A few things about monkeys

Primates: Terms & Definitions

Nonhuman primate or primate

Nonhuman primate means any nonhuman member of the highest order of mammals including prosimians, monkeys, and apes. Example species of prosimians are Lemurs, Bushbabies, etc. Example species of monkeys are the Marmosets and Tamarines, Squirrel monkeys, Macaques, Baboons, Mangabeys, etc. Species of apes include Gibbons, Chimpanzees, Orangutan, and Gorillas. In our laboratory we use exclusively macaque monkeys, usually the species Macaca mulatta (also referred to as Rhesus macaque or Rhesus monkey), but on rare occasion we may use a Macaca nemestrina or Macaca fascicularis. The genus Macaca belongs to the Old World also called catarrhine (downward-nosed) monkeys, and consists of heavily built often terrestrial monkeys that have a dull brownish coat, naked skin on face and rump, and tails up to slightly longer than body length or totally absent. The other large subdivision of monkeys is that of the New World or platyrrhine (broad-nosed) monkeys that includes marmosets and Tamarines, and other small-sized fruit-eaters. The Rhesus monkey is terrestrial and arboreal. It has a head-body length of 45 to 62 cm, tail of 17 to 30 cm, and a weight of 4 to 17 kg. Its diet is insects, young leaves, crops, small animals, and occasionally fruits. In this manuscript the word monkey will be exclusively used to indicate the Rhesus monkey, unless otherwise stated.

Handling

Handling means petting, feeding and watering, cleaning, manipulating, loading, crating, shifting, transferring, immobilizing, restraining, treating, training, working and moving, or any similar activity with respect to any animal.

Bonding

Bonding refers to the formation of social attachments, which when temporarily or permanently disrupted; result in a psychologically distressing syndrome known as separation anxiety.

Positive Reinforcement

The receipt of a pleasant stimulus by an animal after a specified response is made, thereby increasing the probability that the same response will be made again.

Negative Reinforcement

Negative reinforcement occurs when an unpleasant stimulus is stopped when an animal makes a specified response, thereby increasing the probability that the response will be made again.

Social Housing

Social housing refers to a living environment in which two or more animals are maintained together. Social housing necessitates compatibility and may or may not result in bonding. Our monkeys are in social housing.

Social Signal
A visual, tactile, or auditory cue made by one animal in a social situation and interpreted by another animal or the same animal.

Painful Procedure
Painful procedure means any procedure that would be reasonably expected to cause more than slight or momentary pain or distress in a human being to which that procedure was applied, that is, pain in excess of that caused by injections or other minor procedures. For example, cleaning and maintaining recording chambers is not a painful procedure. Stripping the usual outgrowth built on the top of dura matter, on the other hand, is a painful procedure, and it must to be performed only under local anesthesia.

Euthanasia
Euthanasia means the humane destruction of an animal accomplished by a method that produces rapid unconsciousness and subsequent death without evidence of any pain or distress.

Monkey Behaviour and Monkey/Trainer Interaction
The cooperation of the monkeys during experiments is central to the success of the research carried out in this laboratory. The degree to which an animal is willing to cooperate is dependent on a number of factors, many of which are or can be effectively controlled by the trainer, provided that the training techniques employed result in the establishment of the right kind of relationship between monkey and trainer. At the core of a safe and productive training strategy is a respect for the animal being worked with, an awareness of the risks involved, and a basic understanding of the animals' natural, normal behavior.

Basic Rules
Working with monkeys is always associated with certain amount of risk. These risks cannot be completely eliminated, but we can try to minimize them by following certain rules:

1. Only those persons may work with the monkeys who possess at least a basic knowledge of their behavior and can apply this knowledge in their work.
2. The human must **always** be at the top of the dominance hierarchy in a troop of monkeys. If he or she is not, he or she may no longer enter the monkey holding rooms.
3. The monkeys must never be intentionally provoked.

Behavior
Macaques live in a strict social hierarchy. The social standing of an animal is attained and kept in constant, more-or-less ritualized confrontations with the other members of the troop. Since monkey regard humans as conspecifics (i.e. members of the same species), any human handling monkeys has no choice but to participate in these struggles for social rank and see that they are carried out without injury.

This is not as difficult as it may sound. By nature, monkeys are extremely peaceable, even if their appearance may speak otherwise. In addition, humans have the advantage of being bigger. No

“normal” monkey would voluntarily attack such a large, powerful opponent. Such spontaneous attacks are very rare and are only initiated by behaviorally disturbed animals. In my 12 years of working as an animal caretaker I have only experienced one such case. What does happen quite often, however, is that unintentionally a human severely provokes an animal, which misinterprets what it sees to be a strong threat and the overture to an attack. A monkey will almost always try to reach his goals without an actual physical confrontation. All the same, any interaction with monkeys must be carried out with extreme caution. For the most part, rhesus monkeys communicate within a group via optical signals, and they expect the same body language from the humans around them. Monkeys who have been cared for by humans for many years have often learned to ignore the most common body-“speech” defects of their caretakers, but of course we cannot depend on them to do so. Almost all apparent or real attacks by monkeys on humans were caused by such misunderstandings. Here is a short list of actions which should be avoided under all circumstances:

Staring at the monkey or looking directly into the monkey’s eyes
This is interpreted as a mild threat, but can sometimes be used as a minor rebuff. The severity of the threat depends on the length of the stare. A “normal” monkey usually reacts at first with various degrees of appeasement behavior (sinking the eyes, turning the head away, turning the body away, and presenting the buttocks, flight). Up to this point the caretaker has reinforced his dominant position in the hierarchy. The monkey subordinates itself. If the caretaker continues to stare, however, the monkey's fear will turn into confusion and finally into anger. Once this happens it is extremely difficult to extract oneself out of the situation without a loss of social face and without a physical confrontation.

Baring the teeth
It includes laughing, coughing, sneezing, or yawning - even with the hand in front of the mouth. This is interpreted as a major threat. Depending on the monkey's self-confidence and the social rank of the human the monkey will react with submission and fear or with anger and strong counter threats. If sneezing or coughing cannot be avoided inside the cage, the human visitor should turn his or her back to the animals. This is tolerated by the monkeys as long as it is not too loud (see next point).

Making noise (for example by dropping tools)
This causes different reactions in different monkeys. Some interpret it as a major threat and will react accordingly. In rare cases the monkey will suddenly panic. This can be extremely dangerous, because it is impossible to calm the monkey and because the animal also loses its usual inhibitions to attack and bite. This panic can be contagious and can quickly affect the other monkeys in the troop. In this case retreat (slow and cautious!) is the only way to save oneself. It is also the only case in which flight does not lead to a loss of social standing.

In order to recognize the mood of a monkey at a particular moment, it is necessary to learn to interpret its gestures. We must not make the mistake of letting our own feelings guide us and intuitively deciding what the monkey is trying to “say.” Unfortunately, the gestures and facial expressions of monkeys are so similar to those of humans that we automatically decode and interpret them subconsciously. This is exactly what we do with human contacts. Eighty percent of the time our subconscious interpretations of the monkeys’ signals are correct. Unfortunately, in the remaining 20% of our interactions with monkeys we completely misinterpret their gestures and, as a result, react inappropriately.

A well-known example of such a misinterpreted gesture is the smile of greeting. When two human meet they automatically glance in each others' eyes and smile for a moment. This all happens on a completely subconscious level and is usually not even noticed by either of the parties. The message that is exchanged is, "Hello, I see you and I mean you well." If these signals are not sent by one of the two, the other will react with suspicion. When a human meets a monkey, his automatic impulse is to display this smile of greeting. If he does so, he has already made his first mistake. For macaques there is no "smile of greeting", only a smile of threat. The correct way to greet a rhesus monkey is to briefly lower the eyes (but without raising the eyebrows!) or, if we wish to be very polite, to close the eyes and briefly incline the head. This example shows us how easy it is to make mistakes. In any interaction with the monkeys it is essential that we observe them closely at all times and make a constant, conscious effort to understand their signals. This is the only way to gain the practice necessary to learn to recognize and correctly interpret the monkeys' gestures. Through the correct interpretation of the monkeys' behavior and a keen awareness of one's own behavior with respect to the monkeys, one can develop more quickly the proper rapport with the animals while at the same time achieving one's training goals in a safe and efficient manner.

