Macraues
Husbandry, Research and Diseases

Michelle Leland DVM, DACLAM
University of Texas Health Science Center San Antonio
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Why Use Nonhuman Primates?
• Taxonomic similarity
• Phylogenetic similarity
• Genetic similarity
• Anatomic similarity
• Physiological similarity
• Similar social networks

Types of Primates
• The primate order is generally subdivided into four groups
  • Prosimians
  • New World monkeys
  • Old World monkeys
  • Apes

Primate Taxonomy

Macaques- General information
• Around 22 species identified
• 2 Most commonly used macaques in research
  • Macaca fascicularis, Cynomolgus macaque
  • Macaca mulatta, Rhesus macaque
• Macaca mulatta has the longest history of use in research
• Characteristics of Old World Monkeys
  • Large cheek pouches
  • Prominent ischial calllosities
  • Variable sexual swellings
  • Marked sexual dimorphism
**M. mulatta - Behavior**

- Large multi-male/multi-female social groups (range from 10 to 180 or more individuals)
- Strong dominance hierarchy for both males and females
- Female family units are called matrilines
- Kinship is important in dominance with social status of the young dependent upon rank of their mother
- Females remain in the group in which they were born and inherit the rank from their dam
- Males emigrate from their natal group approximately 4 years of age
- Well known for their aggressive behavior
- Estimated to spend 10-13% of their daily activity on grooming
- Distinct breeding season-seasonal breeders

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**Chinese vs Indian Rhesus**

- Genetic differences between Indian-origin and Chinese-origin rhesus macaques are as great as those between some primate species and can influence the results of experiments in which both are used as animal models for the study of the same human diseases
- Differences in the pathogenesis of SIV infection in the two subspecies
  - Immunopathogenesis of SIV in the Chinese rhesus is very similar to that of HIV infection in humans
- Chinese rhesus exhibit more sexual dimorphism
- Behavioral differences between the two have been documented
- Chinese rhesus, more temperamental, more irritable
- Shortage of Indian-origin rhesus right now

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**Macaca Mulatta**

Rhesus macaques

- Adults weigh from 5 to 12 kg
- Males are larger than females
- May live up to 30 years in captivity
- Females sexually mature at 3.5 years, but growth not complete until 6th year
- Males sexually mature at 4.5 years, but growth not complete until 10th year
- Average gestation length is 165 days
- Seasonal breeders: mid September to mid February (Northern Hemisphere)

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**Macaca Mulatta**

Habitat and Diet

- Natural Habitat: Afghanistan through much of India and Nepal, to northeastern China, Indochina
  - Adapted to almost any ecological niche from sea level to ~8200 feet, from snow to intense heat, and from near desert situations to dense forests
  - The only primates with a broader geographic distribution than rhesus macaques are humans
- Diet: Fruits, leaves, seeds, tubers, bark, insects
  - Estimated that up to 92 plant species used by wild populations

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**Sex skin rhesus**

Red wrinkled skin face and buttocks
**Macaca mulatta**

- **Rhesus macaque**
- **Longest History of Use**
- **Current Uses**
  - AIDS
  - Aging
  - Pharmacology
  - Behavior
  - Diabetes
  - Defense vaccines
  - Anthrax
  - Ebola

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**Macaca fascicularis**

- **Models of Reproduction**
- Most commonly used macaque for reproduction
- Research on ovarian cycle control
- Endometriosis
- Anovulatory infertility
- Osteoporosis
- Stress-associated infertility
- Menopausal changes in physiology
- Related metabolic disorders (diabetes, atherosclerosis)

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**Macaca fascicularis**

- **cynomologus macaque**
- **long tail macaque**
- **crab eating macaque**
- Most commonly used macaque in biomedical research today
- Primarily arboreal
- Has the third largest range of any primate species, behind only humans and the rhesus macaque
- There is significant genetic diversity within the species and these differences are classified into at least 10 subspecies
- The tail is longer than the body

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**Macaca fascicularis**

- **Other Research Uses**
  - AIDS
  - Infectious Disease
  - Cardiovascular
  - Reproduction
  - Osteoporosis
  - Periodontitis
  - Diabetes
  - Neuropsychology
  - Drug abuse
  - Depression

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**Macaca Nemestrina**  
**Pig-tailed macaque**

- Adults weigh from 5 to 15 kg  
- Males are larger than females  
- Have an abbreviated tail, less than the length of the body from head to rump, often bare or covered only by sparse fur, resembles pigs tail  
- Fur on top of the head is dark  
- Average gestational length is 174 days  
- Sexual swelling similar to baboons and mangabeys  

