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EVALUATION OF THE NEED FOR A LARGE PRIMATE RESEARCH FACILITY IN SPACE

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Report of the
National Aeronautics and Space Administration
Large Primate Advisory Committee

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SUMMARY:

In the summer of 1983 an advisory committee was organized to evaluate NASA's current and future capabilities for non-human primate research. The advisory committee made the following conclusions.

1. A large primate research facility is needed in order to conduct research on various problems that are important for human safety, health and performance in space.

2. Rhesus monkeys are an excellent model for many problems in space physiology because of their size, posture, and general anatomical and physiological similarities to humans.

3. NASA should develop a large primate facility (LPF) to conduct space research with rhesus monkeys.

3. Because of constraints associated with research in space, several animal technology problems such as life support, zoonosis, animal training and bioinstrumentation need to be resolved.

4. The LPF should be developed and tested in an iterative fashion involving a series of 2 or 3 spaceflights in which successive degrees of complexity are incorporated.

5. The LPF will serve different functions: (a) it will be a facility for conducting 5-10 day experiments in spacelab; (b) it will provide a life support system for monkeys who can be used in other spacelab facilities for acute experiments; and (c) it will serve as a transportation system for bringing rhesus monkeys to and from the space station.

6. A science advisory committee should be formed. The members of this group should have experience with large primates and NASA spaceflight procedures.

7. Members of the science advisory committee should be involved in resolving the animal technology problems, and also be involved in the design, testing and evaluation of the LPF.

INTRODUCTION

At the current stage in the evolution of manned spaceflight, the fundamental question of survival in space has been resolved. Over 130 astronauts and cosmonauts (including 4 women) have flown in space without any known serious lasting medical consequences. Even though almost all of these flights have been short (1 to 3 weeks) and there have been only 10 flights of greater than 30 days duration, some important areas of biomedical concern have surfaced. The process of adaptation has been shown to affect multiple body systems, with certain responses such as space motion sickness and fluid shifts occurring rapidly, followed by cardiovascular deconditioning, and finally more slowly developing alterations in bone and muscle. Once back on earth, readaptation has also been shown to be variable. Depending on the system monitored, readaptation can take days, weeks or months. Numerous publications and reports have documented the significant effects of microgravity on cardiovascular deconditioning, space motion sickness, fluid and electrolyte balance, and bone and muscle metabolism.

As we move into the next stage of manned spaceflight, two important changes will occur. First, the development of the Space Transportation System will enable people of a wider range of physical conditioning, health and age to fly in space. Second, the development of a permanently inhabited space station will mean that many more humans will live in space for longer periods. In order to insure the health and safety of the people that will participate in these future spaceflights, NASA is currently planning and conducting research aimed at a better understanding of the physiological adaptation to microgravity. On earth, research in these areas has benefited from the considerable arsenal of modern tools and techniques for attacking biomedical problems. In contrast, almost all of the space research to date has utilized humans as test subjects, and for practical or ethical reasons many biomedical research techniques cannot be utilized. The level of understanding of the fundamental mechanisms involved in adaptation to microgravity is therefore severely limited. Future research will require animals for procedures which are not suitable for use with human subjects.

Because of these and other factors, much of the biomedical research that has been done in space has been descriptive. The emphasis has been on recording and documenting changes associated with microgravity. This is a natural first step in the assessment of a new problem, but with the development of increased flight opportunities and research capabilities, it is now possible to examine the basic mechanisms involved in adaptation to microgravity. This research will require the use of animal models and human surrogates in order to open the control loops responsible for physiological regulation. That is, research on how physiological control is regulated in space should be able to utilize laboratory techniques that have traditionally been used on earth such as invasive measurement, denervation, gland removal and drug infusion.

