**Macaca fascicularis**
- Pointed crest at crowns of head
  - Females have beards
- Females 2.5-5kg, Males 4.5-8kg
- Inhabit coastal areas of SE Asia
- Good swimmers
- Omnivorous-insects, crabs, fish, veggies etc
- Non seasonal breeders
- 28d menstrual cycle
- Gestation period 163.5d
- Interbirth interval 390d
- Sexual maturity 3.5y
- Live in male dominated multimale-multifemale groups

**Macaca mulatta-Rhesus monkey**
- Native to India and China
- Females: 4.5-11kg, Males: 5.5-12kg
- Shorter tails than cynomolgus
- Generally considered frugivorous or vegetarian
- Seasonal breeders: Sept-Feb in Northern hemisphere
- Often have red-tinged skin
- Females: skin swelling on the face, arms legs and perineal region
- Live in male dominated multimale-multifemale social groups
- Gestation period 164d
- Interbirth interval: 360d
- 93.45% genetic homology to humans
- Popular model for HIV/SHIV research

**Macaca nemestrina- Pigtail Macaque**
- Used as a model for Kyasnr Forest disease and reproductive biology

**Macaca radiata- Bonnet monkey**
- Native to India and China
- Females: 4.5-11kg, Males: 5.5-12kg
- Shorter tails than cynomolgus
- Generally considered frugivorous or vegetarian
- Seasonal breeders: Sept-Feb in Northern hemisphere
- Often have red-tinged skin
- Females: skin swelling on the face, arms legs and perineal region
- Live in male dominated multimale-multifemale social groups
- Gestation period 164d
- Interbirth interval: 360d
- 93.45% genetic homology to humans
- Popular model for HIV/SHIV research

**African Species of OWM**
- Cercopithecus aethiops- Sootey Mousailey
- Chlorocebus aethiops- West African green monkey, vervet, guenon
- Papio anubis- Olive Baboon
Old World Monkey Viruses

- **Retroviruses**
  - Simian Immunodeficiency Virus (SIV)
  - Simian T cell Lymphotrophic Virus (STLV)
  - Simian Foamy Virus (SFV)
- **Herpes Viruses**
  - Macacine herpes virus 1
    - Aka- Herpes B
    - Aka- Cercopithicine Herpesvirus 1
    - Cercopithicine Herpesvirus 2 (aka SAB)
  - Simian Varicella Virus
- **Hemorrhagic Viruses**
  - Ebola, Marburg
  - Simian Hemorrhagic Fever Virus
- **Pox Viruses**
  - Monkey Pox
  - Measles Virus

Old World Monkey Retroviruses

- **Retroviridae**
  - Orthoretrovirinae
    - Betaretrovirus
      - Simian Retrovirus Type D (SRV)
    - Deltaretrovirus
      - Simian T Cell Lymphotrophic Virus (STLV)
  - Lentivirus
    - Simian Immunodeficiency Virus (SIV)
  - Spumavirinae
    - Simian Foamy Virus (SFV)

### Retrovirus Information Table

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**SRV**

Clinical signs
- Viral induced immune suppression
- Opportunistic infections
- Anemia, weight loss, persistent unresponsive diarrhea
- Retroperitoneal fibromatosis mass lesions
  - Retropertoneal sarcoma, undifferentiated sarcoma
  - Presumed associated with a gamma herpes virus (rhesus rhadinovirus, or retroperitoneal fibromatosis herpes virus (RFHV))
  - Model for Kaposi’s Sarcoma in humans
- Noma- severe ulcerative necrotizing gingivitis, periodontitis with osteonecrosis

Impact on Research
- Immune suppression or modulation
- Interpretation of histology and clinical pathology
- Animals may become ill

**SRV**

- Simian Type D Retrovirus
  - Retroviral pathogen of macaque species
  - Classified:
    - Family retroviridae
    - subfamily orthoretrovirus
    - Genus betaretrovirus
  - 5 distinct serotypes
  - All have been isolated from macaques
    - SRV-1- rhesus
    - SRV-2- cyno, pigtail
  - Pleotropic for many cell types and tissues
  - Transmission considered to be horizontal and possibly by contaminated fomites