Factors Promoting the Well-being of Laboratory Monkeys

Research facilities must develop, document and follow an appropriate plan for environment enhancement adequate to promote the psychological well-being of nonhuman primates. Applied ethologists and stress physiologists recognize that a variety of indicators are necessary to assess an animal's psychological well-being. Indicators such as glucocorticoid-levels, responses to preference tests and motivational challenges, immunosuppression, genetic expression, social behavior, and self-directed behaviors such as self-mutilation have opened a window into understanding the needs of the animals in their own language. Observations by field ethologists and laboratory biologists have paved the way for a better understanding of the ultimate and proximate causation of behaviors seen in captivity. While some order-specific generalizations can be made, available research indicates that psychological well-being is also species-specific and varies between individuals based upon experience and genetics. To meet the mandate that psychological needs be addressed, there has been a proliferation of facility designs, enrichment devices, and programs for captive nonhuman primates. What follows reflects the environmental enrichment strategies proposed by the *United States Department of Agriculture* (National Agricultural Library), the *National Institutes of Health* (National Library of Medicine), and the Primate Information Center of the University of Washington, in their document called *Environmental Enrichment Information Resources for Nonhuman Primates: 1987-1992.* The complete document of the 1993-Meeting, together with all the bibliography on environmental enrichment can be obtained from NIH or the Internet. The bibliography is extensive, and thus it is not included in this practical manual. Our environmental enrichment strategies at the Max-Planck Institute for Biological Cybernetics in Tuebingen are in agreement with the description below.

Social Enrichment

Contact Social Experience

It is agreed by most behavioral investigators that a conspecific cage-mate can be a dynamic and enriching stimulus to the environment. It is therefore recommended that social housing be considered one appropriate means of providing enrichment. Both pair and group housing conditions

are categorized as social housing. It is recognized that group housing may limit access to the subject animals in many protocols, therefore, it is recommended that pair housing be considered for those studies requiring frequent investigator/subject contact. This social housing may be full-time or part-time, again as the protocol permits. It should be noted that the formation of social units of animals should be done with care. Part-time pair housing may be applicable for protocols requiring food or water restriction or for studies which require routine removal of the animal from the home cage. The determination of the animal composition of the social housing unit should be flexible as recent data indicate that successful social housing can be accomplished with mixed or like ages (e.g., mother/infant dyads, peer groups, mixed age/unrelated groups or extended family units), and with mixed or same sex. As maternal and peer separation studies have clearly shown detrimental effects on nonhuman primate species-typical behaviors and reproductive capacity, it is recommended, unless the approved protocol requires otherwise, that infant nonhuman primates should be housed with the mother and/or with peers until a species- appropriate weaning time is reached.

Partial social contact may also occur outside of the home cage in a designated exercise area through which the animals are rotated. This exercise area may encompass an entire room in the animal facility or be a large pen in a separate room or in the middle of an occupied animal room (thereby providing social stimulation to the animals remaining in their home cages). In the case of exercise pens, the exercise area would be equipped with devices and "toys" to increase the activity and interest levels of the occupant(s). If a room is dedicated to this purpose, multiple pens could be placed in the room, thus increasing the frequency of rotation through the exercise area. As preliminary evidence indicates that different aged animals of some species (e.g., rhesus monkeys) have significantly different preferences for various types of enrichment (e.g., swinging apparatus for juveniles versus floor toys for adults), a multitude of strategies should be present in each pen, or different pens should be designed for various age groups. Special consideration should be given to the introduction of nonfamiliar animals in the exercise area, and provision should be made for only familiar pairs or groups of animals to be in the exercise area at the same time. Also, training of the animals to a transport cage may facilitate both introduction to and removal of the animals from the exercise area. Training programs have even been proposed for reducing stress levels in laboratory nonhuman primates. Provision for the increased time and personnel needed for these methods of social contact must be made.

The time allotted to animals for socialization and/or exercise may occur between studies of the same protocol, or between protocols for the same investigator, or while animals are awaiting assignment to a different investigator. Rehabilitation through exposure to other animals can result in various degrees of social recovery. Pairs of animals designated for socialization/exercise could be identified and then introduced to each other in a neutral environment. Again, it must be emphasized that caution must be exercised when introducing unfamiliar animals. Incidents of aggression can occur even between familiar animals, resulting in varying degrees of harm to the monkeys involved. The dyad could be composed of two naive animals or composed of one socially experienced animal and one naive animal. Alternatively, a group of naive animals could be formed and introduced to the neutral environment.

A serious consideration in social housing of nonhuman primates is the induction of separation anxiety. This phenomenon results when animals which have bonded together (mother/infant or peer/peer) are physically removed from each other. Typically the social bonding between two animals has occurred early in life. A considerable amount of variability in the impact of separation on

the behavior of the animals involved has been reported, but the number of cases of disturbance resulting from separation (mother/infant, peer/peer) are outnumbered by cases where little disturbance has been observed. The incidence of separation anxiety in animals that were paired as adults will in all likelihood be less. Thus, if social units of nonhuman primates are to be formed, due consideration by the individuals forming the pairs must be made to the species, age and rearing history of the animals.

Another factor which must be closely monitored is the increase in health risks for animals in social units. Clearly, the possibility of a greater incidence of disease transmission and traumatic wounds must be taken into account when considering socially housing animals which are part of a research project. A level of acceptable risk should be established by both the investigator and the attending veterinarian.

Non-Contact Social Experience

Other appropriate means of enriching the environment may occur in a social, but non-contact context. A viable solution to the problem of allowing social interaction between animals in a room whose physical configuration prohibits direct visualization of cage neighbors, is the provision of mirrors along an otherwise empty wall. This would allow the animals to visually communicate with each other via reflections. It has also been shown that many species of nonhuman primates will use social signals when viewing their own reflections in mirrors. This has been demonstrated in stumptail macaques, patas monkeys, Japanese macaques, rhesus monkeys [Gallup, G. G., L. B. Wallnau & S. D. Suarez. 1980. Failure to find self-recognition in mother-infant and infant-infant rhesus monkey pairs. Folia Primatol. 33:210-219.], cynomolgus monkeys, and squirrel monkeys.

The importance of olfactory and visual signals for communication purposes in nonhuman primates has been clearly outlined for the various species. Single housed monkeys do experience a limited degree of social interaction with other animals in the room by auditory, olfactory and visual communication.

Social stimulation of several species of nonhuman primates can also be accomplished by means of non-threatening, non- contact methodologies. An increase in grooming behavior by the provision of an artificial fleece attached to the home cage has been examined at the NIH.

Visual contact between what are generally considered "social" species (i.e., living in formal troops or more loosely structured groups) can often ease the stress from what would otherwise be an isolated environment if special attention is paid to the animal arrangement. It is probable that the maximum benefit from this arrangement comes from housing like species across from each other. The provision of visual contact between these animals can be accomplished by requiring that the animals in a room be housed across from each other as much as is possible (clearly an odd number of animals will result in one animal relying on diagonal social viewing). For rooms with a square rather than rectangular design, the physical arrangement of the cages can be planned to maximize visual contact between the animals.

Visual contact between animals can also be increased by providing the home cages with a mutual wall of translucent materials (for example, impact-resistant plastics such as polycarbonates). This would prevent injuries resulting from loosely woven metal cages and increase neighbor-viewing over the current cages with one solid wall. For those buildings with rooms too narrow to have cages along both walls, windows in the walls between such rooms (also constructed of impact resistant plastics)

could be provided. As many species of nonhuman primates seem to be very curious about activities in the corridors outside their rooms, windows in the doors to the rooms provide a strong focal point for interest. The cages closest to the door, then, should not remain empty.

Much auditory communication occurs between the animals in a room. Communication between rooms might provide further stimulation for these animals (similar to one troop communicating with another). In some facilities, this may be accomplished by having a mesh component to the wall at the ceiling level. Other electronic solutions are conceivable as well. However, there is little available data in this area, and the effects of auditory communication on behavior need to be tested.

