

## 2011 TOPICS IN LABORATORY ANIMAL MEDICINE

MAY 19, 2011

### Disclaimers

- This is not an ACLAM sanctioned presentation
- All information is deemed reliable and correct
  - No warranty for accuracy
- No information presented is known to be specifically included in ACLAM Board examinations

### Laboratory Rats

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GlaxoSmithKline

### Objectives of talk

- Review some basics of rat biology
- Review some basic spontaneous rat models
- Cover a few diseases of rats
- Review some rat pathology
- Review some recent literature
- **Not Comprehensive**

### THANK YOU!

- Pathology and LAS colleagues at GSK
- University of Missouri/Dr. Craig Franklin
- National Institute of Environmental Health Sciences
- Dr. Mary Grant
- Dr. Iris Bolton

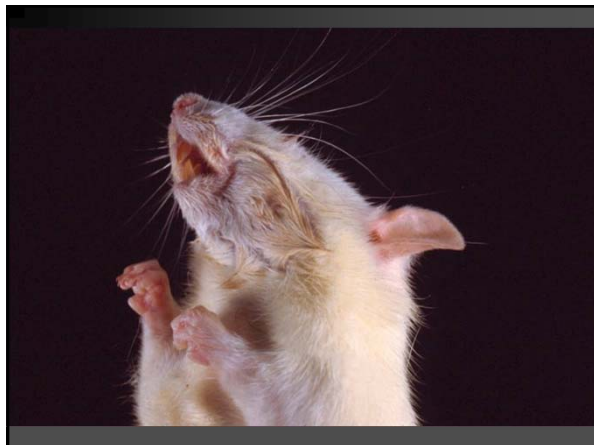
### Rats

- *Rattus norvegicus*
- Not just a big mouse
- Used frequently in toxicological, teratological, carcinogenesis, behavioral, nutritional, endocrinology, aging studies
- Huge physiology database
- Special strains for certain diseases such as diabetes mellitus, diabetes insipidus and hypertension
- GERS just beginning



## Rat misc

- Susceptible to light induced retinopathies
- No gallbladder
- Duplex uterus
- Ad lib feeding shortens lifespan
- Coprophagic



## chromodacryorrhea



## What condition is depicted?

- Ringtail
- Lesion of young animals
- Annular constrictions with or without sloughing of tail
- Associated with high temperature and low humidity (<40%?) ???



## Coat color

- Albino
- Black-hooded
- Brown-hooded
- Fawn-hooded
- Non-agouti brown
- Rats were domesticated for show



## What type of hooded rat is this?

- Fawn hooded rat
- What types of abnormalities does this rat have?
  - Abnormal platelet function
  - Hypertension



## What hooded rat is agouti with a white belly and feet?

- ACI
  - Genitourinary abnormalities
    - Absent, hypoplastic or cystic kidneys
    - Sometimes associated with an absent or defective uterine horn or atrophic testes on the same side



## Other Hooded Rats...

- What is the LEC rat?
  - Long Evans Cinnamon
- What abnormality does this rat exhibit?
  - Hepatitis
- Fulminant hepatitis and jaundice at four months of age.
- About 50% of animals die within 1 week of onset of clinical signs.
- Survivors develop hepatocellular carcinoma after 1-1.5 years.
- Model for Wilson's disease. Also think Bedlington Terrier.

## White/Albino Rats and Their Abnormalities...

- What albino rat is a model for Type 1 Diabetes?
  - BB
- Outbred Wistar rats at Bio-Breeding Labs.
- Abrupt onset of diabetes 60-120d age.
- Lymphocytic insulinitis, destruction of pancreatic beta cells.
- Males > Females.



## Other Hooded Rats...

- What hooded rat develops retinal degeneration?
  - RCS
- RCS (Royal College of Surgeons)
- Carries gene for retinal dystrophy.
- Overproduction of rhodopsin and progressive loss of photoreceptor cells beginning in third postnatal week.