**Natural Habitat**

- Burma to Malay Peninsula and Sumatra  
- Lowland forests and coastal, swamp, dry land, and montane forest (cloud forest)

**Behavior**

- Multi-male/multi-female social groups (15-40 animals)  
- Matrilineal dominance hierarchy  
- Males emigrate from their natal group  
- No distinct breeding season, give birth all year round

**Diet**

- Fruit, seeds, leaves, flowers, insects, nesting birds, termites, river crabs  
- Estimated more than 180 plant species used by wild populations

**Macaca arctoides**  
**Stump tailed macaque**

- Infants born white

**Macaca nigra**  
**Celebes Black Ape**

- Spontaneous diabetes  
- No longer used

**Macaca radiata**  
**Bonnet Monkey**

- Maternal Neglect  
- Metabolic Syndrome  
- Alcoholism  
- Placenta accreta  
An abnormal placental adherence to the uterine wall

**Research**

- Pig-tailed macaques are used for viral and genetic research involved with HIV  
- They are the only Old World monkeys known to be susceptible to human immunodeficiency virus type 1 (HIV-1) infection  
- Rhesus shows different sensitivities to lentiviral infections  
- Chlamydia trachomatis research
Japanese macaque
*Macaca fuscata*

- **Natural Habitat**
  - Japan
- **Pinkish face, short stump tail**
- The average body weight of the Japanese monkey is 11.3 kg (24.91 lb) (M) and 8.4 kg (18.52 lb) (F)
- Japanese monkeys from northern colder areas weigh more than those from warmer areas of Japan
- Excellent swimmers and are reportedly able to swim distances of over half a kilometer
- Fur is a unique adaptation to cold: fur thickness increases as habitat temperature decreases and allows the monkey to cope with winter temperatures as low as -20° C (-4° F)

**Caging Requirements for Monkeys**

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<tr>
<td>Group 5</td>
<td>Up to 15</td>
<td>8.0</td>
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<tr>
<td>Group 6</td>
<td>Up to 25</td>
<td>10.0</td>
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</tr>
<tr>
<td>Group 7</td>
<td>over 30</td>
<td>15.0</td>
<td>46</td>
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</tbody>
</table>

**Social Housing**

- Gang cages
- Corn cribs
- Pair and social housing recommended by the guide
- May be required by AAALAC soon

**Sanitation - USDA Guidelines**
*Non human primates [3.84(b)]*

- Used primary enclosures and food/water receptacles must be sanitized: before being used for another animal(s) [3.84(b)(1)] at least once every 2 weeks, or [3.84(b)(2)] more often as needed to prevent an accumulation of:
  - dirt
  - debris
  - food waste
  - excreta
  - algae
  - mineral deposits
  - other disease hazards

**Animal Welfare Act**

- In 1985, the Animal Welfare Act (AWA) was amended to include, among other things, providing for the psychological well-being of nonhuman primates
- Contained requirements for social housing, inanimate enrichment items, and exercise for nonhuman primates
- Regulations became a final rule in 1991 (9 CFR Sec. 3.81)

**Non social Enrichment**

- Food puzzles
- Foraging boards
- Toys
- Mirrors
- Perches
- TVs
- Radios
Handling

- Chemical restraint is recommended
- Without chemical restraint: special NHP gloves with reinforced leather, usually reserved for infants
- Pole and Collar

Sedation

- Ketamine HCl - Most common
  - 8-10 mg/kg IM/IV
- Ketamine-Medetomidine
  - 3mg/kg; 0.15mg/kg
  - Atipamezole reversal
- Telazol
  - 2-6 mg/kg IM
- Propofol
  - 7.5-12.5 mg/kg IV (to effect)
  - Must get animal out of cage first usually given in restraint chair

Possible Complications Drawing Blood from the Femoral Vein

- May inadvertently cause trauma to the femoral artery
- "Pseudoaneurysm - leakage of blood from an artery into a defined space"
- "Non surgical repair of a pseudoeaneurysm in a cynomolgus macaque" Daviau and Merton
  - JAALAS Vol 49, No 5 Sept 2010
- Arteriovenous fistulas also reported

Occupational Health Program

- TB testing biannually of all personnel
- Measles vaccinations or titers
- Serum banking in some facilities
- Herpes B program for employees
  - Training, Training, Training!
Tuberculosis