Lymphoid follicle in kidney

Lymphoid hyperplasia in spleen
Retroperitoneal Fibromatosis

• Detection can be problematic
  – Three possibilities after infection:
    • Some mount and maintain a robust antibody response but virus and disease are undetectable
    • Viremic without detectable antibody levels
    • Others fall somewhere in between
      – Carriers with undetectable antibody levels
      – Clinical disease

• Essential to test both for antibodies and actual virus
• Antibody screening determines presence of SRV of the population
• Viral detection in individuals is important for eliminating the virus from a population
  – Real time PCR test to detect SRV 1-5 serotypes SRV

STLV

• Simian T-cell Lymphotrophic Virus
  – Orthoretrovirus, deltaretrovirus
  – NHP counterpart to Human T-cell lymphotrophic virus (HTLV)
    • Collectively STLV and HTLV are now referred to as Primate T Cell Leukemia virus (PTLV)
  – Natural host- African and Asian monkeys and Apes
  – Seroprevalence estimates in captive populations noted between 3-12% (Lerche 2003)
  – Highly cell associated- CD4+ and CD8+
  – Transmission thought to occur by
    • Semen and cervical secretions
    • Breast milk during nursing

STLV

• Clinical Disease
  – Most infections are clinically silent
  – STLV related disease most commonly reported in African species (AGM, Baboon and Gorilla)
  • Anorexia, depression, LN enlargement and hepatosplenomegaly
  • Lymphoma, leukemia

• Diagnostics
  – Antibody testing
    • Using STLV or HTLV cross reactivity antigens
  – PCR
    • Primers created from the tax gene region
    • Identified based on homology between HTLV and STLV

Simian Immune deficiency Virus

• Retrovirus, subgroup lentivirus
  – Closely related to HIV-1
    • Natural hosts include many African species of monkeys and Chimpanzees.
    • Infection in these species rarely causes disease.
  – No reports of naturally SIV positive macaques
  • Positive macaques
    – Experimentally infected
      • Model of HIV/AIDS
    – Pigtailed, rhesus
    – Accidentally housed with infected animals
      • African species (Cerocebus)
      • Experimentally infected macaques

Simian Immune deficiency Virus

• Severe immune deficiency and disease in macaque species
  – Decrease in CD4+ T cells
  – Anemia, lymphopenia
  – Opportunistic infections
  – Lymphoma
• Potential confounding effects on research
• Diagnostic testing
  • Testing for proviral DNA is available real-time PCR
  • Antibody screening
    • ELISA, Western
Herpes viruses

- Double stranded DNA viruses
- 3 subfamilies
  - Alphaherpesvirinae
  - Betaherpesvirinae
  - Gammaherpesvirinae

Macacine herpesvirus 1

- Cercopithecine herpesvirus 1
  - Macacine herpesvirus 1
  - Aka Herpes B virus, Cercopithecine herpesvirus 2
  - Alphaherpesvirus
  - Same family as human herpes simplex viruses
- Clinical Disease
  - Typically asymptomatic in macaque species
  - Occasionally may see oral or genital lesions
  - Transmitted horizontally in oral or genital fluids
  - Primary infection controlled, virus invades the axons, travels to the sensory ganglions for latent lifelong infection.
  - Occasionally will reactivate and be shed from mucosal surfaces.
  - Occasionally may cause disseminated infection in immunosuppressed macaques.
- Can cause fatal infections in people or other aberrant primate species

Simian Varicella Virus

- Cercopithecine herpesvirus 9
  - Alpha herpes virus
  - Closely related to human varicella zoster virus
- Acute disease will usually resolve within 21d
  - Rash, depression, dyspnea
- Lesions
  - Multifocal vesicles on skin, oral and esophageal mucous membranes
  - Focal necrosis in liver, lung, spleen, lymph nodes, adrenal, bone marrow, and intestinal tract
  - Herpetic inclusion bodies at the margins of lesions
- Develop immunity to subsequent SVV infection
  - Remain latently infected in neural ganglion and may have reactivation disease when immune suppressed

Betaherpesvirinae

- Macacine herpesvirus 3 (Rhesus cytomegalovirus)
  - Narrow host range
  - Commonly occurs but rarely causes clinical disease
  - Most animals are seropositive by 1 year of age
  - Transmitted in milk, blood, saliva, urine and semen
  - Clinical disease associated with intrauterine infections and immunosuppressed patients
    - Reactivation of virus during immune suppression may result in encephalitis, enteritis, lymphadenitis or fata disseminated disease
  - Valganciclovir may be beneficial
  - Histology: large cytomegalic cells with intranuclear and intracytoplasmic inclusions