Non-Social Enrichment

The room

The shape of the room is considered an important element of an enrichment program as a shape which confers more visibility between animals is desirable. By designing a creative shape to a room or with the placement of additional walls, animals may be able to increase or decrease their visual contact with each other by their choice.

Additional features of the room which could enhance the environment of the animals include a capacity for sound to be available at times (e.g. music or naturalistic sounds) throughout the day. Research in this area is still underway but preliminary data indicate a reduction in aberrant behaviors. Some zoos provide an opportunity for television viewing to their great apes. They report variable success. This strategy is also currently under investigation, and differences in animal responsiveness between commercial television viewing and viewing of animal documentaries is being determined.

It is possible that the form of lighting in the room is important to the psychological well-being of the nonhuman primates housed there. Currently, standard fluorescent lighting is used in most rooms. There is preliminary evidence in both the nonhuman primate and human literature that broad spectrum lighting can have a positive effect on behavior. Some components of the behavioral repertoire of group housed animals have been modified by the use of this form of light. Its effect on singly housed animals, however, is only now being investigated and needs further examination. Broad spectrum bulbs are commercially available and are one means of providing "natural" lighting. Of course, windows and skylights are also potentially viable options.

The physical location of the room may prove to be a critical element of an enrichment program. Its proximity to the people working in the building may encourage authorized personnel to "visit" the room, thereby providing the animals with increased human interaction. The proximity of one animal room to other animal rooms may also have an impact on the well-being of its inhabitants (see non-contact social enrichment).

The cage

At the present time there are many guidelines concerning the cage environment, and only preliminary evidence concerning the impact of cage size on the incidence of aberrant behaviors in the nonhuman primate. Recommendations on cage size and capability for sanitation are clearly outlined in the Guide. Debate still continues concerning the minimum cage size which will allow for psychological well-being. Until this issue is resolved, Guide recommendations should be considered minimum suggestions. The design of the cage can be greatly altered by utilization of a variety of cage

materials (plastics versus metal) and shapes (using the modular concept). Plastic materials for cage construction offer some benefits: 1) less noise is produced by daily activities surrounding the maintenance of the cage; 2) an opaque or translucent environment can be created without compromising the safety of the animals or the people working with the animals; 3) plastics are warmer for the animal; and 4) sanitation principles would not be compromised. However, plastic materials have notable disadvantages as well. They scratch more easily than metal cages, they reduce air movement within the cage and the accumulation of waste material on the cage walls becomes more obvious (thereby reducing the visibility of the animals).

The potential for having a variety of sizes and shapes of cages as a result of a modular concept available for different species and ages of nonhuman primates is desirable. The provision of an escape place for each animal is more likely to occur with a modular design than a fixed design. A modular design is also flexible for partial or full-time pair housing of animals as well.

Enrichment of the home cage environment is most commonly being attempted with a variety of devices or manipulanda. The presence of manipulanda has been shown to have a positive effect on a variety of nonhuman primate species including stumptail macaques and rhesus monkeys. These devices address two main categories of behavior: 1) foraging; and 2) play or manifestation of interest.

Currently foraging behavior is being increased by the use of food puzzles, raisin boards and several substrates in which food items can be hidden (e.g. artificial fleece, wood wool, hay, astro-turf). However, it should be noted that it has long been recognized that monkeys will operate devices without a food reward.

The induction of play behaviors or the increase in behavioral interest (i.e. exploratory behavior) can be accomplished by many means. The provision of cage furniture from which to swing, such as ropes, hoses, chains with crates or tires or PVC piping will result in a decrease in behavioral problems. Perches made out of cage material or wood are routinely used by nonhuman primates. Other objects such as stuffed animals and blankets are very appropriate for young nonhuman primates. It is recommended that for those species of nonhuman primates in which the females routinely form a nest for sleeping or reproductive purposes be provided with a substrate (e.g. towels) with which to do this. A variety of "toys"-- both responsive and nonresponsive-- have been shown to be used routinely by several species of nonhuman primates.

Food

Nonhuman primates which forage for food located in dispersed patches rest less, exhibit more competition over a food source and spend more of their active period engaged in searching and feeding behaviors. Thus, feeding time in the laboratory represents one of the most important events in the day for the captive primate. Therefore, it is probable that environmental enrichment via food presentation is likely to be successful. This strategy is currently being investigated at several facilities. Foraging boards, flexible PVC tubing filled with food treats and Kong toys filled with frozen juice are methods which have been used with success. Nutritionally balanced food treats should be used for enrichment purposes. Considering the potential importance of foraging as an enrichment technique, further research needs to be done in this area.

Three components to the food delivery process that can be altered for enhancement of psychological well-being include: 1) a varied diet, including treats; 2) an increase in the frequency of

food delivery (either by mechanical devices or foraging opportunities); and 3) a systematic analysis of who is the best person to feed the animals (Is the animal care technician who cleans the room and disturbs the animals the same individual who should be feeding?).

Exercise

Exercise activities do not have to be a social event. Many nonhuman primates will use swings and other play objects without a social partner to stimulate interest. Thus, for some animals individual exercise periods to enhance psychological well-being should be considered. The use of spherical cages, which the animals can roll from inside the cage, in an occupied room is being explored for purposes of exercise and social enrichment of both the animal in the cage and animals watching from their home cages.

Environmental Enrichment in the Primate Facilities of MPI

- Pair housing in rooms of 7.67 square meters (width=2.09, depth=3.6, height=2.3).
- Social housing in a room of 14.89 square meters (width=3.17, depth=3.6, height=2.3).
- Exercise swings attached on the ceiling of the room.
- Tree-like structures for climbing, sitting, and exercising.
- Shelves (150cm X 30cm, 2 per room) at different heights for sitting.
- Small visual barriers to allow privacy.
- Isolation-cage for the first a couple of weeks of the animal's training (width=1.5, depth=1.5, height=2.3).
- Perches in the cage.
- Manipulanda in the room and in the cage.
- Puzzle feeders on the cage.
- Computerized, touch-screen based setup for training the animals while in the cage.
- Nonbreakable mirrors.
- Glass window for monkey and care-person communication.
- Daylight through a ceiling window.
- Music and natural sounds for the entire duration of the day.
- Rigorous environment control:
    - Monkey Holding Room Temperature 25 +/-2 C (Zurich 20-25 C).
    - Monkey Holding Room Humidity 40-70% (Zurich 55%).
    - Monkey Holding Room Air Circulation 15 times/hour.
    - Water Pressure 3.4 psig (about 200 mbar or 150 mmHg).
    - Augmented Chair Dimensions (width=53, depth=47.5, height=63.0).

Behaviors Considered to be Abnormal

The well-being of the monkeys among other things greatly depends on observing systematically the animal's behavior and understanding some signs that may indicate distress or illness. Erwin and Deni (1979) [Erwin, J. & R. Deni. 1979. Strangers in a strange land. In: J. Erwin, T. Maple, and G. Mitchell (eds.) Captivity and Behavior. Van Nostrand Reinhold: New York. Pp. 1-28] listed the following behaviors that require attentive, close care of monkeys.

Qualitatively Abnormal Behaviors

Bizarre Postures

Include: Floating Limb, Self-Biting, Self-Clasping & Self-Grasping, Saluting

Stereotyped Motor Acts
Include: Stereotyped Pacing, Head Weaving or Tossing, Bouncing in Place, Somersaulting, Rocking

Appetitive Disorders
Include: Coprophagia and Urine Drinking

Sexual Disorders
Autoerotic Stimulation

Quantitatively Abnormal Behaviors

Appetitive Disorders
Include: Hyperphagia, Hypophagia, and Polydipsia

Agonistic Disorders
Include: Hyperaggression

Diseases and Zooneses

A number of diseases may be transmitted from humans to monkeys or vice versa. Here a brief description will be given of those diseases/Zoonoses that are extremely dangerous for either monkeys or humans or both. A detailed description of the viral infections typically observed in laboratory monkey; see the monograph by Trenton R. Schoeb of the Department of Comparative Medicine of University of Alabama at Birmingham. For a detailed description of other diseases, such as diarrhea and dysentery caused by bacteria, diseases caused by intestinal protozoa, cardiovascular diseases, and diseases of the central nervous system consult the book *Diseases of Laboratory Primates* by Theodore C. Ruch, (W.B Saunders Company, London, 1959).