Unlike humans, animal subjects dedicated to experimental goals can be treated exclusive of operational considerations. Research variables such as ambient temperature, diet, light cycle, activity and stress can be controlled. Complications resulting from the therapeutic use of drugs can be avoided. Unlike human subjects, animals are available for extensive pre- and postflight testing uncompromised by non-experiment-related activities. Among the animals, non-human primates provide the optimal human surrogate with: (1) physiological

and anatomical relatedness to allow for maximal extrapolation to humans; (2) an upright posture in which microgravity produces significant fluid shifts; and (3) sufficient size to permit invasive bioinstrumentation.

In the summer of 1983 an advisory committee was organized that would be able to evaluate NASA's current and future capabilities for non-human primate research in space. Established investigators who have had considerable experience with non-human primates were chosen. Individuals were selected who would act as spokesmen for their research disciplines and who could work together as a team. Four disciplines were chosen because they are widely recognized to be key research areas for enhancing human safety and productivity in space. These areas are: cardiovascular physiology, vestibular neurophysiology, musculo-skeletal physiology, and fluid and electrolyte balance. An additional area was also represented, viz. homeostasis and circadian physiology. The rationale for including this rather broad area was to have input from other physiological disciplines. We did not feel that it was necessary to include representatives from other important disciplines such as pharmacology, radiobiology, development, behavior, etc. because our goal was not to describe all future primate space research but rather to develop a model integrated physiological experiment that would serve as an example. A list of the members of the Large Primate Advisory committee is attached as Appendix I.

The advisory committee has examined NASA's current capabilities for flight research using various animal models. For the reasons that are enumerated below, the committee feels that it is vital to expand NASA's capability to conduct animal research in space. Specifically, the committee recommends that NASA undertake the development of a research facility for rhesus monkeys that can be flown in space. In order to provide advice on what specific measures this facility should be capable of supporting, the committee has developed a model integrated experiment that addresses important biomedical questions. The hardware requirements necessary for the experiment objectives should provide an outline for the development of a large primate research facility suitable for spaceflight. The committee further recommends that scientists who are potential users of the rhesus facility should be involved in its development.

RATIONALE FOR USE OF NON-HUMAN PRIMATES IN SPACE

While it is obvious that the study of many problems in human subjects is highly desirable, many of the measurements normally employed to study them would require the use of frequent invasive procedures, presently neither desirable nor practical. Many of the inflight tests and associated measurements require excessive time (up to days) which would also preclude the use of human subjects. Further, the changes that occur in certain organ systems are subtle and will require rigorous experimental control which is feasible with animal models but not with busy crew members devoted to multiple duties and disciplines. The use of experimental animals provides additional major advantages when studying time variant or dependent changes:

1) Animal species with organ systems known to be sensitive to anticipated stresses can be chosen for appropriate experimental studies.

2) Animals can be maintained under constant nutritional and environmental conditions for long periods of time far more readily than can humans.

3) Experimental animals are frequently bred and kept under controlled conditions in the laboratory before use. The use of a relatively uniform population of subjects can be of great help in reducing statistical variance.

4) Animals can be instrumented with a wide variety of surgically implanted devices that would not be used in humans.

5) Environmental and nutritional variables can be systematically manipulated over a wider range with animals than would be desirable or permissible with humans.

6) Techniques which involve radioactive isotopes or drugs that have not been approved for humans can be used in studies with research animals.

7) Organs can be partially or wholly removed and studied in animal experiments.

8) When necessary, animals can be sacrificed in the course of experiments to provide essential information concerning changes in organ structure or its biochemical contents.

While data from animal experiments can never wholly supplant direct observations on man, at the same time, the use of experimental animals provides physiological insights difficult or impossible to obtain through the exclusive use of human subjects. It is thus the complementary approach of both human and animal experimentation that permits the meaningful advance in basic physiological knowledge and the solution of practical medical problems. However, although it is obvious that animals play a major role as subjects in ground based research, the relevance of these animal models in gravitational physiology must be established. Consequently work must be done with animals to verify the applicability of these human surrogates in space.