## White/Albino Rats and Their Abnormalities...

- What abnormality is exhibited by the SHR rat?
  - Hypertension
- Spontaneously Hypertensive Rat.
- Develop hypertension spontaneously at 7-15 weeks.



### Which rat strain/stock is an accepted genetic control animal for the SHR strain used in hypertension studies?

- BB
- LEW
- WKY
- SHR/SP
- DIO

Godfrey, et al  
Clinical Linoleic Acid Deficiency in Dahl Salt-Sensitive (SS/Jr)  
Rats  
Comp Med 55(5): 470-475, 2005



This rat developed ulcerative dermatitis suspected to be related to a deficiency in what essential fatty acid (EFA)? **Linoleic Acid**

### Which rat strain/stock is an accepted genetic control animal for the SHR strain used in hypertension studies?

- BB
- LEW
- **WKY (Wistar Kyoto)**
- SHR/SP
- DIO

#### References:

- Belanger et al. 2003. Effect of hypertension on reproductive organ weights in various strains of rats. Contemp Top Lab Anim Sci 42(6):39-41.
- Fox JG, Anderson LC, Loew FM, Quimby FW, eds. 2002. *Laboratory Animal Medicine*, 2<sup>nd</sup> edition. Academic Press, San Diego, CA. Chapter 4 - Biology and Diseases of Rats, p. 122.
- Charles River Laboratories Research Models and Services 2006 US Catalog, page 10.

### Gunn Rats

- Model for Crigler-Najjar Syndrome
- Abnormality
  - Hyperbilirubinemia (unconjugated)
  - Jaundice
  - Lacks UDP Glucuronyl Transferase in Liver



### What rat was developed from Sprague-Dawley stock selected for sodium chloride-induced hypertension?

- Dahl Salt Sensitive (DSS)
- Dahl Salt Resistant (DSR)



### WAG/Rij Rat

- Abnormalities exhibited by the WAG/Rij rat
  - Retinal Degeneration
  - Retinitis Pigmentosa
  - Absence Epilepsy
- What albino rat is this strain developed from?
  - Wistar





## BUF Rats

- Strain exhibits autoimmune thyroiditis?
- Autoimmune thyroiditis:
  - Spontaneous
  - After ingestion of 3-methylcolanthrene
  - 100% after neonatal thymectomy



## The Zucker rat is a model for which of the following diseases or conditions?

- Obesity
- Type I diabetes
- Diabetes insipidus
- Prostate adenocarcinoma
- Jaundice

### Reference:

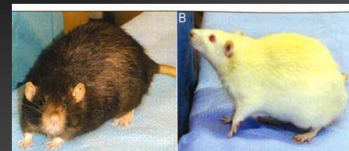
- Fox JG, Anderson LC, Loew FM, Quimby FW, eds. 2002. *Laboratory Animal Medicine*, 2<sup>nd</sup> edition, Academic Press: San Diego, CA. Chapter 4 – Biology and Diseases of Rats, p. 122 (Table I).

## Spotting Lethal Mutant

- Model for Hirschsprungs Disease?
- Aganglionic Megacolon
- Recessive sl/sl (Chromosome 15)
- White coat with pigmented spot on head



## What is the FBN?



FBN

F344

F1 hybrid of F344 female and Brown Norway male (F1)

## The Zucker rat is a model for which of the following diseases or conditions?

- Obesity
- Type I diabetes
- Diabetes insipidus
- Prostate adenocarcinoma
- Jaundice

## How do these animals differ with respect to auditory sensitivity?



- FBN approximately 20dB better hearing at higher frequency
- F344 approximately 20dB better hearing at lower frequency

Comparative Medicine 55(1)Feb2005;12-23

## What type of rat is this?



- Brown Norway (BN)
- What type of renal disease is exhibited by BN rats?
  - Brown Norway Hydronephrosis
- What type of urinary tract disease does BN/Rij rats develop?
  - Spontaneous Ureter Tumors

## Athymic Nude Rat

- Nude mutation: Spontaneous autosomal recessive mutation in the forkhead box N1 gene (*Foxn1<sup>nu</sup>*) on chromosome 10
- *rnu/rnu* (homozygous), *rnu* /+ (heterozygous)
- Hairless, failed development of the thymic anlage → lack of thymic T-cell development