Herpesvirus Simiae

Historical: In 1932, a physician, who had been bitten by a clinically normal rhesus monkey three days prior to onset of disease, died from encephalomyelitis. Specimens from this case were studied separately by two virology laboratories. The first lab reported the isolation of a Herpesvirus from brain and cord specimens that were lethal to rabbits by intradermal or intracranial injection. Transmission attempts to rhesus monkeys failed. Yet, two cebus monkeys inoculated intracranially died 7 and 17 days postinoculation from a neurological disease, but virus could not be reisolated from their brains. The other laboratory reported the isolation of a filterable agent from the brain, medulla, spinal cord, and spleen, but not from lymph node specimens. The agent was lethal to rabbits by intradermal or intracranial routes, but inoculation of mice, guinea pigs, dogs, and rhesus monkeys did not result in disease. The agent was named ***B Virus***. The term is used today combined with the binomial term ***Herpesvirus Simiae***. Other terms such as *herpes B virus*, *monkey B virus*, etc. also appear in the literature with limited usage.

Between 1932 and 1973, a total of 24 human infections with B virus occurred. Of these, 23 resulted in encephalitis, and 18 cases were fatal. Since the original reports the virus has been isolated from tissues or tissue cultures of several species of macaque monkeys. Serological studies using serum neutralization techniques have demonstrated activity in sera from several species of simians and from man. We now know that B virus presents a serious hazard to people who are exposed to

nonhuman primates and a problem to colony managers and laboratory primate facilities directors who are responsible for the safety of animal care personnel. It is certainly very fortunate that new handling techniques and facility management have strongly reduced the hazard, as indicated by the rare occurrence of incidences in the last 20 years. Yet, B Virus must taken extremely seriously, because it still remains one of the most threatening hazards for people interacting with laboratory primates. Recently, for example, the B-virus claimed the life of a veterinarian at the Hazleton Research Products Texas Primate Center in Alice, Texas. The center has approximately 5500 macaques housed primarily in breeding harems within wire corn-crib enclosures. The veterinarian had relatively little direct contact with unanesthetized animals, and the nature of his exposure is not clear. No bites had been reported and no skin lesions suggestive of a bite or scratch were found. A brief summary of the clinical symptoms of this case is presented here to remind all MPI employees that B-virus must be included in the differential diagnosis early in the process of clinical examination in cases of exposure to simian fluids.

In the case of the deceased veterinarian, although B virus is a neurotropic virus, signs of neurologic deficit did not appear until 5 days after the first reported signs of illness. Aching, persistent fever (102-104 degrees), nausea and other flu-like symptoms were the primary signs during the first 4 days of illness. Double vision and difficulty in swallowing were among the early neurologic signs but were not reported until Day 5.

It is particularly unfortunate that the patient decided to seek treatment from his family physician, instead of notifying the physician designated by the primate center, who normally attends to bite wounds of employees and is familiarized with the symptoms of B-virus. The initial differential diagnosis by his family physician included Rocky Mountain spotted fever and typhus. Within 2 days after the first neurologic signs, he had lapsed into a coma, and was placed on life support systems. He died of his illness shortly after life support was withdrawn. The lesson to be learned from this recent case is that in case of B Virus infection:

1. the history need not include evidence of a recent bite or scratch

2. persistent flu-like symptoms in persons at risk, irrespective of their level of exposure to primates, should not be disregarded, and the designated physician should be immediately consulted.

The best strategy for minimizing or even entirely eliminating the possibility of infection is education, excellent technique, and knowledge of the action steps that must be taken if an accident occurs.

Agent: B virus is an alpha-herpesvirus, which is enzootic in rhesus (*Macaca mulatta*), cynomolgus (*Macaca fascicularis*), and other Asiatic monkeys of the genus *Macaca*. It is morphologically, biologically, antigenically similar to HSV-1, HSV-2, and SA-8.

Epizootiology: Macaques (especially rhesus) are natural hosts. Other species are experimentally susceptible. Transmission among monkeys by contact, by fomes such as clothing, towels, or utensils, by aerosol; to man by bites, infected cells or tissues, aerosol. Transmission to humans occurs in connections with exposure to contaminated saliva or other body fluids through bites or scratches from an infected animal, through a handler's existing scratch or sore, or through mucous membranes such as those in the eye. Transmission may occur even through aerosol. Probably monkeys are infected for life and a high proportion, if not 100%, of adult individuals in infected colonies harbor virus.

Clinical: In monkeys, lingual and labial vesicles which rupture leaving ulcers that heal in 1-2 weeks; conjunctival and cutaneous lesions in a few cases. Infection probably also occurs without lesions in many cases. In man, local erythema and vesiculation at site of inoculation, localized neurologic symptoms, fever, regional lymphadenopathy, muscular aches, CNS signs (mostly paralytic), die in coma of respiratory failure within a few days to a few weeks. Twenty of the 22 human patients developed encephalitis. Fifteen of these died. Two of the Pensacola patients had mild disease; they were treated with acyclovir but its efficacy for treating human infections has not been established. The frequency of mild or symptomatic human infections is not known.

Early generalized symptoms of the human illness were described in 16 cases. These were variable in nature, but always included fever, and in most cases, flu-like aches and pains, especially muscular pain, fatigue, and head-ache. One patient had a persistent sore throat and was described as having vesicular lesions on the throat mucosa. In one case, vesicular lesions developed on the skin of the arm and chest, ipsilateral to the wound. Other symptoms included lymphadenitis and lymphangitis, vomiting or nausea, abdominal pain, and hiccoughs. With some overlap, these symptoms, including in all cases, hyperesthesias, ataxia, diplopia, agitation, and ascending, flaccid paralysis. Less common were urinary retention, convulsions, and mental confusion. Spinal taps were reported in five cases, four of which revealed increased pressure. In all cases cerebrospinal fluid contained increased number of leukocytes, which were predominantly lymphocytes, elevated protein, and glucose.

Therapeutic attempts in addition to supportive care were detailed in seven cases. Doses ranging from 20-100 ml of human gamma globulin were given intramuscularly or intravenously to three patients. Of these three, two survived; both survivors also received corticosteroids. Antiviral agents were used in only one case. No conclusions are possible concerning benefits from therapy, based on the variation in dosage, timing, and spectrum of therapeutic measures. Human gamma globulin should be beneficial, since it is known to contain neutralizing activity against B virus.

Histologically demonstrable lesions in man were found predominantly in the central nervous system, including encephalomyelitis-like lesions that were more common and severe in the region of the medulla, pons and spinal cord. They appeared as meningeal infiltrates, perivascular cuffing, focal edema, and demyelinization. Neuronophagia with neuronal satellitosis, hemorrhage, and necrosis within the mesencephalon with acidophilic intranuclear inclusion bodies were described in one case.

Pathology: Microscopic lesions in man and monkeys are similar. “Ballooning” degeneration, multinucleation, and necrosis of epithelial and other affected cells and characteristic nuclear inclusions. In man, multifocal necrotizing encephalomyelitis and multifocal necrosis in spleen, liver, lymph nodes, and adrenals. A similar disseminated disease occurs rarely in rhesus and occasionally in cynomolgus monkeys.

Diagnosis: Signs, lesions, virus isolation, rabbit inoculation. Serologic tests including ELISA and serum neutralization also can be used; however, results of the usual tests can be complicated by antibodies to human herpes simplex virus and to SA-8 virus. (Competition ELISA can be used to distinguish, if necessary.) Furthermore, it is not certain that infected monkeys always have diagnostic titers.

