Minipigs in Health and Disease

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PURPOSE

The purpose of this 2 hours block of instruction is to gain knowledge and experience in the biology and husbandry of the laboratory minipigs. This lecture, unlike the three others presented today, will cover additional topics such as husbandry as well as background lesions. At this time, the body of knowledge on the disease of this laboratory species is still in its infancy, and most animals used in the laboratory are extremely young, laboratory-raised and free of disease.

It should be noted that miniature pigs are sometimes seen in a clinical setting as pets, often outdoors and in small groups. In such cases, the entire spectrum of infectious diseases of swine may come into play, and geriatric individuals may display a wide range of neoplastic and aging changes (particularly dental disease and osteoarthritis.) The diseases of pet minipigs are largely excluded from this lecture.

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<td>HUSBANDRY ISSUES</td>
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<td>COMMON HUSBANDRY MISTAKES</td>
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### HANDLING AND RESTRAINT

**PIG SLING**

### INTEGUMENTARY SYSTEM

| Integumentary | Mental gland | The mental gland on the ventral aspect of the chin is comprised of apocrine & sebaceous glands as well as vibrissae and pressure receptors. It has both marker and tactile functions. |
| Integumentary | Carpal gland | The carpal organ is a tactile elevation with vibrissae associated with tubular glands. It is believed to function as a marker and sexual stimulant, as the boar marks the female with glandular secretions during mating. It is seen in both sexes. |

### SKIN COMPARISON TO HUMAN

**MINIPIG SKIN COMPARISON TO HUMAN (HISTO)**

**MOUSE SKIN COMPARISON TO HUMAN**

**PIG SKIN IN WOUND STUDIES**

| Integumentary | Background Findings | Scabbing/crusting is a common incidental finding; and may be the result of shaving the skin or simple scratching – a pleasurable pastime for a pig. |
| Special Senses | Aural, ocular discharge. | Pet minipigs produce normally copious amounts of dark grown waxy exudate. They may also produce a mucoid ocular exudate normal, which is most common in boars. *Candida* may be isolated from this exudate, but is not considered a causative factor. |