Rodents have traditionally been used as subjects in physiological research, and will undoubtedly continue to provide valuable data in space. However,

because of the wide phylogenetic gap between humans and rodents, there are important biochemical and physiological differences between these two groups, and these differences may be exaggerated in weightlessness. The use of more closely related animals, viz. non-human primates, is the obvious way to fill this gap in research capabilities. Because of their upright posture, large size, physiological and anatomical similarities to humans, and substantial behavioral repertoire, non-human primates provide an excellent experimental model which can be utilized for biomedical research in space.

Apart from physiological relatedness, size is a very important consideration for choosing an animal model. Numerous research techniques and procedures simply cannot be done on small animals. Many medical procedures and surgical techniques would not have been developed if large animals were not available as research subjects. In addition to monkeys, cats and dogs are the large animals that are most frequently used in biomedical research. For reasons cited below, cats and dogs are not recommended for use as research subjects in space, and monkeys appear to be the best large animal model. The committee feels that the monkeys should be 8 to 10 Kg in size to permit instrumentation and biological sampling. Obviously this far exceeds the size of squirrel monkeys (1 Kg).

With respect to which species of monkey, there is an advantage for using rhesus monkeys as subjects since reasonable numbers of captive-bred rhesus monkeys are available from domestic breeding colonies. The use of these animals will obviate histopathologic changes (particularly in muscles) often seen in wild animals due to pre-existing disease, and will provide animals that are nutritionally conditioned and known to be clinically and biochemically in perfect health. Their use will be most important in experiments attempting to detect changes during spaceflight.

In addition to the generic reasons for using non-human primates as human surrogates in space research, there are discipline specific reasons for using these animals.

1. CARDIOVASCULAR: The use of large non-human primates in this discipline is required for several reasons. (a) Many research techniques in this area are invasive (catheters, flow and pressure monitors, etc.). (b) Instrumentation has not reached a stage of miniaturization such that state-of-the-art techniques can be implanted in small primates. (c) At some stage it will be desirable to conduct histopathological examinations of cardiac tissue. Of all the animal models currently used in cardiovascular research, the rhesus is the best subject for research in this discipline in space.

2. VESTIBULAR: A high quality research program with human subjects has already been established and successful flight experiments were conducted on Spacelab 1. However, a recent ad hoc Working Group on Space Motion Sickness pointed out the importance of research aimed at understanding the underlying mechanisms responsible for space motion sickness. By the second half of this decade, the role of the vestibular apparatus in this discipline will be clarified, and studies on vestibular neurophysiology will assume major importance. In order to investigate mechanisms related to space motion sickness, it will be necessary to evaluate both sensory and motor aspects of vestibular function. Sensory processing can be measured directly only by invasive procedures, thus necessitating animal-based studies. Non-human primates are the species of choice primarily because of numerous similarities in vestibular functions

between those species and man. The use of large non-human primates will facilitate neurophysiological experimentation involving the vestibular system since: a) the structures of the vestibular nuclei and the vestibular nerve are larger than in smaller species and thus easier to record from; b) for a given size of recording probe, proportionally less damage will be sustained by the larger brain; and c) certain vestibular reflexes (e.g. the vestibulo-ocular reflex) have close functional characteristics to those of man.

3. MUSCULO-SKELETAL PHYSIOLOGY: The changes which occur in the calcium homeostatic system in response to spaceflight ultimately result in the loss of bone mass and with it, some measure of skeletal integrity. However, a measurement of bone mass only reflects the result of all the processes which have occurred, and so we must direct our efforts toward the investigation of the initiating mechanisms that result in bone loss. This requires the use of bone biopsies (to look at cellular responses to weightlessness) and the ability to perturb the calcium homeostatic system (through the use of drugs, parathyroidectomy, induced renal calcium leaks). The differences between local biomechanical effects such as those due to induced muscle pulls from electric stimulus and systemic or hormonal effects must be determined, and this can only be done in a large animal with invasive procedures. Therapeutic measures should first be tested in animal preparations, especially if they involve pharmaceutical intervention.

