Pathology of the Rat

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Pathology Of Laboratory Animals
CL Davis & SW Thompson Foundation
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THE OHIO STATE UNIVERSITY
COLLEGE OF VETERINARY MEDICINE

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER
Outline

- Anatomy
- Infectious Diseases
- Aging & Miscellaneous Diseases
- Neoplastic Diseases
- References
Rat Anatomy

Difference Between
Mouse  Rat

aKNITomy by Emily Stoneking on Etsy!
Modified Sebaceous Glands: Preputial/Clitoral

Comparative Anatomy and Histology: A Mouse, Rat and Human Atlas, 2017
Mammary Glands

- Rat: 6 pairs
  - Absent in adult male
  - Terminal duct lobular unit
    - F: Many tubuloalveolar ducts, few acini around ducts
    - M: Few lobuloalveolar ducts, many contiguous acini of lobules

*Toxicologic Pathology 35: 199-207, 2007*
Hematolymphoid System

- Hematopoiesis
  - Bone marrow
    - >90% cellular
    - Myeloid:Erythroid – 1.97-1.93:1
  - Spleen
    - White vs. “red” pulp
    - Prominent marginal zone
- Thymus completely involutes
- Mast cells everywhere!
Hematolymphoid System – Lymph Nodes

CD Dijkstra, EWA Kamperdijk, AJP Veerman, pg 129-136, 1990
In Hematopoietic System, TC Jones, JM Ward, U Mohr, RD Hunt (Eds)
Monographs on Pathology of Laboratory Animals
Sponsored by the International Life Sciences Institute

Fig. 124. Lymph nodes, adult rat. Nodes lying dorsally are demonstrated by reflecting muscles and viscera. (Courtesy of N. Tilney (1971), and Journal of Anatomy)
Respiratory System

- Right: cranial, middle, caudal, accessory lobes; Left: single lobe
- Extra-pulmonary bronchi only
- Pulmonary veins contain cardiac and smooth muscle
- BALT!
Cardiovascular

- Cartilage or bone at base of heart
Salivary Glands – Sexual Dimorphism

Submandibular gland: Granular convoluted ducts
Liver

- Binucleated cells
- Polyploidy -> diploid, 2n (rat = 42)
- Anisocytosis/anisokaryosis
- NO GALL BLADDER!

Intranuclear cytoplasmic invaginations
Kidney

- Proximal: P1, P2, P3
- Long segment: short segment nephrons 3:1 → greater concentrating ability
- Medulla: outer (outer & inner stripes) & inner

Flattened epithelium lining Bowman’s capsule – no sexual dimorphism
Urine

• Urinate when handled
• >1.030 specific gravity
• Proteinuria normally!
  ❏ Higher in males vs. females
  ❏ Major urinary proteins = α₂μ globulins
    ✓ Potent human allergens
    ✓ Pheromones
    ✓ Rat n 1
Male Reproductive

Os penis;
Copulatory plug;
Spermatogenesis = 52 days
Female Reproductive

(Comparative Histopathology of Estrous Cycle in Rats, Dogs and NHPs)
Female Reproductive

TABLE 1.—Summary of the defining histological features of the rat female reproductive tract during diestrus, proestrus, estrus, and metestrus.

<table>
<thead>
<tr>
<th></th>
<th>Vagina</th>
<th>Uterus</th>
<th>Ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diestrus</td>
<td>Start defined by epithelium at lowest level with variable leukocyte infiltration. Subsequent epithelial proliferation and thickening (no clear stratum granulosum) with reduction in leukocyte infiltration.</td>
<td>Small, avascular, slit-like lumen. Lined by low columnar epithelium. Initially few mitoses, but some increase during phase. Only occasional degenerate cells. Stromal edema at end of stage.</td>
<td>Large corpora lutea. May be finely vacuolated. Fibrous tissue formation in central cavity.</td>
</tr>
<tr>
<td>Proestrus</td>
<td>Mitotic figures present. Occasional polymorphs. Little if any degeneration or desquamation. Formation of stratum granulosum (defines start), superficial mucoid layer and stratum corneum progressively. At end of stage, fully cornified and generally showing superficial mucoid layer with some desquamation of mucoid cells.</td>
<td>Epithelium cuboidal to columnar. Mitoses present in epithelial cells with little or no degeneration and little inflammatory cell infiltration. Dilatation, particularly toward end of stage.</td>
<td>Corpora lutea often degenerate. Cytoplasmic vacuoles generally present. Fibrous tissue proliferation in central cavity.</td>
</tr>
<tr>
<td>Metestrus</td>
<td>Start defined by virtually complete detachment of cornified layer (generally residual squames in lumen). Continued desquamation with loss of stratum granulosum and upper germinatium. Leukocyte infiltration.</td>
<td>Continued degeneration of endometrial epithelial cells. Return of mitotic activity; both (mitotic activity and degeneration) seen together.</td>
<td>Corpora lutea may still contain fluid cavity. Slightly basophilic cells. Generally devoid of fibrous tissue.</td>
</tr>
</tbody>
</table>