## What type of rat is this?

- Black Rat
- Genus and Species?
  - *Rattus rattus*

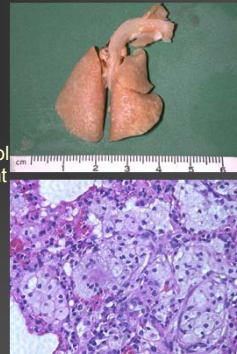


## Tissue from an *rnu/rnu* rat with dyspnea

Histo — pulmonary alveoli distended with abundant foamy macrophages.

Causative agent?

*Pneumocystis carinii*



## What type of rat is this?

- Nude Rat
- What is the gene symbol for the nude rat?
  - *rnu/rnu* (Rowett Hooded)
  - *rnu<sup>nz</sup>* (Albino New Zealand)
- *rnu/rnu* exhibit cyclic hair growth
- T-cell deficient



## Tissue from an *rnu/rnu* rat with diarrhea

Describe lesions

- Inflammation of large and small intestine and hyperplasia of mesenteric lymph nodes

Causative agent?

- Always include *Helicobacter* sp with proliferative disease of large bowel
- *H. bilis*

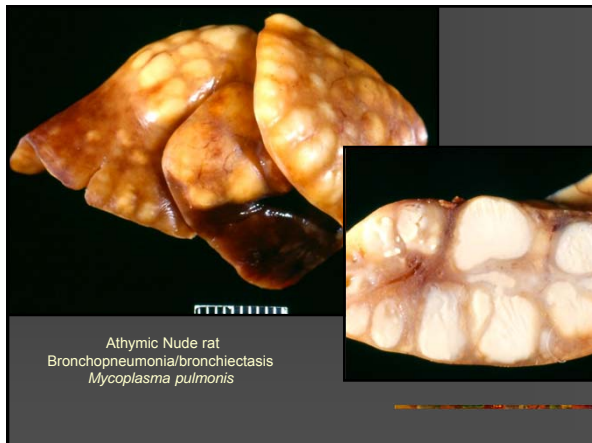
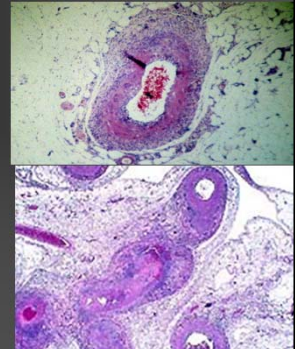


## Athymic Nude Rat: Infectious Disease

- Bacterial agents
  - *Mycoplasma pulmonis* (bronchopneumonia with bronchiectasis, bacterial/viral coinfections common)
  - *Clostridium piliformis* (Tyzzer's disease. Necrotizing typhlocolitis with dissemination to liver, lymph nodes, and heart. Intracytoplasmic groups of rod-shaped bacteria)
- Viral agents
  - Sendai virus (paramyxovirus. Proliferative interstitial pneumonia leads to mortality in Nude rats. Persistent carrier state)
- Mycotic agents
  - *Pneumocystis carinii*

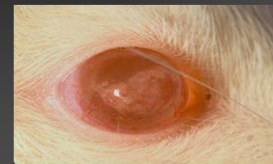
## Periarteritis Nodosa

- Mesentery
  - Medial hypertrophy
  - Inflammatory infiltrates around affected vessels
  - Inflammatory cells in perivascular fat (steatitis)
  - Some arteries have fibrinoid degeneration and/or thrombi



**What anesthetic combination was most frequently associated with corneal lesions in rats in a recent study?**

- Ketamine and xylazine (60 mg/kg and 12 mg/kg)



**What condition is depicted in these slides?**

- Polyarteritis Nodosa (Periarteritis Nodosa): Mesenteric
- Small-Med sized arteries become swollen and damaged
- Immune-mediated disease
- Mesenteric, pancreatic, spermatic arteries