To understand those mechanisms which underlie bone loss in weightlessness, we will have to do both short term (1-10 days) and long term (3-6 months) experiments under controlled conditions. An animal model such as a large primate reaches skeletal maturity somewhat earlier than a human (by a factor of 3-4) so that the equivalent of 1 year of human skeletal aging may occur in 3-4 months in an adult age primate.

A very high priority in musculo-skeletal experiments will be the ability to maintain 6-12 month preflight, 2-180 day flight, and 6-12 month postflight experimental periods under controlled conditions. This is necessary because skeletal transients are on the order of months. In human subjects, this is virtually impossible to do because of variations in diet, sunlight exposure and activity levels throughout the year; however, it is quite feasible in a large primate investigation program.

4. FLUID AND ELECTROLYTE: Because of the practical and ethical constraints of studies in humans, very little data are available for the first few hours and days of weightlessness when most of the major changes in fluid and electrolyte redistribution are taking place. There are major differences between the responses observed in weightlessness analogs such as bed rest and water immersion, and those observed in space. A particularly striking difference is that the prominent diuretic response seen in humans in ground-based weightlessness analogs has not been seen in space. It is essential to study these problems in detail in space to isolate the differences and their causes.

Monkeys provide a compact human surrogate, and yet one that has a physiology that is very similar to that of man. Using this animal surrogate, invasive techniques which involve such procedures as adrenalectomy, renal denervation, and baroreceptor denervation, can be undertaken in order to elucidate the mechanisms underlying the homeostatic responses to the fluid and electrolyte cephalic shift. Unlike most other species, the monkey has a circadian timing system very similar to that of man so that the prominent circadian rhythms in

fluid and electrolyte distribution and in plasma hormonal levels are a true model of the same temporal organization of physiological functions in man.

These studies on fluid and electrolyte homeostasis will provide fundamental information which will benefit our understanding of these mechanisms. This information will have far reaching importance beyond the specialized environment of spaceflight.

5. HOMEOSTASIS AND CIRCADIAN PHYSIOLOGY: As noted above, a large animal is required in order to simultaneously and continuously monitor diverse physiological systems without over-instrumenting the subject. Several functions including body temperature, gas metabolism, sleep, neuroendocrine systems, and behavioral responses are thought to be altered in space. The underlying physiological control mechanisms of these processes varies with species size, morphology and phylogeny. Thus a phylogenetically close relative of humans will allow maximal extrapolation of these results to improve health and performance in space.

OBJECTIVES OF EXPERIMENTS IN SPECIFIC DISCIPLINES

To help identify what scientific measures the primate research facility should support, each of the five disciplines proposed a model experiment. The intent of each of these experiments was to investigate the physiological mechanism involved in microgravity responses. Understanding of the basic mechanism whereby physiological control is altered in space should allow the development of a new generation of counter measures to attenuate the physiological alterations that are detrimental to the health and performance of astronauts. As noted above, the rate of adaptation to weightlessness depends on the physiological system being studied. Table I shows the expected time course of adaptation of various systems to microgravity. This table illustrates that physiological changes caused by weightlessness involve a spectrum of spectrum of responses from relatively rapid adaptation (< 10 days) to long term (1 to 2 years) adjustments. Besides being excellent subjects for 5 to 10 day experiments in Spacelab, the shorter life span of rhesus monkeys will facilitate an evaluation of the consequences of long term adaptation to microgravity. The general objectives of the five research areas are listed below, and are then followed by the specific discipline objectives.

1. Cardiovascular Physiology:

The ultimate objective of cardiovascular research with primates in space is to understand the short term response of the cardiovascular control mechanisms to microgravity, especially autonomic control, and receptor regulatory control, and longer term changes in cardiac structure and function. This information is vital to counter cardiovascular deconditioning in space when longer term space travel is contemplated.

2. Vestibular Neurophysiology:

The practical objective of the vestibular neurophysiology research with primates in space is an understanding of the underlying mechanism of space motion sickness. If the vestibular apparatus is involved in space motion sickness, then countermeasures and optimal drug therapy will require an understanding of its neurophysiology. Further, the validation of the conscious, alert monkey model in space will greatly facilitate ground based research in this area, including drug screening.