Toxicologic Pathology 36: 375-384, 2008 (rat histo grading)
Toxicologic Pathology 43: 776-793, 2015 (rat and mouse cytology)
Nervous System

- Lissencephaly
- C7-T13-L6-S4-Cd27-30
Rat Pathology

• Signalment
  - Strain, age, sex

• Husbandry
  - Caging/bedding, HVAC, diet

• Sentinel health status
  - Know what is on institution’s exclusion list
  - Positive diagnostic ≠ pathology
  - Housing location

• Experimental manipulation

• Institutional/geographical variability

• Communicate with clinical laboratory veterinarians & scientific staff!
Bacterial Diseases

http://www.ehow.com/about_5380594_bacteria-life-cycle.html
Mycoplasma pulmonis

- Murine respiratory mycoplasmosis (MRM)
  - Chronic respiratory disease (CRD)
- Multifactorial
  - Strain, age
  - Concurrent infections, nutritional status
  - Environmental factors
  - Pet/wild rats!
- Transmission: direct contact, aerosol, intrauterine
- Serology, PCR, culture
- Respiratory tract, middle ear, endometrium
**Mycoplasma pulmonis**

- Suppurative exudate, abscessation
  - Same size, curvilinear
  - Bronchiolitis/bronchiolectasis
  - Lymphoid cuffing
- CAR bacillus = frequent co-pathogen
- Pathogenesis
  - Release of cytotoxic substances
  - Ciliostasis and ciliolysis
  - Neutrophils → lysozyme-rich → weakens bronchiolar walls
  - Intact organisms & cell membranes are mitogenic for B lymphocytes
Mycoplasma pulmonis – Acute
Mycoplasma pulmonis – Chronic
**Mycoplasma pulmonis**

- **Veterinary Pathology**
  - 46: 952-959, 2009
- “Lymphomas” in rats in bioassays (Europe)
  - Aspartame, methyl-tertiary-butyl ether, methanol
  - Pleomorphic but immunoblastic
  - Lungs (within first 104 weeks of study)
    - Most common and often only tissue involved
    - Lymphocytes, plasma cells, neutrophils
- Rats were not specific pathogen free (SPF)!
- Slides not provided for review
- 76.6% had bronchiolitis; 21.4% had otitis; seropositive for *Mycoplasma*
M. pulmonis: Eustachian tube → otitis media
**Mycoplasma pulmonis**

- Not the same as cell culture mycoplasmas!
- Lack a cell wall
- Fastidious
- Selective media for enrichment
- Keep for ~2 weeks
- Cross-reactive antigens between *M. neurolyticum* and *M. arthritidis*

http://www.hpacultures.org.uk/services/mycotestinger adipication/mycocultureisolation.jsp
Filobacterium rodentium

- Formerly *cilia-associated respiratory (CAR) bacillus*
- Transmission: direct contact, fomites
- Synergistic with other respiratory pathogens (*Mycoplasma pulmonis*)
- Gram negative bacilli among cilia
  - Warthin-starry positive
- Bronchiolectasis
- Lymphoid cuffing
- Suppurative bronchopneumonia
- Serology, PCR, histology
Filobacterium rodentium – Warthin Starry
Filobacterium rodentium

Sedykh I et al.,
Scientific Reports
6:34437, 2016
Corynebacterium *kutscheri*

- Pseudotuberculosis
- Gram positive bacilli
- Transmission: direct contact, oronasal
- Asymptomatic carriers - persistent infection
  - Oral cavity
  - Lymph nodes
- Systemic suppurative inflammation w/ necrosis
  - Random/embolic (liver, lung, kidney)
  - Prominent bacterial colonies within lesions
Corynebacterium kutscheri