Gammaherpesvirinae

- Lymphocryptovirus
  - Macacine herpesvirus 4, Rhesus lymphocryptovirus
  - Related to Epstein-Barr virus
  - Species specific
  - May cause lymphoid and epithelial proliferative lesions
  - Co-infection with SV associated with malignant B cell lymphomas oral lesions (hairy leukoplakia)
  - Diagnosis by serology or PCR
- Rhadinovirus
  - Rhesus rhadinovirus and Retroperitoneal fibromatosis herpesvirus
  - Widespread in macaque colonies, not usually associated with disease
  - B8HV-
    - Associated with SRV infection and the mesenchymal proliferative lesion known as retroperitoneal fibromatosis
  - Associated with GI stromal cell tumors and SV infection
Filoviruses

- Ebola virus, Marburg virus
  - Single stranded enveloped RNA viruses
- Indigenous to Africa
  - Discovered in 1976 - Democratic Republic of the Congo
- Exact origin, location, natural habitat and reservoir remain unknown
  - Fruit bats (Rousettus aegyptiacus) may be reservoir host
- Cause severe hemorrhagic disease in humans and primates
  - Sporadic outbreaks mainly restricted to Africa
- Main incentive for the Center of Disease Control (CDC) primate import requirements
  - Stringency increased following Ebola Reston incident 1990
  - Disease control measures to protect personnel
  - Requires specialized containment facility
  - Must test any animal that dies (for any reason) during quarantine for filovirus antibodies in serum and antigen from liver tissue

Simian Hemorrhagic Fever Virus (SHFV)

- Simian Hemorrhagic Fever Virus (SHFV)
- Arterivirus - RNA, enveloped
  - First isolated in 1964, after devastating outbreaks of hemorrhagic fever in colonies of captive macaque monkeys (Palmer et al., 1968; Tauraso et al., 1968).
  - Endemic among several genera of African monkeys, in which it causes an asymptomatic persistent infection (London, 1977; Gravell et al., 1986b).
  - Macaque species have an unusual sensitivity to SHFV with the mortality of disease approaching 100%
    - Bleeding diathesis progressing to death
    - Distinguishing lesion - hemorrhagic necrosis of the proximal duodenum
- SHFV transmission from African monkeys to macaques most likely occurs due to accidental transmission during co-housing.
- Main incentive for separation of African and Asian primate species for housing and handling.

Monkey Pox

- Monkey Pox Virus
  - Orthopoxvirus - large DNA virus
    - Same family as smallpox, vaccinia, cowpox
    - First discovered in laboratory monkeys in 1958
    - Native to central and west Africa
    - Reservoir host:
      - African Rodents
- Infects people and NHPs, causes sporadic disease
- Clinical signs include:
  - Cutaneous papules/pustules, “pock lesions”
  - Lymphadenopathy, oral ulcers, fever
- Infection confers life long immunity
- Vaccina or smallpox vaccine effective

Measles Virus

- Genus - Morbillivirus, Family - Paramyxovirus
  - Same virus family as canine distemper virus
- Humans and non-human primates are the only known hosts
- Primates contract the virus from humans
- Highly contagious via respiratory aerosols, not fomites
  - Virus is not stable in the environment
- Recovery from natural infection confers lifelong immunity
Measles Virus

- Hallmark lesion: Koplick spots
  - Usually occur prior to rash and illness
  - White, red-rimmed spots on oral mucosa
- Pathology
  - Pneumonia is the classic lesion
  - Acute bronchiolitis with characteristic multinucleated giant cells
  - Rarely see intranuclear and intracytoplasmic inclusions

Vaccination
- Only one vaccine in use for humans since 1954
- Modified live attenuated virus
- Only one serogroup, genetically stable virus and vaccine
  - Few products available for NHPs
- Human vaccines are effective
  - Are usually multivalent (contain other viruses)
  - Expensive
  - “Vanguard”: Canine distemper vaccine + Measles Virus
    - Efficacy questionable
    - Availability unreliable
  - Vaccination should occur after maternal antibodies wane
  - Vaccine can cause transient immunosuppression
- Prevention
  - Screen and vaccinate humans that come in contact with NHPs