**What stocks or strains of rats were more likely to develop corneal lesions after anesthesia with ketamine/xylazine?**

- Wistar and Fischer 344 were the most likely (F 344 was the worst). Long Evans were intermediate in likelihood, and SD and Lewis had low likelihood

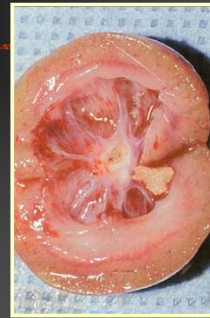


### What condition is depicted?

- Rat on the left is normal
- Rat on the right is abnormal
- Ameliogenesis imperfecta
  - Underdevelopment of enamel-forming ameloblasts
  - Inherited through autosomal single recessive gene (ami)



### What condition is depicted?



Urolithiasis-Hydronephrosis

### What condition is depicted?

- Malocclusion



### What are some clinical signs of urolithiasis in rats?

- Hematuria, red-stained bedding, red-stained or wet pelage, sensitivity to touch in the abdominal area, swollen or palpable kidneys or bladder, unkempt fur, anorexia, reduced urination, reduced water intake, unexpected weight gain or loss

### What condition is depicted?



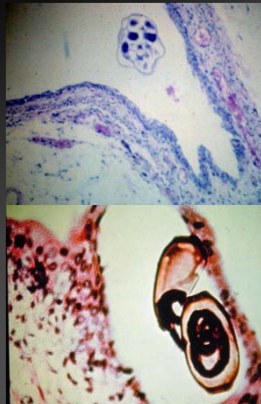
- Unilateral cataract

### Diet-induced urolithiasis

- Rats fed basal diet substituted with choline chloride failed to develop urinary calculi.
- Rats fed basal diet containing FCC grade of choline bitartrate developed urinary calculi.
- Rats fed basal diet containing USP grade choline bitartrate failed to develop urinary calculi.
- P-glycoprotein inhibitor treated rats had significantly reduced risk of developing urinary calculi.

Comparative Medicine 53(4)Aug2003;444-7.

### Trichosomoides crassicauda



- Females in urinary bladder, ureters and renal pelvis.
- Small male worms live and are parasitic in the uterus or vagina of the adult female.
- Eggs passed in urine, infection by ingestion of embryonated egg. Eggs hatch in stomach, larvae enter bloodstream then to urinary tract.
- Primary infection from dams to pups prior to weaning.
- Proliferative changes in mucosa – neoplasia?

### Pituitary Tumor

#### Pituitary Chromophobe Adenoma

- Vast majority of pituitary tumors in rats
- May have prominent hemorrhagic areas
- Generally well circumscribed and compress adjacent brain tissue (head tilt?)
- Females > Males

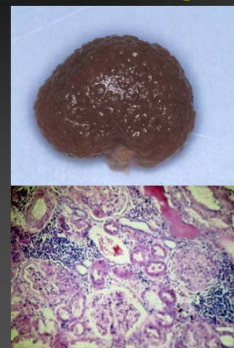


### What condition is depicted in this slide?

- Renal Aplasia
- What rat strains exhibit renal abnormalities?
  - ACI – often lacks right kidney
  - BN – hydronephrosis
  - BN/BiRij – bladder and ureter tumors



### Chronic Progressive Nephropathy

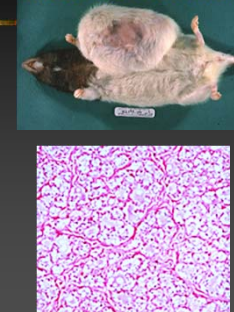


- Gross description
  - Small pale firm kidneys
  - Rough or pitted surface
  - Numerous small foci/cysts
- Interstitial inflammation
- Thickened bm
- Glomerular changes
- Proteinaceous casts

### Major age-associated lesions in rats

- Neoplasms (mammary, pituitary, adrenal)
- Chronic progressive nephropathy
- Myocardial degeneration
- Polyradiculoneuropathy