### DERMAL DRUG STUDIES

<p>| Integumentary | Folliculitis | Folliculitis and furunculosis are common findings with administration vehicles of high viscosity, such as ointments. |
| Integumentary | Dermal Phototoxicity studies. | How to give your pig a sunburn. |
| Special Senses | | A stress-related skin disease resulting in blistering and serum exudation on the lumbar skin surfaces. Affected animals often “dip” their backs, vocalize and show signs of extreme pain. |
| Integumentary | “Dippity pig syndrome” | |
| Integumentary | Bullous pemphigoid | This vascular disease is seen in Yucatan minipigs. There is separation of the dermis and epidermis within the basement membrane. |
| Integumentary/Hematopoietic | Thrombocytopenia purpura | This is a striking but uncommon potentially fatal disease of Gottingen minipigs resulting in arteritis, florid hemorrhage, severe thrombocytopenia, and anemia. |
| | Cutaneous hemorrhages | |
| | Colonic hemorrhages | |
| Integumentary | Porcine juvenile pustular psoriasiform dermatitis | Previously known as pityriasis rosea, this disease of swine affects young white pigs. Early lesions result in perivascular eosinophilic and lymphoplasmacytic inflammation and |</p>
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<td>Melanoma</td>
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<td>50% of Sinclair minipigs have tumors at birth, may metastasize, but usually</td>
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<td>regresses following the development of a tumoral immune response.</td>
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<td>46</td>
<td>Integumentary</td>
<td>Sunburn</td>
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<td>Minipigs, like other swine, may be extremely photosensitive.</td>
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<td>Integumentary</td>
<td>Hyperkeratosis</td>
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<td>A condition that is well-documented in Gottingens, there is proliferative</td>
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<td>crusting of the back of the head neck and dorsum which is exacerbated by</td>
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<td>UV light. Underlying skin is normal when the crusts are removed, and the</td>
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<td>condition is worsened with sunlight.</td>
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<td>48</td>
<td>Integumentary</td>
<td>Sarcoptes suis</td>
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<td>A classic disease of normal swine, this has recently been reported in</td>
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<td>minipigs. Look for infection to begin in the front of the animal, especially</td>
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<td>inside the ears.</td>
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<td>Hematopoietic</td>
<td>Lymph node</td>
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<td>Blood collection may result in hemorrhage within lymph nodes of the neck and</td>
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<td>thorax.</td>
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<td>54</td>
<td>Cardiovascular</td>
<td>Ventricular septal defect</td>
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<td>20% of feti in some Yucatan lines makes for a pretty good model.</td>
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<td>Cardiovascular</td>
<td>Atherosclerosis</td>
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<td>The ascending aorta is a common location for spontaneous plaque development</td>
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<td>in the minipig.</td>
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<td>Metabolic syndrome</td>
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<td>Metabolic syndrome is a serious issue, especially in middle-aged North</td>
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<td>American males, includes obesity, hypertension, dyslipidemia, and insulin</td>
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<td>resistance. Any comparison between them and the minipig animal model,</td>
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<td>Atrial thrombosis</td>
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<td>Atrial thrombosis in the minipig is associated with indwelling catheters</td>
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<td>– either advancing them too far into the atrium, or poor hygienic practice</td>
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<td></td>
<td>with them.</td>
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<td>Spontaneous Arteritis</td>
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<td>Similar to polyarteritis nodosa, affects small to medium arterioles in a</td>
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<td>wide range or organisms.</td>
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<td>Several forms of mycoplasma exist in swine. M. hyorhinis is a common cause of</td>
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<td>polyserositis. As a mycoplasma, airways are almost always affected as well.</td>
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<td>Gastrointestinal Pharyngeal diverticulum</td>
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<td>The pharyngeal diverticulum is a blind-end pouch in the pharyngeal region which may complicate intubation.</td>
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<td>ANATOMIC PECULIARITIES OF THE SWINE GI SYSTEM</td>
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<td>There are often increased numbers of macrophages within alveoli following gavaging.</td>
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<td>Gastrointestinal Gastric ulcer</td>
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<td>Ulcers are a problem in swine of all sizes. In the laboratory, stress is a more likely trigger than feed composition. Ulcers more commonly develop on the squamous epithelial-lined pars esophagea, but may be seen in the glandular mucosa as well.</td>
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<td>Hematopoietic Thymus</td>
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<td>Standard as in most species, but involutes poorly. Hassall’s corpuscles exhibit significant inflammation during involution.</td>
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<td>Hematopoietic Lymph nodes</td>
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<td>As in all swine, the cortex and medulla are reversed. Mesenteric lymph nodes are associated with a prominent vascular plexus.</td>
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<td>Like many species, one of the earliest signs of interstitial nephritis is basophilia of scattered tubules with mitotis activity.</td>
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<td>Tubular damage is often followed by the accumulation of lymphocytes and plasma cells into the surrounding interstitium.</td>
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<td>Cystic endometrial hyperplasia and smooth muscle tumors</td>
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<td>Smooth muscle tumors are commonly seen in the uterus of swine of any size, but increase in frequency with age.</td>
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<td>Smooth muscle tumors may be large enough to resemble pregnancy however, they generally occur in aged animals. This particular specimen weighed 50 pounds.</td>
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Pathology and a Lot of Other Stuff Because Let’s All Admit There Isn’t Much Pathology in Minipigs

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Image Acknowledgments
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Dr. Kristie Mozzachio
Dr. Aaron Sargeant
Dr. Margaret Hanson

Miniature Pigs

- Sus scrofa domestica
- Smaller than 75 kg adult weight, easy to handle
- Require less food, less test material
- Controlled genotype and phenotype

Swine vs Other Species

- Dogs
  - Not prone to vomiting
  - Better NSAID tolerance
  - Tolerate sympathomimetic drugs better, no cardiotoxicity
  - Physiologically more similar to man
- Primates
  - Low cost
  - Early sexual maturity (3-6 months)
  - High reproduction rate
  - No supply or conservation concern
  - Easier to handle, transport, and house

Miniature Pigs

- Common miniature pig breeds used in research: Goettingen, Hanford, Sinclair S-1, Yucatan
- Available as SPF barrier-bred; some are also available as germ-free and GEMS
- Low background lesion incidence in most breeds
- Use of minipigs growing in US; 7.2-10% of non-rodent use (Heining, 2016)
Swine vs Primates