Control: It is recommended that the monkeys used in laboratories are free of the virus and housed so as to prevent infection. Macaques should be handled only with adequate physical or chemical restraint, and handlers should wear protective clothing, gloves, and masks. Routine screening is recommended because the reliability of negative results has not been ascertained and because

handling the monkeys increases the risk of human exposure. Monkeys with oral lesions suggestive of active infection should be quarantined. Handlers and investigators should be educated concerning the risks of exposure to B virus and the need for proper protective measures, immediate reporting and treatment of injuries received while handling monkeys, and obtaining immediate medical attention for any condition suggestive of B virus infection.

Tuberculosis (TB)

Agent: Tubercle bacillus.

Epizootiology and Epidemiology: The Tubercle bacillus can be found in man, nonhuman primates, and a large number of other lower animals. In Western laboratory colonies the tuberculosis rate seems to range upward from 10 or 15 per cent, the lower limit depending partly upon the pre-admission screening practice. Although infection rates are now generally lower, on occasion they can reach high proportions and bring research to a standstill, and this despite tuberculin testing and good diets and sanitation. All seem agreed that tuberculosis is rare in wild monkeys not living near humans. The tuberculosis of the monkey is caused by human, bovine, and rarely, avian tubercle bacilli. Tuberculosis can spread also from monkey to monkey, as was described within a year after Koch's identification of the tubercle bacillus. Tuberculosis can be transmitted to monkeys by inhalation, ingestion, and direct contact (through instruments, cages etc.). The potential for transmission of TB (and also other pathogens) among nonhuman primates and humans underscores the importance of improved surveillance and testing procedures in quarantine (for our monkeys quarantine services will be provided by the primate center in Goettingen), and research facility settings, such as our primate facility at MPI.

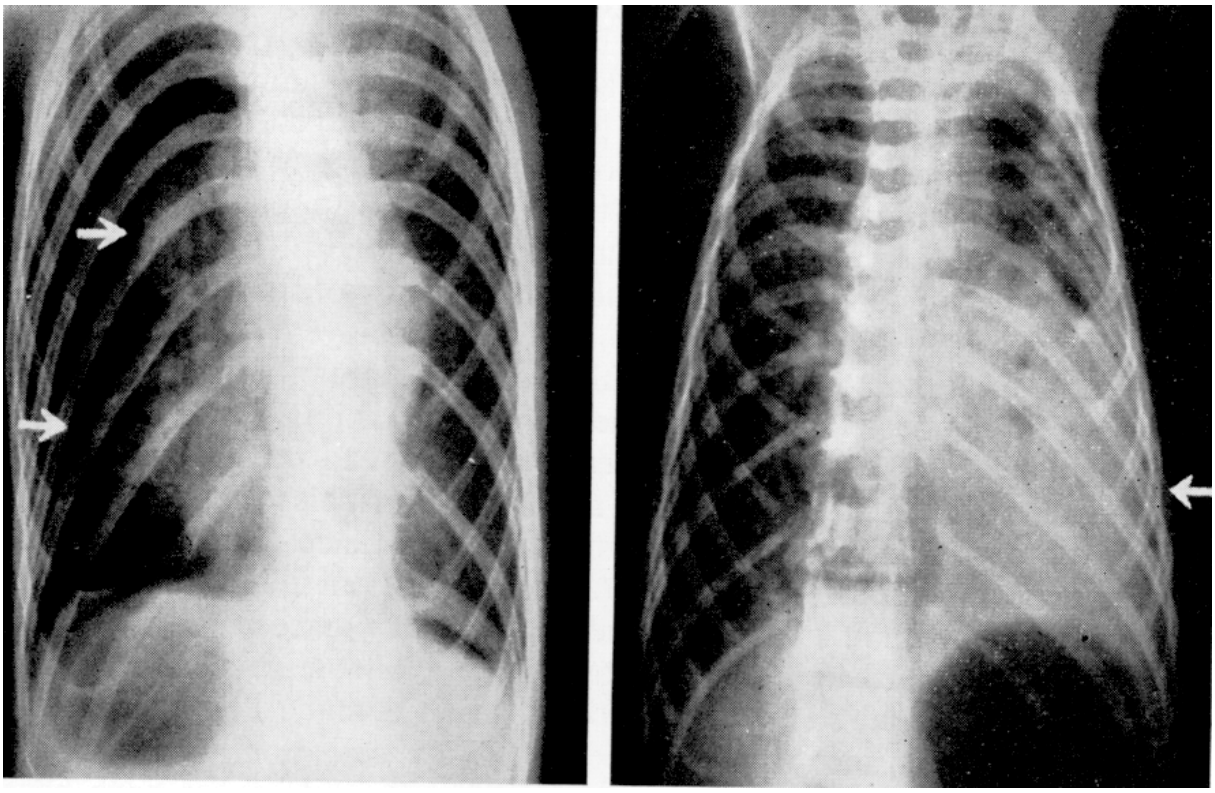
Pathologic Evidence: Usually the disease is so generalized that the primary lesion cannot be distinguished, but the distribution of the tuberculous lesions occasionally is such that an apparent route of invasion can be discerned. The bacilli enter the body either by way of the alimentary tract producing ulcers in the intestines, enlargement and caseation of the abdominal lymph nodes, or through the airway, in which case the lesions are intrathoracic and the bronchial nodes are greatly enlarged and caseous.

Diagnosis: Unfortunately the signs of simian tuberculosis are not striking until the disease is far advanced. In fact, the disease may be quite insidious and unnoticed. A monkey with tuberculosis obeys the general rule that ' a monkey is sicker than he looks'. Fortunately, however, disasters can be avoided by routinely testing for TB. The efficiency of the tuberculin test makes a diagnosis based on symptoms not all that important. Despite of the TB testing animal care people should give particular attention to the behavior of the animals, in especially to possible psychological alterations, that appear very early in the case of tuberculosis. Be alarmed if an animal becomes less playful or less aggressive, moves less and more slowly, and takes less interest in the environment. Monkeys with pulmonary tuberculosis will often cough, but so do monkey without tuberculosis; so attention must be given not to interpret signs. The hair of the tuberculous animal may become dull, roughened, or disheveled, and in some cases may fall out. Loss of appetite and, occasionally diarrhea may also be seen. Skin ulceration or suppurating lymph nodes should be looked for, and enlargement of the liver or spleen can sometimes be detected.

TB Testing: Animals in our facility will be routinely tested for TB. Each animal will be anesthetized and TB tested by intradermal injection of 0.1cc Old Mammalian Tuberculin in each of two sites: **eyelid** and **chest**. Test sites will be observed, evaluated and recorded in the animal's health record

for three consecutive days following the test. If a reaction to the test is observed (redness/swelling) the animal will be radiographed.

Figure III-15 shows an example of the radiographic appearance of macaques infected by tuberculosis. If other symptoms of tuberculosis are observed (coughing, weight loss, etc.) the Veterinarian may request a chest radiograph. While under anesthesia the animal is given a complete physical examination and teeth cleaning. Blood is drawn for baseline values. Any health problems encountered will be evaluated and treated accordingly. After four consecutive negative TB tests, administered two weeks apart, the animals may be released for experiments.



Left, radiopaque abscesses are present in the inferior (lower arrow) and superior (upper arrow) lobes of the right lung. Right, radiopaque tuberculous lesions in the lower left lung. (From Dolowy et al. Amer. J. vet. Res., 1958, 19, 225.)

Control: Current programs for management of tuberculosis in a nonhuman primate colony generally include detection of infected animals by the tuberculin testing described above, and by radiographic examination. Animals that are infected are usually euthanitized, while those that may have been in contact are monitored very intensely. Such programs are only moderately effective because of the fallibility of the tuberculin test and of the extended length of time for which the exposed animals must be observed until they either develop diagnosable levels of diseases or are proven free of infection. Moreover, during the relatively long quarantine period of contact animals, exposure of personnel and other animals in the facility is a potential problem.

Alternate approaches to management of tuberculosis have been explored through chemotherapy. For example, the course of tuberculosis in macaques could be modified by treatment with either isoniazid or streptomycin. Monkeys treated with these drugs show rapid clinical and radiographic resolution of disease. Yet, with these methods the disease is only arrested or attenuated and not cured. Recently, the tuberculosis caused by Mycobacterium bovis in a colony of macaques was

treated successfully with a modern multidrug therapeutic regimen. It seems that the combination of isoniazid, rifampin and ethambutol caused rapid resolution of radiographically demonstrable lesions. This multidrug therapy was considered successful and practical at the 12 month treatment interval, and it appears to provide a reasonable alternative to destruction of valuable animals infected by tuberculosis.