### What is depicted?

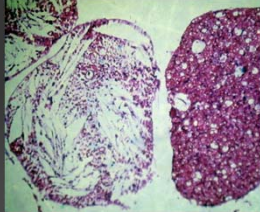


- Benign fibroadenoma (most common tumor of rats)
- Can occur anywhere there is mammary tissue
- Hyperplastic fibrous and glandular tissue

## Name the tissue and give the histological description...

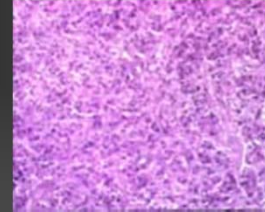
### Tissue

- Lumbosacral spinal nerve root
- Histological description
  - Nerve root on the right appears normal
  - Nerve root on the left severe degeneration
  - Cholesterol clefts



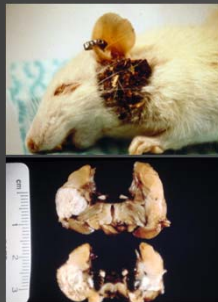
## What is the most common testicular tumor in rats?

- Interstitial Cell Tumor
  - Although these tumors may become very large, most appear benign
- What strain has high spontaneous occurrence of this tumor type?
  - F344

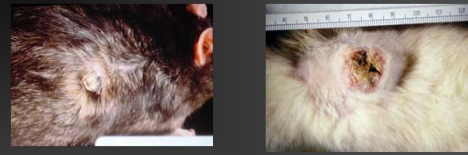


## What structure and condition are depicted?

- Structure
  - Zymbal's Gland
- Zymbal's Gland Tumor
  - Usually present as an ulcerated mass within or just below the external ear canal



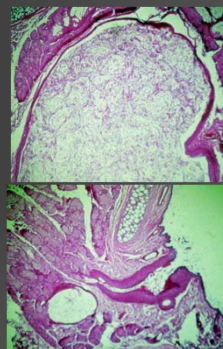
## What condition is depicted?



- Cutaneous nodular lesion (chest, back, tail)
- Crusted, thickened surface
- Keratoacanthoma

## Zymbal's Glands

- Modified sebaceous glands
- Surround external ear canal
- Tumors can be induced by a variety of carcinogenic compounds
- Tumors may be either sebaceous or squamous or admixtures

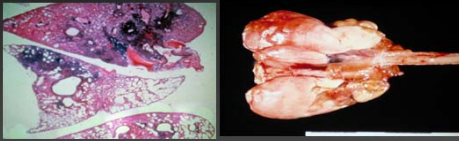


## What diagnostic technique is depicted?

- Nasal Swab
- What type of swab is used?
  - Calgi (calcium alginate) swab
- CAR Bacillus PCR done on nasal swab
  - Advantage – can detect infection in younger rats (>=3wks) before colonization of lung occurs



## Differential Diagnosis?



- *Mycoplasma pulmonis*
- CAR bacillus
- *Corynebacterium kutscheri*

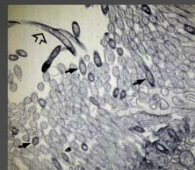
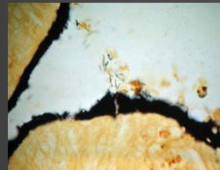
## *Mycoplasma pulmonis*

- What media is used to culture this organism?
  - Dutch Agar
  - PPLO (Pleuropneumonia-like Organisms) broth
  - Hayflicks, SP4
- In what other sites can this organism be found?
  - Genital tract (uterus, ovary, oviduct)



## What type of stain?

- Silver stain
- Bacteria densely clustered at ciliated surface of respiratory epithelium
- Organisms
  - Gram negative
  - Motile
  - Non-spore forming
  - Gliding bacteria



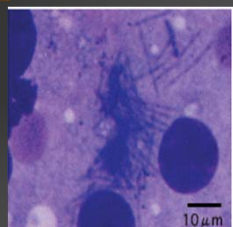
## What is this mite?