(Fixed lung)
Corynebacterium kutscheri
Streptococcus pneumoniae

- Gram positive diplococcus
- Transmission: direct contact, aerosol
  - Human/rat carriers (nose/ears)
- Systemic serofibrinopurulent inflammation
- Pathogenesis
  - Polysaccharide capsule
    - Resistant to phagocytosis
    - Activation of alternative complement pathway
    - Serotyping

Pathology of Rodents and Rabbits, 2016
Streptococcus agalactiae

- B-hemolytic, Lancefield group B
- Munich Wistar Frömter X F344
  - Transgenic for human diptheria toxin receptor driven by podocin promoter
- 38.5% of 21-24 day-old rats
- Spontaneous myocardial necrosis, glomerulonephritis, abscesses, bacteria +/- inflammation
- Resembles late-onset postnatal group B Strep infection in babies
**Clostridium piliforme**

- Intracellular, gram negative, spore-forming, filamentous bacilli
- Tyzzer’s disease
- “Species-specific”
- Ingest spores which remain infective for long periods in environment
- Poor husbandry, immunosuppression
- Organisms invade intestinal epithelium → dissemination
Clostridium piliforme

- Necrotizing hepatitis
- Necrotizing enterotyphlocolitis
  - Megaloileitis
- +/- Necrotizing myocarditis
- Warthin-Starry silver stain
- PCR on feces
- Cortisol provocation test for identification of subclinical carriers
Clostridium piliforme
Viral Diseases
Coronaviruses

- **Sialodacryoadenitis virus**, Parker’s rat coronavirus
- Transmission: aerosol, direct contact, fomites
  - Highly contagious!
- High morbidity, low mortality
- Salivary, harderian and lacrimal glands
- Rhinitis, tracheitis, bronchiolitis, alveolitis
- PCR, serology, IHC
- Prior infection protective up to 15 mo.

**Chromodacryorrhea**
Rat Coronavirus – Salivary Glands
Rat Coronavirus – Salivary Glands
Rat Coronavirus – Harderian Glands
Rat Coronavirus – Nasal Cavity
Rat Coronavirus – Ocular Sequela 2 to Lacrimal Gland Damage
Rat Parvovirus

- Nonenveloped SS DNA viruses
  - Kilham’s rat virus (RV), Toolan’s H-1 virus, rat minute virus (1a-1c), rat parvovirus 1 and 2
- Transmission: oronasal, transplacental, milk, feces, fomites
- Persistence and reactivation
- Dividing cells (S) for replication → cytolysis (NS1 and NS2)
- Serology (ELISA → screen; IFA → confirmation), PCR
Rat Parvovirus

- Endothelial cells and megakaryocytes
  - Hemorrhage, thrombosis, necrosis
- Cerebellar cortex, periventriculus
  - Cerebellar hypoplasia
- Hepatocytes
  - Vacuolar degeneration
- Intranuclear inclusion bodies
- Decreased fertility, fetal resorption, small litters, runts
Rat Parvovirus
Rat Parvovirus

Pathology of Rodents and Rabbits, 2016
Fungal Diseases

http://www.biologyjunction.com/fungi_notes_b1.htm
**Pneumocystis**

- Species specific
  - Rats: *P. carinii*, *P. wakefieldiae*
- Ubiquitous
- Asexual: binary fission $\rightarrow$ trophic form
- Sexual $\rightarrow$ ascus w/ 8 ascospores
- Pathogenic if immunodeficient
- Asymptomatic or 2° bacterial/viral infections
- Dyspnea, rough hair coat, hunched, cyanosis, death

*PLoS Pathogens 6: e1001009, 2010*
**Pneumocystis**

- Inhalation of asci
- Ascospores released in alveoli
- Attachment to type I pneumocytes and macrophages by fibronectin-binding integrins
- Necrosis of pneumocytes w/ damage to alveolar basement membranes
- Type II pneumocyte hyperplasia
- **Proposed:** *Pneumocystis* binds to surfactant protein altering function
Pneumocystis - Immunodeficiency
“Rat Respiratory Virus”