Vestibular function can be evaluated both in short and long duration missions. The objective of short term studies (1 - 10 days) would be to investigate in detail the activity and response characteristics of neurons in the vestibular nerve and in vestibular nuclei that are expected to reflect dynamic changes accompanying early vestibular adaptation to the microgravity environment. Studies carried out for longer term flights, i.e. three to six months and one to two years, would involve both pre- and postflight as well as inflight measurement of neuronal activity and vestibular reflex responses to applied head acceleration. The emphasis of work on longer flights is on both the status of vestibular system function after prolonged exposure to reduced gravity and also on readaptation of the vestibular system following return to earth gravity conditions. In addition, direct examination of the vestibular end organ can be undertaken postflight in order to relate observed changes in vestibular function to potential altered morphological conditions especially in the otolith organs.

3. Musculo-Skeletal Physiology:

   The objectives of the research in musculo-skeletal physiology are to: (a) determine the underlying mechanisms causing the early changes in calcium metabolism during spaceflight, and to use this information to interpret the skeletal responses to the stimulus of zero-g; (b) to study the adaptive responses of the calcium metabolic and skeletal homeostatic systems in zero-g over the short and long term and to develop measures to prevent the bone loss which occurs; and (c) understand the cellular mechanisms underlying the development of accelerated muscle breakdown in space and develop measures for its prevention.

4. Fluid and Electrolyte Balance:

   Research in space in this area will focus on the mechanism of fluid and electrolyte homeostasis, and which elements of the control system (neural, endocrine, etc.) are the keys in controlling the responses to microgravity.

5. Homeostasis and Circadian Physiology:

   Research in this general area requires integrative long-term monitoring, and will also provide objective measures of the health status of the monkeys. Furthermore, it is necessary to build capabilities into the research facility to accommodate disciplines which are not currently recognized as biomedical problems (eg. metabolism, sleep, exercise, thermoregulation and reproductive physiology) but which may become more important in the future. Neuroendocrine changes, which are suspected in several of the disciplines mentioned above, can also be rigorously examined using this facility. Provocative testing with LBNP, LBPP or exercise can be used to examine the regulatory capacity of different physiological systems in flight.

TABLE I

Time Course of Adaptation of Various Physiological Systems to Microgravity

< 10 Days	3 - 6 months	1 - 2 years
ric	Remodeling of body due to alteration in graviperception	
te responses including -->	chronic responses including -->	consequences of regulation
rt term adaptation and	regulation at new steady-	at new levels on systems
overy	state levels	such as growth, develop-
		ment, and reproduction
	readaptation to 1 G	readaptation to 1 G
iovascular		
oral changes -->	cardiac structural changes -->	atrophy of the heart
od volume shifts -->	redistribution of blood vol. -->	resetting of vascular
		responses both centrally
		and locally, e.g.
		reduction in number of
		peripheral capillary beds
lex responses -->	resetting of CV reflexes -->	alteration of CV reflexes
reased intracranial -->	shift in hydrostatic -->	alteration in cerebral
essure	indifference point	blood flow adaptation
tibular		
ace motion sickness	steady-state alterations -->	continued adaptation
ssible alteration in -->	but possible susceptibility	of sensory systems to the
ferent input and/or	to novel stimulation, esp.	microgravity environment
ntral neural processing	vestibular-visual interactions	
culo-Skeletal		
crease in urinary Ca -->	decrease in intestinal Ca -->	decrease bone mass
ormonal responses	absorption	possible resetting of
	some decrease in bone mass	endocrine regulation
creased osteoblast -->	? regain of osteoblast -->	? regain of osteoblast
unction	function	function
primary increase in -->	acute loss of bone and bone -->	? does bone resorption
one resorption	remodeling	return to normal
increased muscle -->	muscle atrophy -->	? regain lost muscle mass
atabolism		
id/Electrolyte		
distribution of fluid -->	? consequences of altered electrolyte levels	
ute reduction in fluid	? consequences of change of K reservoir with loss of	
olume	muscle mass	
mples From Other Disciplines		
armacology: ? drug efficacy	? drug absorption and	
	metabolism	
	? target sensitivity	
eep: shifts in duration,	? steady-state levels	? consequences
type, quality and		
timing		
ythms: entrainment, phase	? change in free running	? persistence and
steady-state levels	period, internal synchrony,	development of
	steady-state levels	rhythms
ermoregulation: ? body temperature	? steady-state levels	? consequences for
? metabolism	? regulation (exercise)	exercise
	? body composition	? development