- Ethics
- Lower costs
- Early sexual maturity (3-6 months)
- High reproduction rate
- No supply or conservation concern
- Easier to handle, transport, and house
- Fewer zoonotic diseases

Gottingen

- Developed in the 1960’s
- Well-defined and strictly managed genetic background
- White-skinned, short snout, pot belly
- 6-mo weight ~12 kg, adult weight is ~35 kg.
- Many study types including juvenile and

Hanford

- Supplied by Sinclair Bio-resources
- Looks like a conventional pig
- White-skin and hair, less SQ fat
- 6-mo weight ~40 kg
- Surgical and cardiovascular research
- Develops adult human-sized organs and structures between 6-8 months of age

Sinclair

- Supplied by Sinclair Bio-resources
- First mini stock developed specifically for research purposes - 1949
- 6-mo weight ~25 kg Adult - ~55-75 kg
- Different colors; easy identification
- White strain now available
- Used for cardiovascular, osteoporosis, diabetes, and fetal alcohol syndrome research
- Melanoma model line

Yucatan

- Naturally occurring breed found in Mexico, Central & South America
- Characterized as research animal in 1970’s
- Grey to black skin, sparse hair, docile
- Supplier: Sinclair BioResources
- Adult weight: 70-80kg
  - Micro-Yucatan: 55-70kg
HUSBANDRY

Behavior
• Prey species
• Herd animals with a social hierarchy
• Highly food motivated
• Rooting behavior
• Nesting behavior
• Vocal
• Clean

Enclosures
• Floor space requirements vary
• Consider natural social behavior & dominance hierarchy
• Group or pair-house if possible (except adult intact males)
• Visual, auditory or olfactory contact if single-housed
  – Single pet pig households have higher incidence of human-directed aggression

Enrichment
➤ Hay/straw
➤ Chains
➤ Balls
➤ Brown paper
➤ Social interaction (other pigs or humans)
➤ Exploration of new environment

Husbandry Issues
• Hoof overgrowth
• Traumatic injury
Husbandry Issues

- Slippery floor → stressed pig
- Ad libitum feed → obese pig
- Lack of water → salt

Handling & Restraint

- Pigs can learn to willingly accept:
  - Being picked up
  - Sling
  - V-trough
  - Weighing
  - Masking
  - Dermal dosing
- Operant conditioning (clicker training)

Panepinto Pig Sling

Image: WIL-Lyon

Mental Gland

Image: WIL-Lyon

Integumentary System

Carpal Glands
Skin: comparison to humans

- Epidermal thickness & dermal-epidermal thickness ratio
  - Epidermis:
    - Rat: 10-20 µm
    - Pig: 70-140 µm
    - Human: 50-120 µm
  - Remember, epidermal thickness varies with location!
- Dermal collagen and elastic content biochemically

Differences:
- Eccrine sweat glands limited to snout and carpal glands
- Less vascular

Normal Skin: Pig vs. Human

Normal Skin: Mouse vs. Human

Skin
- Standard model of wound healing/burns (a standard plastic surgery model)
- Heals primarily by reepithelialization rather than contraction
- High surface area available

Drug Administration
Dermal Studies

Continuous subcutaneous infusion (24 hours for a 10-day period) is possible
**Folliculitis/furunculosis**

Common with high viscosity ointments or vehicles

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**Dermal Phototoxicity Studies**

- Continuous subcutaneous infusion (24 hours for a 10-day period) is possible


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**Aural, Ocular Discharge**

- a.k.a. Bleeding back syndrome
- Likely multifactorial etiology (genetics, stress?). Signs are similar to those of sunburn (pigs dip their backs, vocalize, and show signs of extreme pain) but with no history of sun exposure. Circular, serum-oozing lesions of various sizes are seen on lumbar skin surfaces.
- Recover in several days with restricted activity with or without symptomatic treatment. May recur in some animals.
- Reportedly, these pigs can then develop secondary staph infections of the skin