Herpesvirus hominis

Agent: Herpesvirus hominis type 1 (herpes simplex) and type 2 (genital herpes).

Epizootiology: Man is the natural host; most people are infected. Generalized disease reported in owl monkeys, gibbons, tree shrews, and gorilla. Serologic evidence (ELISA + immunoblotting) indicates that HSV-1 infections are common in gorillas and gibbons. Marmosets and Cebus spp. are susceptible experimentally. Genital infections (HSV-2) have been reported in chimpanzees.

Clinical: In man, acute infection (usually in children less than 3 years old) produces vesicular gingivostomatitis. Recurrent exacerbations are characterized by vesicles and ulcers on the lips ("fever blisters"). Owl monkeys: high morbidity and mortality, conjunctivitis, nasal discharge, lethargy, course 4-7 days. Gibbons: oral ulcers; some develop CNS signs and die. Tree shrews: emaciation, conjunctivitis, some die. Generalized disease in a gorilla also has been reported. Genital herpes in chimps: localized herpetic ulcers.

Pathology: Morphologically indistinguishable from Herpesvirus tamarinus in owl monkeys, although encephalitis occurs in more cases. Gibbons: necrotizing meningoencephalitis, inclusions. Tree shrews: multifocal necrotizing and hemorrhagic hepatitis and adrenal adenitis with inclusions.

Diagnosis: Signs and lesions, virus isolation and identification.

Control: Persons with active herpetic infection must stay away from susceptible nonhuman primates.

Marburg Virus (or Ebola)

Historical: Marburg disease was first recognized in 1967. Severe disease in lab workers in Germany and Yugoslavia working with tissue cultures from African green monkeys from Uganda; 7/30 affected died. Monkeys not ill in German lab but there were deaths among new monkeys in Yugoslav lab. Since then, sporadic in Africa.

Agents: Previously thought to be rhabdoviruses, these agents are morphologically quite different from Vesiculovirus spp. (vesicular stomatitis group) and Lyssavirus spp. (rabies group). Some authors propose that Marburg virus and the similar Ebola virus be placed in a new, as yet not official, family, the Filoviridae.

Epizootiology: Transmission by aerosol, handling infected tissue, saliva, urine. Monkeys are susceptible to even small doses of virus; thus are probably not natural or reservoir host. If this be true, the natural host is unknown. Antibodies to these viruses are found at low prevalence rates in wild-caught primates in Kenya, but the significance of this is not known.

Clinical: (i). Man: 5-8 day incubation. Fever, headache, impaired consciousness, vomiting, diarrhea, rash, conjunctivitis, lymphadenopathy, hemorrhagic diathesis. (ii). Experimental disease in African green, rhesus, and squirrel monkeys: Febrile until about 24 hours before death, then temperature dropped to subnormal; diarrhea, rash, dyspnea, course 6-13 days, uniformly fatal.

Pathology: Man: Cerebral edema, multifocal necrosis of many tissues especially liver, lymphoid tissue, kidney, pancreas, adrenal, and skin; lymphocytic encephalitis. Monkeys: Similar to man. Multifocal to diffuse hemorrhagic necrosis of liver, spleen, lungs; lymphoid necrosis, multifocal interstitial pneumonia, pulmonary vasculitis.

Diagnosis: Signs and lesions, virus isolation and identification. Marburg and Ebola diseases are indistinguishable.

Control: Effective measures unknown—source unknown. Use care when working with African green monkeys and cells derived from them.

Measles (Rubeola)

Agent: A paramyxovirus, genus Morbillivirus.

Epizootiology: Macaques (especially rhesus), baboons, African green, marmosets, tamarines, squirrel monkeys, chimps, and Presbytis cristatus are susceptible to human measles. Can be fatal if complicated by bacteria. Not a disease of wild monkeys, but most wild- caught monkeys seroconvert within a few months of capture. Virus is shed in most secretions and in urine.

Clinical: Can be asymptomatic or rapidly fatal. Marmosets are said to be especially susceptible. Course of clinical disease usually is less than 10 days, and is characterized by maculopapular skin rash, serous to mucopurulent nasal discharge, ocular discharge, maybe Koplik's spots, diarrhea, and rarely, abortion. Immuno- suppression during measles virus infection is clearly documented.

Pathology: Interstitial pneumonia with syncytial giant cells in alveoli and bronchioles, with nuclear and cytoplasmic inclusions. This commonly is complicated by secondary bacterial invaders, such as Streptococcus pneumoniae, resulting in suppurative bronchopneumonia. In such cases, the lesions due to the viral infection may be obscured. Skin lesions include focal acanthosis, hyperkeratosis, and parakeratosis; hair follicle necrosis; epidermal and follicular giant cells; no inclusions. Lymphoid tissues can have syncytial giant cells (Warthin-Finkeldey cells). Similar cells can occur in the liver and transitional epithelium of the urinary tract, although these are rare, and on occasion can be seen in other epithelia throughout the body and in the choroid plexus. It is more usual for transitional epithelium to have inclusions without much cellular change. Such inclusions must be differentiated from the nonspecific inclusions in transitional epithelium of macaques, especially cynomolgus. Enterocolitis with inclusions in some cases. Rarely, endometritis. SSPE-like disease reported in baboon.

Diagnosis: Signs and lesions, virus isolation and identification, various serologic techniques such as hemagglutination inhibition. Remember that macaques, especially cynomolgus, often have nonspecific inclusions in the urinary bladder epithelium that resemble measles virus inclusions.

Control: Keep known exposed personnel and children away from primates. Newly imported primates will have been exposed before reaching lab. Zoonotic (monkeys can transmit back to people). Chick embryo measles vaccine can be used. Not necessary if already exposed, but primates raised in closed colonies could be susceptible; vaccine could be helpful prophylaxis.

Monkeypox

Agent: A poxvirus antigenically related to smallpox and vaccinia viruses.

Epizootiology: Reported in rhesus and cynomolgus macaques, owl-faced monkeys (Cercopithecus hamlyn), gorillas, gibbons, squirrel monkeys, marmosets, chimpanzees, and humans. Occurs naturally in West and Central Africa. A high prevalence (24.7%) of monkeypox-specific antibodies was found in two species of squirrels (Funisciurus anerythrus and Heliosciurus rufobrachium), suggesting that these animals may serve as reservoirs or vectors. (The animals commonly are trapped by natives.) Three of 39 primates were seropositive for monkeypox, but as yet it is not known whether primates maintain the virus or, like humans, are merely occasional hosts. About 10 or so outbreaks in captive primates have been reported. Apes appear to be quite susceptible.

Clinical: Fever, "pocks" over trunk, tail, face, and limbs, including palms and soles. Wide range of susceptibility: in some, general health unaffected but others become ill and some die.

Pathology: Pathogenesis is classical for systemic poxviral disease, with local multiplication, primary viremia, secondary internal multiplication, secondary viremia, disseminated pox. Skin lesions begin as firm elevations resulting from epithelial proliferation. As "ballooning" degeneration then necrosis proceed from the center outward, lesions develop into umbilicated pustules ("pocks"). Crusts then form over healing lesions. Other lesions include multifocal necrotizing pneumonitis, orchitis, and lymphadenitis with lymphoid hyperplasia.

Diagnosis: Microscopic exam of lesion scrapings, morphology, EM, virus isolation.

Control: An uncommon disease. Common sense and good colony management should suffice.

Viral Hepatitis

Agents: Hepatitis A virus is a picornavirus; hepatitis B virus, a hepadnavirus; the delta or hepatitis D agent is an unclassified, defective RNA virus; and non-A-non-B agents are not identified with certainty.

Epizootiology: Hepatitis A ("infectious hepatitis") in man is transmitted by fecal-oral route. Monkeys and apes get it from man. Serologic evidence of infection in chimps, marmosets, baboons, and patas, African green, and Cebus monkeys. Chimps and marmosets susceptible to overt disease (marmosets used as model), in others inapparent. Zoonotic. Human hepatitis A has a short incubation period and is generally mild with very low mortality.