- Tropical Rat Mite
- Genus and Species?
  - *Ornithonyssus bacoti*
- What diseases can be carried by this mite?
  - Murine Typhus
  - Rickettsial Diseases
  - Q Fever
  - Plague



## What organism is this?

- Hint: Gram + Rods (Chinese letters)
- *Corynebacterium kutscheri*
- Hematogenous spread
- Where do you culture for this organism?
  - Oral cavity (carry here)
  - Cervical LN
  - Liver ?
  - Brain ?
  - Kidney ?



## Which of the following is a characteristic of *Ornithonyssus bacoti*, the tropical rat mite?

- The mite has a life cycle of 28 days from egg to egg production
- The protonymph stage has been shown to survive for 43 days without food
- The principle host is *Mus musculus*
- A single female can lay as many as 1400 eggs during its 90-day lifecycle

**Which of the following is a characteristic of *Ornithonyssus bacoti*, the tropical rat mite?**

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- The principle host is *Mus musculus*
- A single female can lay as many as 1400 eggs during its 90-day lifecycle

**Which of the following neoplasms represents the majority of mammary tumors described in older rats?**

- Endothelioma
- Adenocarcinoma
- Lymphosarcoma
- Fibroadenoma
- Histiocytoma

**Other Rat Mites...**

- Genus and Species of the Spiny Rat Mite?
  - *Laelaps echidninus*
- What is this mite a vector for?
  - *Hepatozoon muris*
- Genus and Species for Ear Mange Mite?
  - *Notoedres muris*

**Which of the following neoplasms represents the majority of mammary tumors described in older rats?**

- Endothelioma
- Adenocarcinoma
- Lymphosarcoma
- Fibroadenoma
- Histiocytoma

**What condition is depicted?**

- View of tympanic bullae
- Right and left bullae appear to have whitish material in them.
- Otitis media
- Causative agent?
  - *M. pulmonis*
  - *P. pneumotropica*



**Double Operculated Eggs**



- *Dirofilaria immitis*
- *Anatrichosoma*
- *Capillaria*
- *Trichuris*
- *Prosthenorchis*
- *Trichosomoides*



## Single Operculated Eggs

- Fasciola
- Paragonimus
- Diphylobothrium
- Athesmia
- Gastrodiscoides



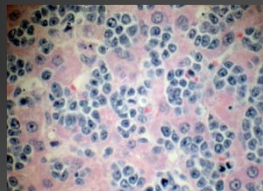
## What conditions are depicted?

- Top photo
  - Squinting
  - Photophobia
  - Cervical swelling
- Bottom photo
  - Exophthalmos
  - Cloudy cornea



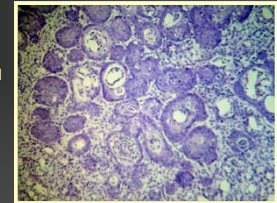
## Name the tissue and give the histological description...

- Tissue
  - Liver
- Histological description
  - Diffuse sinusoidal infiltrate, large mononuclear cells
  - Basophilic polyhedral cells
  - Prominent nucleus



## Name the tissue and give the histological description...

- Tissue
  - Glandular tissue
    - Parotid, Harderian, Submandibular, Exorbital Lacrimal
- Histological description
  - Inflammatory infiltrate
  - Interstitial edema
  - Necrosis of ducts
  - Squamous metaplasia



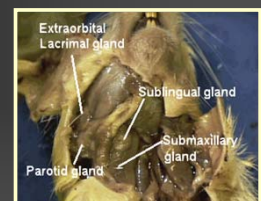
## Diagnosis?

- Large Granular Lymphocytic Leukemia
- Formerly called Mononuclear Cell Leukemia/ Fischer Rat Leukemia
- Very common in aged F344
- Can involve virtually any organ in the body (commonly splenomegaly, hepatomegaly, lymphadenopathy)
- Large granule lymphocytes are of NK cell origin.

## Diagnosis?

- Sialodacryoadenitis virus (SDAV)
- Coronavirus
- Affects serous or mixed glands
- Which salivary gland spared?