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**Dippity pig syndrome”**

- Reported in Yucatans
- Vesicobullous disease
- Separation of the dermis and epidermis at the lamina lucida of the basement membrane
- May be preceded by local erythema, pruritus
- Few inflammatory cells
Thrombocytopenic Purpura Syndrome

- Severe thrombocytopenia, Multiorgan hemorrhages

McInnes et al. A brief review of infrequent spontaneous findings, pecuilar anatomical microscopic features, and potential artifacts in Gottingen minipigs. ToxPath 2016: 338‐345
Porcine juvenile pustular psoriasiform dermatitis (Pityriasis rosea)

- Etiology unknown
- Young white breeds
- Microscopic lesions
  - Early: perivascular eosinophilic and lymphoplasmacytic inflammation, spongiform pustules, & psoriasiform hyperplasia
  - Later: Hyperplastic plaques with little inflammation, resolve completely after 6-8 weeks
  - Can be experimentally induced with IL-23 injections

Melanoma

- Sinclair minipig
- 50% of piglets have tumors at birth, 85% by 6 weeks of age
- Aggressive metastasis
- However: spontaneous depigmentation and regression between 6-12 months of age

Hyperkeratosis

- Brown crusting of the back of the head, neck & dorsum
- Etiology unknown
- Exacerbated by sun exposure in pet pigs

Sunburn

Sarcoptes suis
Cardiovascular

- Hanford heart/vessel size more like humans vs. dog or NHP
- No collateral blood supply

Gross Anatomy

- Pig heart nearly identical to man
- Little collateral coronary artery blood supply
- Spontaneous as well as inducible atherosclerotic plaques

Cardiovascular parameters

- Alternative to dog or primate for anesthetized or conscious cardiovascular profiling and telemetry
- Growth of CV system from birth to 4 months is analogous to that of humans into the mid-teens
- Suitable model to identify effect of compounds on QT interval

Ventricular septal defect

- Specific Yucatan lines are models
- ~20% of fetuses
- 65% are high membranous defects
- Polygenic defect
Atherosclerotic Plaque

Atherosclerosis

- High lipid/high carb diet or GEM
- Similar pathophysiology of hyperlipidemic vasculopathy in humans


Metabolic syndrome

- Obesity
- Hypertension
- Dyslipidemia
- Insulin resistance
- Increase in C-reactive protein

Metabolic syndrome in minipigs

- High caloric diet (high fat/high fructose)
  - Yucatan, Ossabaw
  - Osabaw 0 low insulin binding affinity for liver microenzymes
- GEM
  - Increased activity of proprotein convertase subtilisin/kexin (PCSK) => reduced hepatic LDL receptors


Metabolic syndrome in minipigs

- Heart – oxygenation greatly reduced
- Kidney – increased interstitial fibrosis and inflammation
- Adipose tissue – increased abdominal fat tissue volume and adipocyte size
- Increased C-reactive protein
Atrial Thrombosis

Spontaneous arteritis
- Gottingens
- Lesions similar to polyarteritis nodosa in rats
- Degenerative vascular lesions in small- to medium-sized muscular arteries
- Usually coronary arteries and vessels of the renal pelvis
- Intimal proliferation, medial thickening +/- necrosis, endothelial proliferation, luminal stenosis, thrombosis, disruption and fragmentation of the internal elastic lamina

Inhalation studies

Respiratory System

Nasal studies

The NALT in minipigs is a single organ, located at the roof of the nasopharyngeal duct, comparable to the adenoid or nasopharyngeal tonsil in humans and dogs.

Respiratory

• Porcine Respiratory Disease Complex
  (Rare in SPF animals but possible)
  ◦ Primary pathogens
    - M. hyopneumoniae
    - A. pleuropneumoniae
    - SIV
    - PRRSV
    - PRV
    - PRCV
    - PCV
  ◦ Secondary pathogens
    - P. multocida
    - S. suis
    - H. parasuis
    - B. bronchiseptica
    - A. pyogenes
    - A. pleuropneumoniae

Mycoplasma hyorhinis

Pharyngeal Diverticulum

Gastrointestinal System
Gastrointestinal & Hepatobiliary
- 2-3 days to empty
- Torus pyloricus: muscular outpouching at level of pylorus
- Cecal tonsil: 2 cm-wide Peyer's patch opening
- Unbranched pancreatic like humans (can pancreatic secretion)
- P450s CYP 1A, 2A, 3A metabolize same test substrates as