Bacterial Pathogens

- Respiratory
- Gastrointestinal

Structure of Bacteria

Essential structure:
- Cell wall
- Cell membrane
- Cytoplasm
- Nuclear material

Types of structures:
- Capsule
- Flagella
- Pili
- Spore

Tuberculosis

- Agent
  - Mycobacterium tuberculosis is most common
  - M. bovis, M. africanum is occasionally reported
- Route of infection
  - Inhalation of organism
  - Exposure to infected humans or other NHPs
- Clinical signs:
  - Weight loss, anorexia, lethargy
  - Coughing, dyspnea, cyanosis
  - Asymptomatic
- PE findings
  - Lymphadenopathy, splenomegaly or hepatomegaly
- Pathology
  - Caseous nodules: LN, lung
  - Tubercles: lungs, thoracic pleura
  - Military disease or foci of caseation in spleen, liver, kidney

Tuberculosis - Diagnostics

- Intradermal TB Skin Test (TST)
  - 0.1ml Mammalian Old Tuberculin
  - Score for signs of delayed-type hypersensitivity
  - 48 to 72 hours post administration
  - Grade based on induration and erythema: 1-5 subjective scale
  - Ineffective in immune compromised or suppressed animals
- INF-γ Release assay - “Primagam”
  - In-vitro
  - Still relies on an intact/functional immune system
  - More quantitative than the TB skin test - but still lacks specificity and sensitivity
- Antibody detection
  - ELISA, MAMA, Lateral Flow
- PCR
  - Relies on more invasive samples: gastric or BA lavage, tissues
- Gold standard remains bacterial Culture
  - Fastidious organism - difficult to grow
  - Takes 6-8 weeks
  - Special medium?
Other Bacterial Respiratory Pathogens

• *Streptococcus pneumoniae*
  - Normal commensal of upper respiratory tract of healthy macaques
  - Opportunistic pathogen
  - Gram-positive cocci in short chains or pairs
  - Severe fibropurulent pneumonia

• *Klebsiella pneumoniae, Bordetella bronchiseptica, Pasteurella multocida*
  - Gram negative rods
  - Opportunistic commensal organisms
  - Fibropurulent pneumonia or bronchopneumonia

• *Moraxella catarrhalis*
  - Gram-negative diplococcus
  - Normal commensal organism of the nasal passage

Clinical Signs

• Epistaxis, sneezing, peri-orbital swelling
• “Bloody nose syndrome of cynomolgus macaques”
  - May be associated with low humidity
  - Responsive to treatment with Penicillin

Enteric Bacterial Diseases

• *Salmonella*

• *Shigella*

• *Campylobacter*

• *Yersinia*

• *Helicobacter*

Salmonellosis

• Gram negative bacteria.
  - *Salmonella enterica*

• Clinical disease in NHP
  - Humans are the main reservoir
  - Fecal-oral transmission, contaminated food
  - Can be asymptomatic with clinical signs precipitated by stress
  - Diarrhea, enteritis, septicemia, edema, and variable mortality
  - High percentage of survivors become carriers

• Diagnosis
  - Fecal culture with selective media
  - Serotyping may be useful for epidemiologic investigation

• Treatment
  - Fluoroquinolones and third-generation cephalosporins, fluid therapy
  - Many antibiotic resistant isolates
  - Zoonotic

Shigellosis

• *Shigella flexneri*
  - Gram negative bacterial rod

• Fecal oral transmission, contaminated food or water, fomites

• Shed from clinically ill or asymptomatic humans and NHP.
  - Only minimal contact is necessary for transmission.
  - Recovered animals often are carriers and serve as a reservoir of infection
  - High mortality is possible

• Diagnosis
  - Isolation of Shigella sp. from fresh rectal swabs, sequential samples recommended
  - PCR of fecal samples

• Pathology
  - Cecum and colon, fibrinopurulent exudate, pseudomembranous enterocolitis
  - Treatment:
    - Fluids, electrolytes, and antibiotics (fluoroquinolones)