- Emerging disease (1997)
  - Worldwide distribution
  - 6% incidence in North America via histopath; 18% via serology/PCR
- Lymphohistiocytic interstitial pneumonia w/ perivascular lymphocytic cuffing
- Causative agent identified as *Pneumocystis carinii* in fall 2010
- Pneumocystis DNA by PCR in 87% of paraffin-embedded lung lesions attributed to RRV
- Koch’s postulate
- PCR (1-10wks), serology (5-8wks), histopathology (4-10wks)
**Pneumocystis - Immunocompetency**

1. Image 2: Gross appearance with an arrow indicating the site of pathology.
2. Image 3: Histological section showing inflammatory infiltrates.
3. Image 4: Higher magnification of the inflammatory infiltrates.
4. Image 5: Close-up view of the affected tissue.

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The Ohio State University College of Veterinary Medicine
Comparative Pathology and Mouse Phenotyping

Veterinary Pathology 46: 992-999, 2009
Pneumocystis - Immunocompetency

Natural “RRV” positive rat

P. carinii-inoculated rat

Filtrate-inoculated rat

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

Pneumocystis - Immunocompetency
Pneumocystis - Immunocompetency
**Pneumocystis/"RRV"**

- Immunocompetent rats
  - Anesthetic complications/death
  - Inhalational toxicology studies

- Similar lesions in immunocompetent mice
  - *P. murina*

- *P. jirovecii* in immunocompetent humans
  - SIDS
  - COPD
  - Asthma
  - Bronchiolitis

http://www.earthenvesseljournal.com/static/images/KentArticles/TwoSidesCoin.jpg
Parasitic Diseases
Cysticercus fasciolaris

- Larval stage of cat tapeworm
  - *Taenia taeniaformis*
- Ingestion of eggs in cat feces
- 1-2 cysts in liver
- Granulomatous inflammation, fibroplasia → fibrosarcoma

Cysticercus fasciolaris
**Trichosomoides crassicauda**

- Bladder threadworm (nematode)
- Urinary bladder and renal pelvis
- Embryonated, bi-operculate, brown eggs
  - Passed in urine
  - Hatch in stomach → systemic
  - Only larvae reaching urinary system survive
- White masses
  - Epithelial hyperplasia
  - Paucity of inflammation
- “Association” w/ calculi and neoplasia
Aging & Miscellaneous Diseases

Polyarteritis Nodosa (PAN)

- NPA: Mouse counterpart → vestibular syndrome
- PAN: Rat (Sprague Dawley, SHR, ACI) → no clinical signs - hemoabdomen
- PAN: NHP
- K9: Beagle pain syndrome / juvenile polyarteritis → neck pain
- Small- to medium-sized arteries
- Fibrinoid degeneration, neutrophilic to lymphoplasmacytic inflammation, myointimal hyperplasia and fibrosis
- Segmental, acute to chronic, multiple arteries
- Immune complexes
  - Cause?
  - NOTE: “PAN” in sheep due to ovine herpesvirus-2
    - Pesavento et al., *Veterinary Pathology*, 56: 87-92, 2019
Polyarteritis Nodosa

Comparative Medicine 57: 370-376, 2007
Polyarteritis Nodosa
Chronic Progressive Nephropathy (CPN)

- Chronic progressive nephrosis; chronic nephrosis; glomerulosclerosis; progressive glomerulosclerosis; glomerulonephritis; chronic nephritis; nephropathy; old rat nephropathy
- ≥75% incidence
- Age: ≥12 months
- Sex: M (castration = protective)
- Strain: Sprague Dawley, F344, SHR
- Diet: *ad libitum*, high protein
- Immune: mesangial IgM deposition
- Hormones: high prolactin
  - Chronic prolactin: no Δ in specific gravity, pH, volume, K; ↓ Na
  - Inhibition: ↑ volume, pH, K & Na excretion
  - Impaired renal degradation; pituitary neoplasia
- Microbe status: microbe-associated
CPN – Associated Clinical Findings

- Hypoproteinemia
- Proteinuria
  - Normal!!!
  - Albumin, $\alpha_2\mu$-globulin
- Azotemia
- Hypercholesterolemia
- Weight loss
- Hydrothorax, ascites
- Soft-tissue mineralization
- $2^\circ$ hyperparathyroidism $\rightarrow$ fibrous osteodystrophy
- Hypertension
- Polyarteritis nodosa
CPN – Precursor Lesion (Basophilic Tubules)
Chronic Progressive Nephropathy
Chronic Progressive Nephropathy
Nephrocalcinosis