Gastrointestinal
- Gavage dosing
- Don’t tolerate capsules as well as dogs
- Not as sensitive as dogs to ulcer-inducing effects of NSAIDs
- renal papillary necrosis also unlikely

Restraint chair for gavaging

Alveolar macrophages

Procedural trauma
- Long soft palate and laryngeal diverticulum make intubation or gavage difficult
- Edema / acute inflammation in the pharynx, larynx, and cervical region
- May see red frothy fluid following procedure; can bite tongue

Foaming at the Mouth
Background findings

Gallbladder
- Cholecystitis (acute or chronic)
- Acute: necrotizing with hemorrhage
- Chronic: Fibrosis with mononuclear cells
- May not be visible grossly (hypoplasia is differential)

Liver
- Focal inflammatory cell infiltrates
- Hematopoesis
- Single cell necrosis
- Nodular hyperplasia in Yucatans (Garlick, 2001)

Cholelithiasis
- Often develops in obese pigs on a poor diet (i.e. table scraps, dog food)
- No clinical signs or biochemical abnormalities
- Incidental finding at necropsy

Gastric ulcer syndrome
- Complex syndrome
- +/- early hyperkeratosis of the esophagus and/or pars esophagea
- Related to anorexia or finely ground, pelleted feed – decreased gastric emptying
- Damage to squamous epithelium → ulceration
- Exacerbated by stress

Stomach erosions
- Nonglandular
- Glandular
Pig mucus is good for you!

- Mucus from pig stomachs is effective as antiviral agent: May be useful in cosmetics and baby formula
  (Lieleg O et al. Mucin biopolymers as broad-spectrum antiviral agents. Biomacromolecules, 2012.)
  - Broad-spectrum antiviral mucins
  - Possible addition to toothpastes, mouthwashes, wound ointments and genital lubricants

Hematopoietic System

Lymph Node

Renal
- Kidney anatomy more similar (even than NHPs) to human
- Spontaneous glomerulonephritis in 2.5% Gottingens
  - Membranous or membranoproliferative

Urinary System

Image: Lydia Andrews-Jones
Interstitial Nephritis

- Göttingen and Sinclair breeds, especially
- Features include:
  - Interstitial mononuclear cell infiltrates
  - Tubular degeneration and loss
  - Tubular ectasia and proteinosis
  - Basement membrane thickening
  - Glomerulosclerosis
  - Fibrosis

Renal tumors in diabetic model

Development of a Novel Model for Streptozotocin-induced Renal Cell Tumors and Chronic Diabetes in Goettingen Minipigs
(Fukuoka A et al. 2005 J Toxicol Pathol)

- Adenoma and carcinoma 5 years after STZ injection
- A stable diabetes animal model plus a chemical-induced tumor model developed with a single administration of STZ

Urinary Issues

- Crystal or urolith formation
- Urinary tract obstruction
- Recurrent UTI's
Urinary Obstruction

- Most often associated with damage to mucosa; often urolithiasis
- Congenital


Lymphoma (kidney)

Reproductive

- Sexually mature in 4-6 months (economic benefit vs. 3-4 years for macaques)
- Not good model for penile or ureteral procedures
- Must clean the preputial diverticulum before surgery
- Diffuse epitheliochorial placentation
- Slowly increasing use in embryo-fetal studies

Reproductive: Male

- Penis ~60 cm, relatively thin
- Coitus lasts up to 30 min; boar is said to "soak"
- Contraction/relaxation of retractor penis* muscle is responsible for movements of intercourse; mostly smooth m.; attaches just distal to sigmoid flexure
- Implications of drugs affecting smooth m.; e.g. possible paralysis of smooth m. by sympatholytic

Reproductive: Female

- HOWEVER: Tortereau A et al. showed only 50% of females are mature at about 6.5 months old (11.8 kg bw), and 100% were not mature until about 7.5 months old (13.1 kg). Higher uterine wt with sexual maturity, but ovarian wt not

Reproductive

- Colostrum needed for maternal antibody transfer (not placenta)