Campylobacter jejuni

• Gram-negative microaerophilic, bacteria

• Fecal-oral transmission

• Clinical signs:
  - Asymptomatic carriers are common
  - Watery diarrhea, sometimes hemorrhagic
  - Dehydration
  - Associated with abortions

• Pathology
  - Edematous, reddened, roughened, proliferative hyperplasia small intestine and/or colon

• Diagnosis: Rectal culture
  - Selective CAMP media

• Treatment:
  - Usually self-limiting
  - Severe or prolonged cases may require ciprofloxacin, erythromycin, azithromycin or norfloxacin

Yersiniosis

• *Yersinia enterocolitica, Yersinia pseudotuberculosis*
  - Gram negative rod shaped facultative anaerobe

• Fecal-oral transmission

• Animals that recover may become asymptomatic carriers

• Increased incidents in wet/cold months

• Clinical Symptoms:
  - Diarrhea, lethargy, dehydration, abdominal pain, chronic lymphadenopathy, sudden death

• Pathology
  - Hepatic, splenic necrosis
  - Abscessation of mesenteric lymph nodes and organs
  - Ulcerative enterocolitis

• Diagnosis:
  - Fecal culture-hard to isolate
  - Fecal PCR

• Treatment: Aggressive antibiotic therapy
  - Fluoroquinolones, aminoglycosides, TMS
Helicobacteriosis

- **Agent:** Helicobacter pylori
- **Transmission:** oral
- **Clinical signs**
  - Often no detectable signs
  - High prevalence if infected rhesus in captivity
  - Vomiting, abdominal discomfort
  - Chronic gastritis, gastric ulceration
- **Diagnosis**
  - PCR
  - Serology
  - Silver stain of tissues samples
- **Pathology**
  - Mononuclear inflammatory cell infiltrate in lamina propria – antrum and body of stomach
  - Lymphocytic plasmocytic gastritis
  - Treatment:
    - *triple therapy*: metronidazole, bismuth subcitrate, tetracycline
    - Other antibiotics
      - cephalosporins, penicillin, amoxicillin

E. Arifin, 2007

Mycotic and Parasitic Diseases

- **Pneumocystis**
- **Coccidiomycosis**
- **Chaga’s Disease**

Pneumocystis spp

- **Pneumocystis carinii**
  - Ubiquitous in the environment
  - 95% healthy asymptomatic cynomolgus monkeys had antibodies to Pneumocystis (Kling, 2009)
- Disease often associated with other debilitation
  - Recent importation, bacterial infection, neoplasia, immunodeficiency
- **Clinical signs**
  - Weight loss, anorexia, pyrexia, dyspnea, cyanosis, polycythemia
  - Radiographs: extensive infiltrates in lung lobes
- **Diagnosis**
  - Serology or PCR
  - Silver or PAS stain of sputum or biopsy
- **Treatment**
  - TMS

Coccidiomycosis

- **Coccidioides immitis**
  - Saprophytic, dimorphic, fungi
  - Endemic to southwestern US and South America
  - California, Texas, Arizona
- **Transmission via aerosolization from the environment**
  - Not contagious between animals
- **Clinical signs**
  - Respiratory: nasal discharge, cough, dyspnea
    - Firm white nodules, cavitating lesions in lungs
  - Neurologic: paralysis
    - Paravertebral masses or abscesses, lysis of vertebral bodies
- **Diagnosis**
  - Cytology, Serology
  - Histology with GMS
- **Pathology**
  - Pyogranulomatous, multinucleated giant cells, thick walled spherules w/endospores
Chaga’s Disease

- Trypanosomiasis
  - Hemoflagellate, protozoal parasite
- Transmission
  - Intermediate host required: Triatomid insects (Reduviid bugs, kissing bugs)
  - Bite or contamination of open wounds with insect droppings, or ingestion of infected insects
- Epidemiology
  - South and Central America, Southern US
- Clinical Disease
  - Asymptomatic, lethargy, anorexia
  - Cardiopathies
    - Arrhythmias and conduction abnormalities
    - ECG abnormalities: Right Bundle Branch Block
  - Heart Failure
    - Biventricular congestive heart failure
    - peripheral edema, hepatomegaly, pulmonary congestion and dyspnea
- Pathology
  - Amastigotes in cardiac or skeletal muscle
  - Lymphoplasmacytic inflammation, fibrosis, degeneration