Non-A-non-B hepatitis in man is transmitted primarily via blood or serum and is the major cause of post-transfusion hepatitis. NANB hepatitis tends to be chronic. There are probably two (possibly more) forms of NANBH: hepatitis C, which is transmitted parenterally, and an epidemic form, which is transmitted enterically. Agent(s) can persist for up to 6 years. NANBH has been experimentally transmitted to chimps. Zoonotic?

Clinical: Usually inapparent but can have fever, jaundice, even death.

Pathology: Resembles that in man: Hepatocellular degeneration and necrosis which is multifocal or irregular but tends to greater severity in the centrilobular zone, accompanied by Kupffer cell hyperplasia and mononuclear inflammatory response. Inflammatory infiltrates tend to be mostly portal, but there can be some around the central veins also, and in sinusoids depending on severity. Chronic active NANB hepatitis reported in chimps.

Diagnosis: Serologic, morphologic.

Control: Hygiene, training of personnel, exclusion of any known infected persons, prophylactic immune globulin for handlers.

Simian Acquired Immunodeficiency Syndrome (SAIDS)

Historical: Human AIDS was first reported by CDC in 1981. Simian AIDS-like conditions have been recognized in New England, California, Washington, Oregon, and Delta Regional Primate Research Centers.

Agent: Retroviral, probably several different ones.

Cause: The family Retroviridae is divided into three subfamilies. The Oncovirinae include three unnamed genera comprising the types B, C, and D viruses. The Spumavirinae (foamy viruses) include the single genus Spumavirus, and the Lentivirinae (slow viruses) include the single genus Lentivirus. Morphology and gene organization are major criteria for classification. Typical oncoviruses have a more nearly round (eicosahedral) core than lentiviruses, which have a cylindrical or bar-shaped core, although some type D viruses have an eccentric elongated core intermediate between that of a typical oncovirus and that of a lentivirus. The basic distinction between types C and D viruses is that the core of type D particles forms in the cytoplasm first, then migrates to the cell membrane where the viral envelope forms and budding occurs. The core of type C particles, on the other hand, forms as the envelope assembles and budding occurs. Size, growth characteristics, antigenic relationships, nucleic acid homology, and host range also are used in various classification schemes.

Human AIDS is caused by HIV-1 (human immunodeficiency virus-1), a lentivirus. Synonyms include LAV (lymphadenopathy virus), and HTLV-III (human T- lymphotropic virus-III). HIV-2 (HTLV-IV), another human lentivirus, is found only in west Africa. It appears to be less pathogenic than HIV-1; most people from whom it has been recovered were apparently healthy. SAIDS also is associated with retroviral infections, but information concerning the specific agent or agents responsible is somewhat confused. Lentiviruses have been isolated from macaques with SAIDS at NERPRC, CRPRC, and WRPRC. These agents are closely related genetically and are now generally considered to cause SAIDS in macaques. They currently are designated SIVmac (simian immunodeficiency virus of macaques). In terms of sequence homology in gag and pol genes and in gene organization, SIVmac viruses are more closely related to HIV-2 than to HIV-1. Another simian lentivirus, SIVsmm (STLV-III/Delta), is closely related to SIVmac and apparently is prevalent in captive sooty mangabeys (Cercocebus atys). No evidence of immunodeficiency disease has been found in the mangabeys; however, macaques inoculated with lepromatous material from sooty mangabeys developed combinations of lymphoma, CMV disease, candidiasis, cryptosporidiosis, wasting, lymphoid atrophy, marrow hyperplasia, amyloidosis, gastritis, hepatitis, and syncytia in the meninges, lung, liver, lymph nodes, kidney, and gastrointestinal tract. This appears to have been due to SIVsmm infection in the macaques.

Still another nonhuman primate lentivirus, SIVagm (STLV-IIIagm), has been isolated from apparently healthy wild-caught African green monkeys, and serologic evidence indicates that infection is common. It has not been associated with disease. It cross-reacts serologically with HIV-1 and HIV-2, but based on sequence homologies SIVagm viruses form a group distinct from HIV-1 viruses and from the HIV- 2/SIVmac/SIVsmm group. An additional SIV has been found in mandrills (Papio sphinx), but its prevalence and pathogenicity are unknown.

Knowledge of the cause(s) of SAIDS is clouded by the isolation of type D retroviruses from affected monkeys at NERPRC, CRPRC, WRPRC, and ORPRC. The relationships among these agents have not been clarified, and it is unclear whether or not any of them can cause or contribute to SAIDS. The New England type D agent did not cause disease after experimental inoculation. The California virus, which is easily transmitted and which is reported to cause SAIDS-like disease experimentally, is referred to as SRV-1 (simian retrovirus-1). SRV-1 has antigenic similarities to Mason-Pfizer monkey virus. The Washington type D virus, which is antigenically similar to SRV-1, is called SRV-2; it appears to cause a fibroblastic proliferative disease affecting mostly the abdominal viscera and called retroperitoneal fibromatosis. The Oregon virus is reported to be serologically similar to, but nonetheless distinct from, the California virus; its relationship to SRV-1 has not been established. Thus, there are at least 2, and possibly more, type D retroviruses that have been associated with SAIDS in addition to the aforementioned lentiviruses.

Epizootiology: SAIDS is most common in rhesus and other macaques. Natural reservoir, mode of transmission, incubation period, etc., are not fully understood. It is possible that lentiviruses that cause immunodeficiency diseases are derived from lentiviruses that are not pathogenic in the natural host species. However, up to 50% of the African green monkeys in their native habitat (sub-Saharan Africa) have antibodies to SIVagm, up to 80% of captive sooty mangabeys have titers to SIVsmm. The widespread occurrence of SIVs in these species without apparent adverse effects suggests a long evolutionary relationship. Macaques appear not to have SIV infections in the wild; SIVmac is closely related to SIVsmm. Simian immunodeficiency viruses replicate well in cultured human T cells, and the area of Africa in which HIV-2 (closely related to SIVsmm) is endemic corresponds to the range of sooty mangabeys.

Clinical signs and laboratory results: Human AIDS is characterized by lymphoid depletion, depressed cellular and humoral immunity, opportunistic infections, and neoplasms such as Kaposi's sarcoma (endothelial origin) and lymphoma. There usually is lymphopenia and decreased ratio of T4+ (helper-inducer) lymphocytes to T8+ (suppressor-cytotoxic) lymphocytes. Human patients usually have normal or increased immunoglobulins. Some patients have CNS signs.

Signs of SAIDS are not specific and usually are related to secondary infectious conditions. M. cyclopis at NERPRC in 1980-81 had anemia, neutropenia, bizarre circulating mononuclear cells, increased hepatic enzymes, decreased serum albumin, hypogammaglobulinemia, wasting, diarrhea, lymphoma, and diseases such pneumocystosis or noma. Responses of their lymphocytes to mitogens and mixed lymphocyte culture were decreased, but their lymphocyte counts and T4/T8 ratios were normal.

Rhesus monkeys from which SIV was isolated did, however, have decreased numbers of T4+ lymphocytes. Naturally infected monkeys had lymphoma, opportunistic infections, or both. Monkeys inoculated with lymphoma tissue or plasma died rapidly with conditions such as candidiasis, generalized cytomegalovirus disease, cryptosporidiosis, intestinal trichomoniasis, and encephalitis. At the California RPRC, 42 rhesus monkeys were found to have lymphoma and concurrent progressive multifocal leukoencephalopathy or disease due to M. avium- intracellulare or Herpesvirus simiae from 1965-1975. A second outbreak began in 1976 in stumptailed macaques, and featured high mortality with encephalitis, oral candidiasis, and enteric mycobacteriosis (M. avium). In 1976-1981, a third outbreak affected rhesus monkeys and was characterized by generalized lymphadenopathy, severe anemia and lymphopenia, secondary bacterial infections, and high mortality. A fourth outbreak began in 1981 and continues at present.