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<th>Histiotypic Type</th>
<th>Species</th>
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<td>Diffuse, epitheliochorial</td>
<td>Horse, pig</td>
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<tr>
<td>Cytotrophoblastic, epitheliochorial</td>
<td>Ruminants (cattle, sheep etc.)</td>
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<tr>
<td>Zona r, endodermal</td>
<td>Canines (dog, cat)</td>
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<tr>
<td>Discord, hemorrhodial</td>
<td>Humans, primates, rodents</td>
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Normal Uterus

Ovarian Cyst

Uterine Cystic
Endometrial Hyperplasia

Miniature pet pig
Leiomyosarcoma

1
Diffuse CEN
Leiomyosarcoma

2

Miniature pet pig

Ilha M R S et al. Vet Pathol 2010;47:1071-1075
Fibroid Model?

- Spontaneous uterine leiomyoma occurs at a very high frequency in minipigs (5+ yrs)
- Tumors appear to be hormonally responsive
- Pregnancy is protective

Uterine Carcinoma & Cystic Endometrial Hyperplasia

Epididymal cysts

Atrophy/Hypoplasia
Testes: focal segmental atrophy or tubular hypoplasia

Other background findings

- Seen in many different organs:
  - Liver
  - Adrenal cortex
  - GI tract
  - Lung
  - Heart
- May indicate normal immune function

Testicular Tumor

Metastatic Testicular Tumor

Melanosis

- Pigmentation in internal organs – Normal in pigmented swine
- Meninges, lungs, spleen, heart valves, liver, lymph nodes
“Necrotizing myositis”
- Gottingens
- Multifocal skeletal muscle degeneration and necrosis
- Mononuclear cell infiltrates
- +/− myofiber regeneration

Porcine stress syndrome/ Malignant hyperthermia
- Newly diagnosed in a Gottingen (2014)
- Ryanodine receptor defect in farm pigs, may be dystrophin gene in minipigs
- Unregulated release of calcium from sarcoplasmic reticulum → excessive myofiber contraction → increase in body temp
- Triggered by anesthetic agents (halothane) or stress
Rare MS incidental findings

- Osteochondrosis dissecans

Rare MS incidental findings

- Lingual chondrocytes = ectopic? (McInnes 2015)

Nervous/special senses

- CNS development; brain growth spurt before birth
- Majority of CNS cell division before birth
- Myelination largely postnatal
- Blood-brain barrier relatively immature at birth
- Highly developed eye
- Ideal for teratology studies
- Massive skull bones limit use in cranial surgery

Good model for spinal surgery

- Model for intraspinal delivery of gene and cell therapies due to size, anatomy and vulnerability of the spine/spinal cord
- Surgical process of exposing and manipulating the spinal cord, and closing the wound, is virtually indistinguishable from human

Eye

- Retina, pupil, lens have closest resemblance to human eyes after NHPs
- No tapetum
- Harderian glands
- Transcleral drug delivery
- Retinal rosettes less common than in NHPs
Diabetes models

- Provides large animal model of Type 1 and Type 2 diabetes models to study diabetes treatments and wound healing in diabetic patients
- No spontaneous diabetes in swine
- Induced
  - Streptozotocin (STZ)
    - Severity depends on dosage (commonly 150 mg/kg)
    - Residual insulin-positive cells in pancreas
- Alloxan
  - Similar to glucose in structure
  - When in beta cell, binds glucokinase, inhibiting glucose-induced insulin secretion

Cataracts in Diabetic Minipigs

Diabetes models

Total pancreatectomy
• Better at removing endogenous insulin, but requires intensive postoperative care
• More health problems than STZ, greater time and resources
• Post-op survival only ~10 days unless receive islet transplants, then live several months

Swine as xenograft models?!

• Human xenografts are not rejected in a naturally occurring immunodeficient porcine line: A human tumor model in pigs

Organ transplants

• α-gal problem:
  alpha-1,3-galactose (α-gal) coats the surface of pig blood vessels but is absent from human tissues
• Antibodies against this protein → complement → holes punched in membranes of the foreign cells on contact
• Progress being made with genetically engineered pigs lacking gene that makes α-gal
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Minipig Research Forum on LinkedIn