in NA
- Diagnosis by microscopy
  - Lymphohistiocytic interstitial pneumonia w/ perivascular lymphocyte cuffs
- Lesions in young rats, naive rats introduced to an affected colony
- Rare in older rats, closed colonies

*Vet Pathol 46: 992-999, 2009*
Parasitic Diseases

Pinworms

- *Syphacia muris, Syphacia obvelata, Aspicularis tetraptera*
- Direct life cycle
- Eggs are persistent in environment – very difficult to eliminate once it is in a facility
- May affect growth rate, immune function, intestinal electrolyte transport
- No zoonotic risk

Mild @3 wks, severe @5 wks, resolved by 7 wks

Comp Med 61: 45-52, 2011
Oxyurids:
- Platymyarian musculature
- Rhabditiform esophagus (corpus, isthmus, and bulb)
- Thick shelled, embryonated eggs
- +/- lateral alae

Cysticercus fasciolaris
- Rare in lab, occasional in pets, common in wild rats
- Larval stage of cat tapeworm
  - *Taenia taeniaformis*
- Ingestion of eggs in cat feces
- 1-2 cysts in liver
- Granulomatous inflammation, fibroplasia → fibrosarcoma
Trichosomoides crassicauda

- Bladder threadworm
- Common in pet, wild rats
- Urinary bladder and renal pelvis
- Embryonated, bi-operculate, brown eggs
  - Pass in urine, ingested, hatch in stomach, systemic spread, larvae that reach urinary tract develop into adults
- Epithelial hyperplasia, little inflammation
- Association w/ calculi and neoplasia
Hyperplasia / Neoplasia

Mammary Glands

"Biology of the Laboratory Mouse", EL Green (ed), 1966

Fibroadenoma

- Most common mammary neoplasm (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
Mammary Adenoma / Adenocarcinoma

- Discrete epithelial mass with scant stroma
- Adenoma > carcinoma
- Criteria to differentiate benign from malignant are somewhat controversial
- Malignancy - atypia, high N/C ratio, mitotic activity, variable growth patterns
- Invasive growth, mets are uncommon signs of malignancy
Foci of Cellular Alteration

- Common in old rats
- Distinct areas in which hepatocytes differ in size & staining quality from surrounding hepatocytes, usu without compression
- Basophilic, eosinophilic, clear, vacuolated, or mixed
- Significance controversial, basophilic foci generally 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

Endocardial Hyperplasia/Schwannoma

- Endocardial spindle cell proliferation
- Size & extent of lesion -> hyperplasia vs schwannoma
Nephroblastoma

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

- Rat specific tumor with mixed mesenchymal elements
- Composed of primitive mesenchyme with differentiation into nervous tissue, muscle, adipose, cartilage or bone
- May entrap epithelial elements
- Arise near corticomedullary junction
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 with infiltrative growth
- Carcinomas have atypia & pleomorphism
- True invasive growth is rare
Interstitial Cell Tumor

- Common in F344 (~95% at 2 yrs), <5% in SD & Wistar
- Expansile mass of microvacuolated polygonal cells, +/- hemorrhage, necrosis
- Hyperplasia progresses to ICT
- Hyperplasia < three tubules diameter < ICT
- May be multiple or bilateral
- Nearly always benign
Teratoma

- Tumor of germ cell origin, usu in ovary or testes, rarely adrenal
- 2 or more germ cell layers present
- Neural tissue & epithelium usu most prominent; may have muscle, fat or other tissues
- Usually benign
Endometrial Stromal Polyp

- Polypoid mass of endometrial stroma
- Common; F334 > SD
- May undergo torsion / infarction
- Atypia & invasive growth → sarcoma
Pituitary Hyperplasia / Adenoma

- Hyperplasia
- Nonexpansile
- Very common in aged rats
- Adenoma:
  - Expansile, may compress ventral brain
  - Usu sharply demarcated (some diagnose carcinoma if infiltrative growth)
  - Common in SD (~80% females, 60% males); slightly less F344 & Wistar
  - Usu prolactin+ with IHC

Islet Cell Hyperplasia / Adenoma / Carcinoma

- Criteria not well defined; continuum
- Size, compression, atypia
- Carcinomas often well encapsulated +/- evidence of breaking through the capsule
- Metastasis rare
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 growth of well-differentiated C-cells
- Adenomas: >5 avg follicles in diameter
- Carcinoma: invasive with atypia, mitoses, or mets (lungs), +/- hemorrhage, necrosis, or mineralization
- Incidence low (<5%); more common than follicular tumors
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)
- More cytoplasm than most lymphomas
- May not see cytoplasmic granules
Lymphoma

- Typical monomorphic lymphocytic / lymphoblastic infiltrates in any organ
- Low incidence
- Most are reported to be B cell origin
Histiocytic Sarcoma

- Monomorphic histiocytic infiltrates in any organ, often with spindle cell morphology
- Multinucleate giant cells
- Low to moderate incidence
- IHC: Lysozyme+ & ED-1+
- Hyaline droplets (lysozyme) in renal tubules
Granular Cell Tumor

- Discrete, expansile mass of polygonal cells with PAS+ cytoplasmic granules
- Uncommon, benign
- Arise in meninges
- IHC positive for vimentin, S-100, α₁-antichymotrypsin
- Morphologically similar tumors may also occur in vagina/cervix
Zymbal’s Gland Tumors