- F344, BD1X
- Microlithiasis
- >3% incidence
- F > M
- ↓ magnesium
- ↑ calcium
- ↑ phosphorus
- ↓ calcium:phosphorus
- Calcium phosphates at corticomedullary junction
Hydronephrosis

- Hereditary
  - Brown Norway
  - Gunn
  - Sprague Dawley
  - Zucker
- Spontaneous
- Males
- Polygenetic
- Right kidney in males
  - Passage of internal spermatic vessels across ureter

Urinary Calculi

- Renal pelvis, ureter, bladder, urethra
- Variable composition
  - magnesium ammonium phosphate (struvite) (Long Evans - *Comp Med* 65: 486-491, 2015);
    carbonate, oxalate; carbonate-phosphate, magnesium, calcium
  - Alkaline urine + NH₃; urease-producing bacteria: *Proteus*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Ureaplasma*, *Staph*
- Genetic; retinoid supplementation, radionuclides
- Ddx: copulation plug!

“Spit on Cornell University!”
- Struvite (O)
- Oxalate
- Cysteine
- Urates (L)
Hematuria / Renal Papillary Hyperplasia

- Lewis X Brown Norway
- M > F
- +/- uni- or bilateral hydronephrosis
Cardiomyopathy

- Rodent progressive cardiomyopathy, chronic progressive cardiomyopathy, myocardial degeneration and fibrosis
- ≥25% → 100% with “enhanced sectioning”
  - Sprague Dawley
  - M > F
  - Ad libitum diet, environment, stress
- Little evidence of cardiac insufficiency
- LV, papillary muscle, IVS
- Degeneration, interstitial mononuclear cells, atrophy, fibrosis, mineralization, cartilaginous/osseous metaplasia
- *Veterinary Pathology* 52: 201-208, 2015
- *Toxicologic Pathology* 41: 1126-1136, 2013
  - Serum troponin WNL
Cardiomyopathy
Miscellaneous Cardiac Lesions

- Intracardiac thromboses
  - LA >> RA > LV
- Valvular endocardiosis
- Arterio-/atherosclerosis
- Hypertension
  - Renal disease, polyarteritis nodosa
- Endocardial/subendocardial proliferations
  - Hyperplasia vs. schwannoma vs. sarcoma
    - Fibroblast-like, precursor to schwannoma
    - Superficial round cells; deep spindle cells whorling around chordae tendinae
    - Infiltrates into myocardium
Alveolar Histiocytosis

- Subpleural histiocytes
  - FFA, cholesterol, phospholipids
- Not infectious!
- Resolved inflammation
  - Rat coronavirus/SDAV
- Localized pulmonary clearance deficit
- Pulmonary injury → type II pneumocyte hyperplasia → surfactant overproduction → accumulation in macrophages
Spontaneous Radiculoneuropathy

- Degenerative myelopathy
- Posterior paresis, loss of tail control, urinary incontinence
- Bilaterally symmetrical
- T4-L4 (lateral & ventral funiculi), cauda equina, ventral spinal nerve roots, sciatic & brachial plexus, lower brainstem
- Axonal swelling (spheroids), axonal sheath swelling, axonophagia
- Astrogliosis
- Demyelination
- Lipofuscin
- Muscle atrophy
Aspiration Pneumonia
Bile Duct Hyperplasia & Portal Fibrosis
Auricular Chondropathy

- Auricular chondritis, cauliflower ear
- Uni- to bilateral misshapen ears
- +/- ear tag → trauma
- Degeneration, chondrolysis, cartilage hyperplasia, osseous metaplasia
- Granulomatous inflammation
- Humans: relapsing polychondritis
  - Multiple sites (hyaline & elastic cartilage)
  - Autoantibodies to collagen types II, IX, X
Auricular Chondropathy
Eosinophilic Granulomatous Pneumonia

- Brown Norway Rats
- Asthma animal model
  - ↑ bronchiolar responsiveness
  - ↑ IgE following exposure to allergens
- Pneumonia presents without experimental manipulation
- Cause? Hypersensitivity reaction?
Corneal Dystrophy