Prevention/Exclusion
- Diagnostics
  - Serology, PCR
  - Culture-blood, cell culture
  - Microscopy: blood smears, histopathology
- Treatment
  - Two drugs—Benznidazole and Nitfurtoxin
  - Not FDA approved
  - Difficult to access in US
  - May not be that effective in chronic stages
- Control of Environment
  - Removal of plants near the cages
  - Rodent and insect control
- Screen
  - Cull or don’t accept positives
  - Randomize across experimental groups in study design

Other Macaque Diseases

Fatal Fasting Syndrome of Obese Macaques

- Etiology:
  - Stressors: such as a change in husbandry procedures, new social pairing or other underlying disease process resulting in anorexia
  - Obese, middle aged, females > males
  - Synonyms: Fatal fatty liver syndrome, Fat macaque syndrome, hepatic lipidosis
  - Similar disease seen in several other species
    - Cats, Cows (fat cow syndrome), Ponies (hyperlipidemia), Guinea pigs, woodchucks
- Clinical Disease
  - Severe acute weight loss, anorexia, lethargy
  - Azotemia
  - Hepatomegaly
- Diagnosis
  - Clinical signs and lab results
  - US-diffuse increase in echogenicity
  - Biopsy
- Pathogenesis: not well understood
  - Negative energy balance and weight loss → fatty acid mobilization from fat depots → fatty changes in liver and kidney
  - Renal and hepatic lipidosis are hallmarks
- Treatment
  - Supportive care: nutritional support, IV fluid therapy, glucose/insulin management

Endometriosis

- Pathogenesis
  - Deposition/proliferation of functional endometrial tissue outside of the uterus
  - Retrograde ovulation
    - “seeding of the abdomen during laparotomy (especially hysterotomy)
- Clinical disease
  - Abdominal pain, inappetence—coincides with monthly menses
  - Irregular menses
  - Anemia
  - Palpable abdominal mass, cysts
- Diagnosis
  - Ultrasound, radiographs
  - Fine Needle Aspiration of mass
    - “chocolate fluid”
  - Cytology: degenerate RBCs, Hemosiderin laden macrophages, necrophils
- Treatment
  - Surgical resection, ovarioectomy, hysterectomy
  - Progesterone to control menstrual cycle
  - Gonadotropin releasing hormone agonists—halts menstrual cycle
  - Pain Management
Amyloidosis

- Pathologic deposition of 7S residue N-terminal fragment of serum amyloid A (SAA) protein
  - Associated with chronic inflammation
- Liver, GI tract, spleen, kidney

- Clinical signs:
  - Asymptomatic
  - Nonspecific: Cachexia, weakness, weight loss, syncope, recurrent diarrhea, hepatomegaly, anemia
- Clinical pathology: Hypoproteinemia, hypalbuminemia, elevated liver enzymes
  - Renal: Proteinuria, nephrotic syndrome, renal failure, uremia
- Cardiac: Congestive heart failure, arrhythmias
  - GI: malabsorption, diarrhea, disturbances in digestion
  - Death

- Diagnosis: morphologic identification on biopsy specimens
  - Gross: enlarged, firm, waxy organs that are yellow on cut surface
  - Histology: Congo red stain to differentiate from other hyaline deposits; high specificity, low sensitivity; electron microscopy

- Prognosis: poor with generalized amyloidosis
  - Grave for clinically ill nonhuman primates with secondary hepatic amyloidosis

Intestinal Adenocarcinoma

- Clinical
  - Aged, rhesus monkeys
  - Positive correlation established between age and intestinal cancer in rhesus monkeys
  - Closer to 30 years old, the more likely
  - Up to 20% incidence rate recorded in some aged rhesus colonies
  - Generalized weight loss, minimal stool production or diarrhea
  - Mild to moderate microcytic hypochromic anemia, thrombocytosis
  - Fecal occult blood positive
  - Palpable abdominal mass
  - Most common location: ileocecal junction
  - Radiographs consistent with intestinal obstruction
  - “Napkin ring” lesion on ultrasound exam

Histopathology

- Intestines, H&E

Intestinal Adenocarcinoma

- Pathology
  - "Napkin ring" lesion of intestine
  - Thickened intestinal wall with constriction of lumen
  - Well-differentiated, locally invasive, adenocarcinoma