- External auditory sebaceous gland
- Gross: Resemble abscesses, express caseous material
- Micro: proliferative sebaceous & squamous elements
- Can grow very large very quickly, may invade into brain
- Mets to lungs may occur
Preputial/Clitoral Gland Adenoma / Carcinoma

- Acinar / squamous differentiation
- Acinar tumors have eosinophilic cytoplasmic granules
- Uncommon
- Carcinoma may metastasize to lungs
Chordoma

- Multilobular tumor of primitive notochord elements (physaliferous cells)
- May have chondroid or osseous differentiation, or pools of PAS+ mucin
- IHC: cytokeratin+ and vimentin+
- Uncommon
- Usualy located along the cervical or anterior thoracic spine
Hibernoma

- Multilobular tumor of brown fat (microvesiculate round to spindle cells)
- Usually on midline (intrascapular, periaortic)
- Historically rare; recent reports of moderate incidence in SD, Wistar
- Distinctive ultrastructural appearance
- IHC: Uncoupling protein+
- Mets to lungs are not uncommon
Mesothelioma

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

\[ \text{Mesothelioma} \]

\[ \begin{aligned}
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\end{aligned} \]
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

CPN

• Incidence varies with strain; SD may have early lesions by 3 months of age
• Calorie & protein restriction lowers incidence & severity
• Can be difficult to distinguish from drug-related effects in toxicity studies

CPN

• Gross: Shrunken, pale, 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

- Renal tubular hyperplasia
- Soft tissue mineralization (lung, stomach, blood vessels, pleura)
- Fibrous osteodystrophy
Hyaline Droplets
• Protein resorption droplets in lysosomes of the tubule epithelium
• α2µ globulin in male rats (can be normal in P2 segment of PCT, more extensive with protein overload)
• Lysozyme in animals with histiocytic sarcoma

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
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
Alveolar Histiocytosis

- Common in old rats
- Cause unknown
- Gross: 1-3mm pale tan areas on pleural surface
- Micro: subpleural clusters of foamy macrophages in alveoli
- Do not confuse with centrilobular clusters of foamy macrophages that are often seen in inhalation or gavage studies
Alveolar Histiocytosis

Centrilobular infiltrates of foamy macrophages due to inhalational (or gavage) dosing on study
Malocclusion

- Incisors grow throughout life; malocclusion prevents normal wear
- Decreased food intake, weight loss
- Low incidence
- More common with powdered diets, not pelleted food

Gastric Erosion/Ulceration

- Gross: red or black areas in the glandular nonglandular mucosa
- Histology: necrosis/loss of epithelium with inflammation, granulation tissue
- Multifactorial; may be related to stress, irritating test articles, or powdered diets
Hepatodiaphragmatic nodule

- Nodule on anterior surface associated with small diaphragmatic hernia
- Microscopically normal hepatic tissue
- F344 > SD
- Must differentiate from neoplasia

Pancreatic Lobular Atrophy

- +/- grossly apparent
- Micro: acinar atrophy/loss with retained ducts, +/- mononuclear inflammation, fibrosis
- Common finding; increases with age
Hypospermatogenesis

- Testicular atrophy
- Primary aging change, or secondary to polyarteritis or interstitial cell tumors
- Multinucleated spermatids can occur in association or independently
- End-stage tubules contain only Sertoli cells
Ovarian Cysts

- Intraovarian
- Follicular
- Luteal
- Glandular
- Paraovarian
- Mullerian duct
- Bursa

Islet Fibrosis / Pigmentation

- Idiopathic
- Sporadic
- Affected islets and normal islets in the same section
Adrenocortical Cystic Degeneration

- Aging change in rats
- Females > males
- SD > F344 & Wistar
- Affected adrenal glands may be enlarged, soft, dark red, and mass-like
- Cell vacuolation & loss; dilated, cystic spaces that contain blood +/- thrombi
Thymic Atrophy / Involution
• Normal, age-related process
• 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

Degenerative Myelopathy
• Common in old rats – near 100% at 2 years
• Posterior paresis, ataxia, incontinence
• Symmetrical demyelination, axon swelling & loss, Gitter cells, reactive gliosis in the ventral & lateral tracts from T4 – L4
• Sciatic and tibial nerve degeneration; polyradiculoneuropathy
• Calorie restriction slows onset, reduces incidence
Retinal Degeneration / Atrophy

- Light-induced retinopathy; aging change in albino strains
- Thinning / loss of the outer nuclear layer, rods & cones
- More common in polycarbonate caging
- Minimize by rotating cages on racks or putting solid “roof” on cage racks to minimize light exposure
Corneal Dystrophy

- Wistar >50%, less in F344, SD
- Early: basophilic granules (mineral) on epithelial basement membrane
- Later: mineralized plaque along basement membrane and into superficial corneal stroma, disruption of outer corneal layers
- Larger or more advanced lesions are visible on eye exams

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, granulation tissue; +/- hyperostosis of underlying bone
Galactoceles

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

- Trauma related (ear tags, bites); may be immune-mediated reaction to Type II collagen
- Gross: distorted thickened pinnae
- Micro: cartilage degeneration with hemorrhage & pyogranulomatous inflammation