- Sublingual salivary gland
- Morbidity high, mortality low
- Animals infected and immune within 3-5 weeks.
- Stop breeding for 6-8 wks



### Rat bite fever can be caused by *Streptobacillus moniliformis* or what other organism?

- *Bartonella henselae*
- *Spirillum minus*
- *Staphylococcus aureus*
- *Brucella rattus*
- *Pasturella multocida*

### Tyzzar's Disease

- *Clostridium piliforme*
- Flaccid dilatation especially ileum
- ("Triad") - hepatitis, myocarditis, enteritis
- Fecal-oral transmission by spores
- Demonstration of intracellular organism in tissues: Steiner/Warthin-Starry, Giemsa and Methylene Blue.

### Rat bite fever can be caused by *Streptobacillus moniliformis* or what other organism?

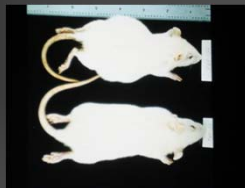
- *Bartonella henselae*
- *Spirillum minus*
- *Staphylococcus aureus*
- *Brucella rattus*
- *Pasturella multocida*

### Choral Hydrate

- Hypnotic
- Short acting light anesthesia
- Poor analgesia
- Irritating to peritoneum
- Causes adynamic ileus in rats when given IP

### What condition is depicted?

- Abdominal swelling
- Rule outs:
  - Ascites
  - Organomegaly
  - Neoplasia
  - Adynamic Ileus (megacolon)
- What are possible causes of megacolon?
  - Tyzzar's Disease
  - Chloral hydrate

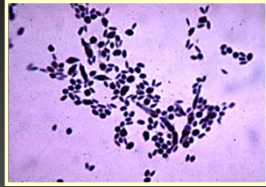


### Give the gross description...



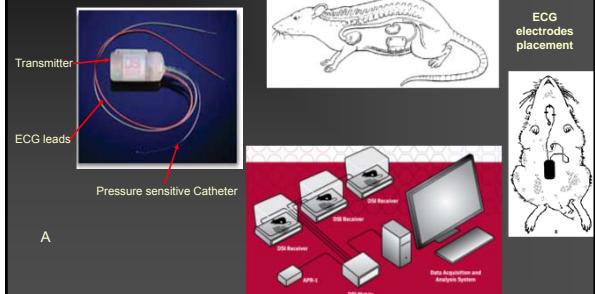
- Gross:
  - Fibropurulent pleuritis, pericarditis, and pneumonia
  - May also see:
    - Suppurative arthritis
    - Meningitis
    - Splenitis
    - Orchitis
  - Infarcts
    - Spleen
    - Testes
- Diagnosis?

## Streptococcus pneumoniae



- Histopathology
  - Characteristic organisms
  - Tissue impression smear gram stain (grams + in pairs)
- Culture:
  - Blood agar (10% CO<sub>2</sub>)
  - Optochin inhibition (ethylhydrocupreine)
  - Quellung reaction
  - Capsular types 2, 3, 19

## Conscious Telemetered Rat CV Model



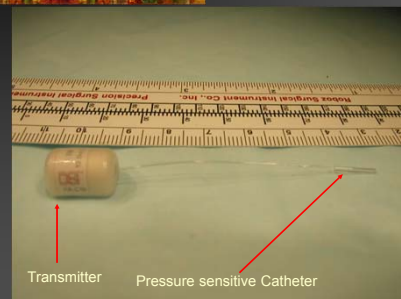
All of the following blood vessels can be used for intravenous injections in the rat **EXCEPT** ?

- Dorsal metatarsal vein
- Sublingual vein
- Brachial vein
- Penile vein
- Lateral tail vein

### Reference:

- Fox JG, Anderson LC, Loew FM, Quimby FW, eds. 2002. *Laboratory Animal Medicine*. 2<sup>nd</sup> edition. Academic Press: San Diego, CA. Chapter 23 – Techniques of Experimentation, pp. 1009-1010, 1012.

## Miniature DSI Rat Pressure Transmitter



## Lesions of Pneumocystis in Immunocompetent Rats