- F344: 10-15%
- Wistar: 53-58%
- Punctate to linear opacities
- Ca & P w/ less Fe, Zn, Na, Al
- Calcific band keratopathy
- Anesthesia (ketamine/xylazine)
  - ↓ blink response → corneal ulceration
  - Vasoconstriction → hypoxia
- Ammonia
Retinal Degeneration

- Age-related photoreceptor attrition
- Light intensity
  - Recommended: 325-400 lux
- Environmental & body temperature
- Exposure time
- +/- cataracts
Malocclusion

- Ptyalism, cellulitis, weight loss
- Powdered diet
Ringtail

- ↓ humidity (<25%)
- Genetic susceptibility
- ↑ environmental temperature
- Hydration status
- Nutrition
- Preweaning rats
- Annular constrictions
- Dry gangrene
Chloral Hydrate Ileus

- Anesthesia; euthanasia
- IP injections
- Up to 5 weeks post-administration
- Segmental atony and distention
- Peritonitis and gastric ulcers
- Abdominal wall necrotizing myositis
Neoplastic Diseases

**Table I. Rate of Tumor Bearers Comparing F344 (National Toxicology Program 2010), Hsd: SD (Weber, Kaiser, and Klein 2012), and RccHan™: WIST Rats from Studies Performed at Harlan Laboratories Ltd., Switzerland, during 1981 to 2006 (Weber, Razing, et al. 2011)—Total Incidence (%).**

<table>
<thead>
<tr>
<th>Strain/gender</th>
<th>F344</th>
<th>Hsd: SD</th>
<th>RccHan™: WIST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Number of rats</td>
<td>1,298</td>
<td>1,250</td>
<td>120</td>
</tr>
<tr>
<td>Tumor bearers (%)</td>
<td>99.08</td>
<td>94.0</td>
<td>75.84</td>
</tr>
<tr>
<td></td>
<td>70.2</td>
<td>80.6</td>
<td></td>
</tr>
</tbody>
</table>

Note. F344 = Fisher 344; Hsd = Harlan Sprague-Dawley strain; RccHan™: WIST = Wistar Hannover (Han)-derived strain, continued breeding by RCC Ltd., Switzerland, thereafter continued breeding by Harlan.

**Table VI. Incidence of Most Prevalent Tumors in Two-Year-Old Rats**

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Sprague-Dawley (Crl:CD BR)</th>
<th>F-344 (CDR/Crl BR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ/tissue</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Testes</td>
<td>4.8</td>
<td>—</td>
</tr>
<tr>
<td>Uterus</td>
<td>—</td>
<td>4.1</td>
</tr>
<tr>
<td>Endometrial stromal polyp</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Ovary</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Granulosa cell and theca cell tumor</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>2.0</td>
<td>31.4</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>1.0</td>
<td>17.7</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Liver</td>
<td>6.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Hepatoellular adenoma/carcinoma</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphoepithelial</td>
<td>—</td>
<td>1.5</td>
</tr>
<tr>
<td>Large granular lymphocytic leukemia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Histiocytic sarcoma</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Pituitary</td>
<td>67.1</td>
<td>82.6</td>
</tr>
<tr>
<td>Adenoma/carcinoma, pars distalis</td>
<td>2.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>15.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Cortical adenoma</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pheochromocytoma, benign</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pheochromocytoma, malignant</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Islet cell adenoma</td>
<td>2.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Adapted from Lang (1990, 1992).
Lymphoma & Leukemia

- INHAND (in preparation!)
- Morphology only
  - Lymphoblastic
  - Pleomorphic, Pleomorphic/Follicular or Follicular
  - Immunoblastic
  - Plasma cells
  - Marginal Zone
  - Lymphocytic (small cell)
  - Cutaneous T cell
  - Large granular lymphocyte (LGL) leukemia
Large Granular Lymphocyte Leukemia

- F344 rats
- ↑ incidence with certain chemicals
- Spleen → systemic
- NK cells…maybe!
  - “Mononuclear cell leukemia” (NTP to date)
    - Fundamental & Applied Toxicology 12: 252-257, 1989
    - Staged according to extent of disease
- Acute leukemia
- Concurrent IMHA, thrombocytopenia, DIC
- Similar leukemia in humans!
- No retroviruses
- Syngeneic transplantation