At the Washington center, SAIDS has affected primarily pigtail macaques but also other species of macaques. These animals had persistent diarrhea, progressive weight loss, anemia, lymphopenia, opportunistic infections, and a high incidence of retroperitoneal fibromatosis, a neoplasm-like condition whose cells bear some similarities to those of Kaposi's sarcoma.

The ORPRC retrospectively recognized a SAIDS-like condition seen as early as 1978 in Celebes black macaques and rhesus monkeys. These animals had weight loss, diarrhea, anemia, lymphopenia, lymphadenopathy, splenomegaly, hypoproteinemia, and retroperitoneal fibromatosis.

Pathology: Lesions related specifically to SAIDS include lymphoid hyperplasia followed by progressive depletion. Some monkeys have had lymphoproliferative lesions such as infiltrates in liver, kidney, and bone marrow, or outright lymphosarcoma. Encephalitis similar to that occurring in human AIDS (perivascular granulomatous inflammation with multinucleated giant cells) occurs in some cases. Other lesions result from infections with CMV, SV40, Pneumocystis carinii, mycobacteria, Cryptosporidium, Candida, and other agents.

The pathogenesis of the disease still is unclear; however, the California group has reported that monkeys dying of fulminant SAIDS after inoculation with SRV-1 had much circulating virus and did not have detectable antibody responses to the virus. Monkeys that developed a milder form of the disease had chronic mild viremia, and those that did not develop signs of SAIDS had no or transient viremia and high concentrations of antibody against the virus. Chakrabarti et al (1987) reported that SIV causes disease more similar to human AIDS in that it also is tropic for lymphocytes of the T helper phenotype.

Diagnosis: Serologic techniques, such as indirect IFA and ELISA; immunoblotting; virus isolation & identification

Control: Isolation may be difficult because of long incubation period, and best measures not really known because transmission not fully understood.

Anthropometric Parameters of Macaca mulatta

Circumference

Parameter	Range (mm)	Mean (mm)	Std. Deviation
Head	257-314	280	17.48
Neck	190-247	217	16.36
Shoulder	377-458	405	25.83
Chest-1	330-437	364	28.87
Chest-2	307-422	351	29.24
Waist	253-313	278	17.89
High thigh	227-320	258	24.51
Mid thigh	200-266	226	16.32
Calf	124-163	139	11.43
Ankle	8-110	95	7.41
Biceps	139-178	157	12.19
Wrist	82-107	87	7.64

Length

Parameter	Range (mm)	Mean (mm)	Std
Total length	707-795	748	24.74
Head/buttocks	445-520	474	20.22
Leg	255-348	294	24.76
Arm-1	305-395	347	23.40
Arm-2	380-465	413	24.19
Arm-3	335-400	364	16.89
Forearm	232-266	248	10.01
Hand males and females	100-113	106	4.17
Males	103-113	108	3.94
Females	100-106	103	2.17
Foot	134-153	141	4.94
Tail	222-294	255	19.13
Head	84-105	89	5.73
Lower leg	17-211	192	9.43
Thigh	187-211	198	8.19

Width

Parameter	Range (mm)	Mean (mm)	Std
Foot	42-59	47	4.77
Hand	34-49	42	4.19
Chest-3	61-87	75	7.84
Chest-4	60-81	69	5.66
Shoulder	12-167	143	10.96
Waist	77-101	88	7.06
Hip	103-127	113	6.35
Face	70-88	77	4.80

Depth

Parameter	Range (mm)	Mean (mm)	Std
Chest	93-114	100	6.47
Pubis	53-77	62	7.54
Weight in grams	4410-5700	5185.8	360.9

Physiological Parameters

Hemodynamic Parameters

Label	Measurement	Unit	Mean	Range
HR	Heart Rate (mean weight (mw) 7.6kg)	bpm	168	95–235
HR	Heart Rate (mw 5.3kg)	bpm	174	125-240
C.O.	Cardiac Output (mw 7.6kg)	mL/min	1800	500-3300
C.O.	Cardiac Output (mw 5.3kg)	mL/min	1070	350-1700
SV	Stroke Volume (mw 7.6kg)	mL	10.7	4.7-16.7
SV	Stroke Volume (mw 5.3kg)	mL	5.8	2.8-10.6
ABP (s)	Systolic art. pressure (mw 7.6kg)	mmHg	120	68-172
ABP (d)	Diastolic art. pressure (mw 7.6kg)	mmHg	84	60-108
ABP (m)	Mean art. Pressure (mw 7.6kg)	mmHg	101	80-120
ABP (s)	Systolic art. pressure (mw 5.3kg)	mmHg	158	122-194
ABP (d)	Diastolic art. pressure (mw 5.3kg)	mmHg	101	81-121
ABP (m)	Mean art. Pressure (mw 5.3kg)	mmHg	127	103-151
ApH	Arterial pH		7.44	7.20-7.48
VpH	Venous pH		7.34	7.34-7.54
BV	Blood Volume	mL/kg	54.1	44.3-66.6
PV	Plasma Volume	mL/kg	36.4	30.0-48.4
ECF	Extracellular Fluid Volume	mL/kg	208	121-295
TBW	Total Body Water	mL/kg	695	628-721
WHGB	Whole blood hemoglobin	gm/100mL	12.7	11.2-14.6
Hct	Hematocrit	%	41	38-45
T	Temperature	°C	38.4	37.8 – 39.0

Respiratory Parameters

Label	Measurement	Unit	Mean	Range
Vd	Dead Space	mL	12.6	7–26
COMP	Lung Compliance	mL/mmHg	12.3	9-27
RQ	Respiratory quotient	%	77	76–78
V_T	Tidal Volume	mL	42	28-65
RESP	Respiration Rate	1/min	39	27-56
MINVOL	Minute Volume	mL/min	2198	756-3640
SpO_2	Arterial oxygen saturation	%	87.8	85–93
CaO_2	Arterial oxygen content	% vol	13	14–18
PaO_2	Arterial O_2 tension	mmHg	65	65–94
$CaCO_2$	Arterial CO_2 content	% vol	58	50–67
$PaCO_2$	Arterial CO_2 tension	mmHg	31	28–42
$avDO_2$	Arterial-Venous oxygen difference	%	5.25	4.5–6.0
VO_2	Oxygen Consumption (weight 3-4.5kg)	mL/min	70	55-85

Mean Blood-Test Values (N=6) for Rhesus Monkeys

Test	*Units*	*Average*	*Std Deviation*
WBC	$x10^6$/ L	6.828	1.302
RBC	$x10^3$/ L	5.511	0.463
HGB	g / dL	12.589	1.408
HCT	%	40.033	4.935
MCV	fL	72.511	4.49
MCH	pg	22.878	1.502
MCHC	%	31.533	0.711
RDW	%	12.857	0.374
HDW	g/dL	1.93	0.137
PLT	$x10^3$/ L	290.778	42.825
MPV	fL	9.714	1.056
PDW	%	39.3	6.161
PCT	%	0.26	0.036
RBC FLAGS		0	0
NEUT	%	56.222	8.353
LYMP	%	34.978	8.166
MONO	%	4.922	2.866
EOS	%	2.944	0.899
BASO	%	0.2	0.1
LUC	%	0.744	0.27
NEUT	$x10^3$/µ L	3.794	0.794
LYMP	$x10^3$/µ L	2.42	0.786
MONO	$x10^3$/µ L	0.351	0.239
EOS	$x10^3$/µ L	0.199	0.067
BASO	$x10^3$/µ L	0.014	0.005
LUC	$x10^3$/µ L	0.053	0.022
LI	$x10^3$/µ L	2.058	0.288
MPXI	$x10^3$/µ L	-13.878	4.361
WBC FLAGS		4666.667	6557.439
SODIUM	mEq/L	146.333	4.274
POTASSIUM	mEq/L	4.083	0.36
CHLORIDE	mEq/L	107.167	4.446
GLUCOSE	mg/dL	55	8.602
CREATININE	mg/dL	1.45	0.288
CALCIUM	mg/dL	9.6	0.613
PHOSPHORUS	mg/dL	5.15	0.758