- Macaques highly susceptible
- Inhalation of infected aerosols from animal or human
- Ingestion of the organism - rare
- Mycobacterium tuberculosis complex (MTB) includes
  - *M. tuberculosis* ** ABSL3**
  - *M. bovis*** ** ABSL3**
  - *M. africanum*
  - *M. microti*
  - *M. pinnipedii*
  - *M. canetti*
- All of the above species pathogenic zoonoses
- Atypical: *M. avium-intracellulare*

Other diagnostic modalities for screening and diagnosing TB
- Thoracic radiographs
- Gastric lavage with culture
- Bronchial alveolar lavage and culture

False negatives occur with latent infections, T cell anergy, vaccinations, specifically for measles. (TB test recommended >4 weeks after vaccination)
False positives: exposure to non TB bacteria, vaccination with Complete Freund’s adjuvant (contains cell wall of tubercle bacilli)

TB testing Non human Primates

- Intrapalpebral tuberculin skin test (tst)
  - Gold standard test for NHP
  - Mammalian old tuberculin
- Primagam (Prionics USA)
  - Whole blood in vitro cell mediated, humoral based diagnostic test
  - Measures the interferon-gamma response to purified protein derivatives (PPD) of *M. bovis* and *M. avium*
  - Sensitivity lower than tst
  - Not recommended as sole source test
  - Specific for diagnosis/differentiation
  - In 2007, PRIMAGAM® was fully licensed by the US Department of Agriculture (USDA) for the testing of Cynomologus and Rhesus Macaques

Scoring of intrapalpebral skin test

Recorded at 24, 48 and 72 hours

- Grade 1 - slight bruising of eyelid (negative)
- Grade 2 - erythema of eyelid without swelling (negative)
- Grade 3 - varying degrees of erythema with minimal swelling (indeterminant)
- Grade 4 - obvious swelling with dropping of eyelid (positive)
- Grade 5 - marked swelling and/or necrosis of eyelid (positive)

Screening TST

- Positive or Suspect

Abdominal and Contralateral Eye TST

- Positive or Suspect

PCR Feces (ID species)

- Atypical
- Positive MTC or suspect

No action
BAL/Gastric Aspirate
PCR or Culture
- Positive MTC

Cull and Necropsy
Extra Pulmonary Tuberculosis
- Latent infections with extra pulmonary tuberculosis not common in macaques, 20% in human populations
- Pott's disease - spine
- Hepatic or enteric infections
  - "Primary Hepatic Mycobacterium Tuberculosis Complex Infection with Terminal Dissemination in a Pig-Tailed Macaque (Macaca nemestrina)" JAALAS Vol 50, No 2 March 2011 Stockinger et al.

Macacine herpesvirus 1
- Clinical manifestations in macaques are variable
- May be fatal in several non-macaque species of monkeys
- May be fatal in humans
- Majority of macaques are asymptomatic when shedding the virus
- Occasionally vesicles and ulcers on the oral mucosa and esophagus

Personal Protective Equipment (PPE)
- Masks
- Goggles/face shield
- Double gloves
- Long sleeves
- Dedicated work shoes or booties
- Bonnet

Macacine herpesvirus 1
- Formerly known as Cercopithecine herpesvirus 1
  - SYN. Herpes virus simiae, herpes B virus, monkey B virus
- Alphaherpesvirus
- DNA virus
- B virus is classified as a select agent, with the potential to pose a threat to public health and safety, by the U.S. Public Health Service, Department of Health and Human Services

First reported case of Herpes B
- Herpes B virus, was named after a colleague of Dr. Albert B. Sabin
- Oct. 22, 1932, a patient identified as Dr. W.B. was bitten on 2 fingers by a macaque while researching the poliomyelitis virus
- A neurological illness ensued and on Nov. 9, 1932, the patient succumbed to respiratory failure secondary to acute ascending myelitis in New York
- The patient was an accomplished young doctor, Dr. William Bartlet Brebner
- His work included publications on purification of the poliomyelitis virus and the host immune response
**Macacine herpesvirus 1**

- People develop a fatal ascending encephalomyelitis
- **No vaccine**
- Post exposure anti-viral therapy is prescribed if caught early
- It is necessary to take anti-virals for the rest of your life
- Herpes B infection is rare given the fact that thousands of reports of monkey bites and scratches are reported to the CDC each year, but if you get infected the results can be catastrophic
- Of note: no herpes B virus exists in a population of long-tailed macaques introduced 400 years ago on the island of Mauritius, and no reports in Japan