<table>
<thead>
<tr>
<th>Feature</th>
<th>F344 rat</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype of leukemia cell</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NK cell</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>NK cytotoxicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute with high fatality</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lympahadenopathy</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased numbers of LGL</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anemia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
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</tr>
<tr>
<td>Spleen red pulp</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatic sinusoids</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Lung</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhages in various organs</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>+/-</td>
<td>+/-</td>
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</tbody>
</table>

Toxicological Sciences 99: 3-19, 2007
Large Granular Lymphocyte Leukemia
Large Granular Lymphocyte Leukemia
Large Granular Lymphocyte Leukemia

Wright-Giemsa

Formalin

Bouin’s
Large Granular Lymphocyte Leukemia

1 - Early

2 - Intermediate

3 - Advanced

OX-8 (CD8a)

Granzyme
Mammary Gland Tumors

- Males and females!
- Sprague Dawley
- Genetic, dietary, environmental, endocrine
- ↓ w/ food restriction, ovariectomy
- Prolactin levels
- Not associated with retroviruses!
- Fibroadenoma >>> carcinoma
- Recurrence vs. new tumor(s)?
- Rarely metastasize
- Syngeneic transplantation
Mammary Fibroadenoma
Mammary Fibroadenoma
Pituitary Gland Tumors

- Sprague Dawley, Wistar
- Age, genetics, diet, breeding
- ↓ w/ food restriction, mating
- Adenomas > carcinomas
- Pars distalis > pars intermedia
- Chromophobe, prolactin-producing
  - ↑ incidence of fibroadenomas?

*J Toxicol Pathol* 31(3S): 1S-95S, 2018
Tumors of Skin & Other Glands

- Zymbal’s gland
  - Base of external ear
  - Locally invasive
  - Not metastatic
- Preputial/clitoral gland
  - Locally invasive
  - Metastasize to regional LNs and lungs
- Keratoacanthomas
  - Up to 8% incidence depending on strain
  - Chemically-induced!
Zymbal’s Gland Carcinoma
Preputial/Clitoral Gland Carcinoma
Keratoacanthoma
Interstitial Cell Tumor

- Leydig cells
- Aged strains
- F344
- Concurrent hypercalcemia
Interstitial Cell Tumor
Mesothelioma
• F344
• 2 subtypes in humans and rats (repeated IP ferric saccharate)
  ❑ Epithelioid/epitheliomatous
    ✓ 1° site = tunica vaginalis of testes
    ✓ Papillary growths
  ❑ Mesenchymal/sarcomatous
    ✓ Cranial abdominal organs
    ✓ Invasiveness
    ✓ CDKN2A/2B null and amplification of ERBB2
• Look for concurrent mesothelioma and interstitial cell tumor!
Mesothelioma – Epitheliomatous
Mesothelioma – Sarcomatous
Rat: 3 Diagnoses?
Multiple Endocrine Neoplasia (MEN)

- Frequently diagnosed concurrently in aging rats:
  - Islet cell tumor
  - Pheochromocytoma
  - Thyroid follicular adenoma
  - Thyroid parafollicular (C-cell) adenoma
  - Pituitary gland, pars distalis adenoma

- Documented in humans & veterinary species
**MEN**

- **MEN1**
  - Loss of function mutations in Menin
  - Parathyroid, gastroenteropancreatic, anterior pituitary

- **MEN4**
  - CDKN1B (↓ p27)
  - Same tumor spectrum as MEN1
  - MENX = spontaneous rat model (autosomal recessive)
    - Parathyroid adenomas, islet hyperplasia, C-cell hyperplasia, pheochromocytomas, paragangliomas, cataracts

- **MEN2**
  - Gain of function mutations in RET
  - Adrenal and thyroid medullary tumors

- **MEN3 (2B)**
  - Adrenal/thyroid medullary tumors
  - Mucocutaneous neuromas, intestinal ganglioneuromas, marfanoid habitus, prominent corneal nerves
Thyroid Gland

- **Follicular**
  - Hyperplasia
  - Adenoma
    - Microfollicular, macrofollicular, cystic
  - Carcinoma
    - Metastases to regional LNs, lungs
  - Thyroglobulin