**Macacine herpesvirus 1 Preventative Measures**

- Proper work practices markedly reduce the chances of infection
- When working with macaques, exercise caution at all times
- Wear appropriate, protective clothing
- Work together with at least one other person when handling if possible
- **If an exposure occurs:**
  - FIRST: scrub lesion/ eye wash for 15 minutes
  - Report incident immediately, bleed monkey if known, go to occupational health clinic, send monkey and human samples to Atlanta, repeat in 2-3 weeks
  - [http://www.gsu.edu/ltvirus](http://www.gsu.edu/ltvirus)

**Simian Varicella Virus**

- **Differentials:**
  - Measles
  - Monkey Pox
  - Rubella
  - Herpes B
  - SIV

**Gammaherpesviruses**

1. **Rhesus lymphocryptovirus (RhLCV)**
   - Many species of nonhuman primates are infected with lymphocryptoviruses
   - Similar to human Epstein–Barr Virus (EBV)
   - Primary infection of immunocompetent animals
   - Model of acute EBV infection and various lymphoproliferative disorders
2. **Rhesus Rhadinovirus**
   - The rhadinovirus genus contains Kaposi sarcoma associated herpesvirus (Human herpesvirus 8)
3. **Retrofibromatosis associated herpes virus (RFHV)**

**Simian varicella virus (SVV)**

**Cercopithecine herpesvirus 9**

- Medical Lake Macaque virus, Delta herpes Virus (Patas monkeys), Liverpool vervet monkey virus
- Alphaherpesvirus
- Homologous of human varicella-zoster virus (shingles)
- Like all herpes viruses - latent in ganglia
- Transmitted via the respiratory tract
- Cause herpetic rash, depression and respiratory difficulty
- Intracellular inclusion bodies present in various organs
- Appears when latently infected monkeys get stressed or immunosuppressed and have reoccurring infections
- When this occurs they become infectious to other monkeys

**Measles**

- **Genus Morbillivirus**
- **RNA paramyxovirus**
- Not naturally occurring in NHPs
- Infection result of contact with humans
- Infected primate can then infect man
- Fever, conjunctivitis, bronchitis and impetigo spots on the oral mucosa
- Skin rash
- Leukopenia
**Simian Betaretroviruses (SRV)**
- Formerly known as simian type D retroviruses
- Macaques: natural host, endemic in many populations
- Often infections are initially subclinical
- Can establish permanent infections in the host that may exhibit a broad spectrum of pathogenicity, from highly pathogenic to nonpathogenic
- Induce an immunosuppressive disease which can complicate studies involving HIV pathogens
  - 6 distinct genetically related serotypes affect macaques
  - SRV 1-5 and SRV/D-T described in 2005 in Japan in cynomolgous macaques
- SRV-1 more common in Rhesus
- SRV-2 more common in cynomolgous and pigtail macaques
- Transmission: Primarily direct contact between animals, virus-containing body fluids, particularly saliva, via biting or scratching, transplacentally
- Indirect sources of infection are also possible through contaminated instruments or equipment (fomites)
- Control – Test and removal

**Retrovirus**
- Simian Immunodeficiency Virus (SIV)
  - Lentivirus subgroup of retroviruses
  - Related to HIV-1 and HIV-2
  - Natural infections common in African species and don’t cause disease
  - Not seen in Asian or South American species
  - Causes AIDS like illness in susceptible macaques
  - Macaques are useful models for the study of HIV when infected with SIV

**Retroperitoneal Fibromatosis**
- Retroperitoneal fibromatosis (RF) occurs in macaques coinfected with SRV2 and Retrofibrmatosis herpes virus - RFHV
  - RFHV mnu in M. mulatta
  - RFHV mne in M. nemestrina
- In recent years, the number of recognized RF cases has decreased markedly, possibly due to more SPF colonies
- SRV-1 and SRV-2 associated with Subcutaneous Fibrosarcomas < 5%

**Simian T-leukemia virus type 1 (STLV-1)**
- Type C-retrovirus
- 90-95% homology to human T-leukemia virus (HTLV-1)
- HTLV-1 causes leukemia and lymphoma in people
- Affects CD-4 T cells in macaques, CD-8 T cells in African monkeys
- Effects of STLV-1 in macaques immune system not well defined
- **Causes T-cell lymphoma in baboons, primarily seen in the lung**