- **C cell**
  - Focal-diffuse hyperplasia
  - Adenoma
  - Carcinoma
    - Amyloid
  - Calcitonin
Thyroid Follicular Adenoma
Thyroid C-Cell Adenoma
Adrenal Medulla

- F344, M > F
- Environment, strain, endocrinopathies, diet, chemicals
- Lack catecholamine synthesis/release, urinary excretion or elevated BP
- Basophilic focus $\rightarrow$ hyperplasia $\rightarrow$ benign/malignant
- Pheochromocytoma
  - Chromaffin cells
- Ganglioneuroma
  - Ganglion, satellite cells, Schwann cells, nerve fibers (>80%)
- Neuroblastoma
  - Neuroblasts (>80%)
- Complex: mixture (neural component < 80%)
Rat: 3 Diagnoses?
Adrenal Medullary Pheochromocytoma with Corticomedullary Lipogenic Pigmentation
Pancreatic Islets

- **Hypertrophy** → dissecting fibrosis
- **Hyperplasia**
  - Duct ligation w/ destruction & atrophy of acinar parenchyma
  - Variable numbers of islets affected
- **Adenoma**
  - Insulin > stomatostatin, glucagon, pancreatic polypeptide
- **Carcinoma**
  - Local/capsular invasion, anaplasia +/- lung metastases
Islet Cell Tumor
Granular Cell Tumor

- Brain/meningeal: rat, dog, ferret
- Rat: uterus
- Dogs: tongue, heart
- Horses: lung
- Granules: PAS + w/ diastase resistance
- Alcian blue +
Granular Cell Tumor

• Controversy: muscle or Schwann cell origin

• IHC immunoreactivity
  - Positive: vimentin, S-100, NSE, myelin-related protein → Schwann cell origin
  - Negative: GFAP, canine leukocyte antigens, epithelial markers, macrophage markers, muscle antigens

• *Vet Path* 45: 654-662, 2008
  - Uterine tumors in B6C3F1 mice: +/- desmin or SMA → smooth muscle origin (no cross striations, PTAH negative)
Granular Cell Tumor
Granular Cell Tumor
Nephroblastoma

- Rare except subline of Sprague Dawley – Upj:TUC[SD]spf.nb
  - Genetically predisposed
  - 14% incidence
- Chemically-induced
- Model for Wilm’s tumor in humans
- 3 components
  - Blastema
  - Stroma
  - Immature epithelium forming tubules
- Precursor lesion: intralobar nephroblastomatosis
  - Embryonal tissue in rat present until d. 7-8
Nephroblastomatosis
Chordoma

- Intraosseous remnants of notochord
- Lumbosacral/sacroccocygeal > sphenep-occipital
- Slow growing, recur, metastasize
- Ferrets > dogs, cats, rats, mink
- Sprague Dawley, F344
- 56/115K
- M>F 3:1
- Paresis, paralysis, megacolon
**Chordoma**

- Physaliphorous cells
  - Vacuolated, eccentric nucleus
  - Cytokeratin + AND vimentin +
- Fibrous trabeculae
- Pools of mucin
  - PAS, mucicarmine, alcian blue
- Humans
- Variant = chondroid chordoma
  - Spheno-occipital
  - Better prognosis
Volume III = Systems Toxicologic Pathology
References - 3

• National Toxicology Program Nonneoplastic Lesion Atlas
  https://ntp.niehs.nih.gov/nnl/index.htm
• International Harmonization of Nomenclature and Diagnostic Criteria,
  www.toxpath.org/inhand.asp
• Proliferative & non-proliferative lesions of mice & rats:
  - Cardiovascular
  - Bone, joints, teeth
  - GI tract, pancreas, salivary glands
  - Female reproductive system
  - Male reproductive system
  - Soft tissue, skeletal muscle, mesothelium
  - Integument
  - Mammary, Zymbal's, preputial, clitoral glands
  - Urinary system
  - Central and peripheral nervous systems
  - Hepatobiliary system
  - Respiratory tract
  - Endocrine
  - Special Senses
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- Paul Stromberg
- Jerry Ward
- ACLAM Lab Animal Medicine and Science Series II
- Joint Pathology Conference - VSPO
- Noah’s Arkive
- The Jackson Laboratory
- Dean Percy – Pathology of Laboratory Rodents and Rabbits, 4th Edition
Questions?

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