**Simian hemorrhagic fever virus (SHFV)**
- Acutely fatal disease of all Asian macaques, mortality approaches 100%
- Enveloped RNA virus- Arterivirus
- Patas monkeys (Erythrocebus patas) are natural hosts, to a lesser extent African green monkeys and baboons
- All outbreaks have occurred in primate holding facilities
- Does not cause disease in humans
- Is not listed as a select agent (AABB-2)
- SHFV may be a valuable tool for developing nonhuman primate models for human viral fever viruses
  - arena-, bunya-, flavi-, and filovirids
**Pneumonyssus simicola**
- Gaztrodiscoides hominis
- Strongyloides sp.
- Trichuris trichuris

**Bacterial Diseases**
- Moraxella (Branhamella) catarrhalis
  - Gram negative cocci
  - Causes mucohemorrhagic rhinitis - epistaxis, “bloody nose” syndrome macaques
  - Occurs in both immunocompetent and immunocompromised macaques
  - Usually mild and self-limiting, occurs primarily in winter and has been attributed to lower environmental humidity levels
  - Characterization of a Moraxella species that causes epistaxis in macaques
  Embers, Monica et al, Veterinary Microbiology, Vol 147, Jan 2011

**Scurvy - Hypovitaminosis C**
- Swelling of the epiphyses of long bones
- Cephaloematoma
- Vitamin C added to all NHP diets
- Non stabilized vitamin C shelf life 3 months
- Microencapsulated vitamin C – 180 d
  - L-ascorbyl-2-polyphosphate (stabilized vitamin C)
- Maintenance levels of vitamin C are 1-4 mg/kg daily
- Treatment doses are up to 25 mg/kg twice daily for 5 days in severe cases

**Acute necrotizing stomatitis (NOMA)**
- Gangrene of the gingiva, underlying bone, lips and cheeks
- In rhesus has been associated with concomitant infections with immunosuppressive betaretrovirus (SRV-1)
- SRV-1 causes a profound neutropenia
- In people NOMA associated with poor nutrition and hygiene
- Poly microbial opportunistic infection - Anaerobic and aerobic bacteria have been cultured from lesions
  - Bacteroides, Shigella flexneri serotype 4, Pseudomonas, Klebsiella, Fusobacterium, spirochetal organisms and recently MRSA

**Vitamin D3 deficiency**
- Both New World and Old world primates need Vitamin D3 supplementation living in environments without sufficient light
- Deficiencies
  - Metabolic bone disease
  - Long bone deformities
  - Multiple fractures
  - Increase serum ALP
- Treatment 2000 IU/kg D3
  - Halts progression of the disease
  - Bone deformities are irreversible
  - UVB and natural sunlight may be helpful in prevention of disease

**Bacteria and Parasites**
- **Bacteria**
  - Shigellosis the most common bacterial disease of captive NHPs
  - Rhesus most susceptible followed by cynomologus macaques
  - *Shigella flexneri* and *S. sonnei* most common

- **Parasites**
  - *Trichuris trichuris* - nematode - most common
  - *Strongyloides sp.* - nematode
  - *Gastrodiscoides hominis* - fluke, macaques and people
  - *Pneumonyssus simicola* – lung mite, pulmonary acarasis - most common rhesus
    - Ivermectin has virtually eliminated this disease from most colonies
  - *Balantidium coli* in colon, usually no clinical signs

**Non Infectious Diseases**
- **Trauma**
  - Out door housing – fighting
  - Indoor housing- Self Injurious Behavior (SIB)
- **Acute gastric dilatation**
- **Gastric foreign bodies**
- **Amyloidosis**
- **Endometriosis**
Amyloidosis

- Serum amyloid A protein (SAA)
- Termed secondary or reactive amyloidosis
- Small intestine most common site for amyloid deposits in rhesus and pig tail macaques
- Seen in all organs
- Sequela to chronic inflammation
- Has been associated with chronic catheters

References:


Questions?

Endometriosis

- Chocolate cysts (Endometrioma)

Intestinal Adenocarcinoma

- Most common life threatening malignant neoplasm in rhesus macaques, substantial cause of morbidity and mortality in the elderly

References:

- The Laboratory Primate, ed. Sonia Wolfe-Cooke 2005
- Spontaneous Intestinal Adenocarcinoma in Geriatric Macaques (Macaca sp.) Valverde, Celia et al.; Comp Med. 2001 Oct;51(5):546-8