1. **Cardiovascular Physiology**

The marked physiological changes in the cardiovascular system that occur with adaptation to weightlessness and the subsequent readaptation to earth's gravity has been the subject of numerous NASA and Soviet reports. For many reasons, it has not been possible to conduct exhaustive investigations of cardiovascular physiology in humans during space missions especially in the first few critical hours and days. It is impossible to use some of the invasive techniques necessary to determine underlying basic mechanisms in human subjects and thus both human and animal experiments are necessary to increase our basic knowledge, and for future crew protection.

"Studies on experimental animals in space have not added a great deal to the understanding of cardiovascular deconditioning. However, limited data was acquired from dogs (Soviets) and non-human primates (US) before many human space flights, and studies of animals in space may ultimately prove to be the only feasible means of acquiring certain types of data on cardiovascular deconditioning and other biochemical problems of space flight." This is a quote from the final report prepared by a scientific task force convened for NASA by FASEB and published in February, 1983.

The suggestions by this task force of specific areas of research needed to understand the basic mechanisms of cardiovascular deconditioning were:

a. Assessment of cardiovascular function and autonomic control at various stages of actual or simulated weightlessness with the measurement of multiple endpoints of cardiovascular function. These endpoints would include central venous pressure, heart rate, ECG, systolic and diastolic arterial pressures, cardiac output, pressure-volume dynamics of cardiac chambers, the magnitudes and spatial distributions of pulmonary blood and gas volumes and flows.

b. Assessment of atrial and ventricular receptor regulatory control of the heart and blood vessels and of the release of vasopressin and aldosterone during zero-G. Associated with changes of this type would be the question of changes in adrenergic receptors (alpha and beta).

c. Assessment of whether changes in cardiac mass and structure occur with zero-G.

d. Assessment of the particular significance of documented changes in levels of circulatory and excreted hormones and whether such changes exert any influence on the function of the cardiovascular system during and after zero-G. Are these hormonal changes triggered by cephalic fluid-shifts and changes in intracranial hemodynamics?

With these questions in mind, the following hypothesis can be proposed to address some very important basic mechanisms concerning the cardiovascular system.

The hypothesis to be tested by the proposed study of cardiovascular function is that upon entry into the weightless environment the central shift of fluid occurs rapidly and results in an increase of right atrial volume and cephalic venous pressure. The increase in volume of the right side of the heart leads to activation of cardiopulmonary mechanoreceptors

which will cause central neural alterations in the baroreceptor reflex. Ultimately, the peripheral vascular responsiveness will also be altered. In conjunction with the central shift of fluid is an increase in the filtration of fluid across the capillaries in the head and neck region. This increased fluid filtration in the cranium will elevate intracranial pressure and cause a reduction in cerebral vascular resistance. Cerebral tissue CO_2 will increase causing a centrally mediated hyperventilation and a further reduction in cardiac blood flow. The degree of cerebral hypoxia and the alteration in afferent visceral input seem to alter the centrally mediated cardiovascular adjustment to an orthostatic stress. Return to 1G environment will reverse the above changes but not in the same time frame as the original change. These alterations contribute to cardiovascular deconditioning through central neural mechanisms.

Measurements of right atrial pressure and dimensions, arterial pressure, intracranial pressure, and cerebral blood flood in the restrained non-human primate will allow us to directly address this hypothesis. Other experimental alterations will be used to open neural control loops to directly test the validity of the hypothesis.

2. **Vestibular Neurophysiology**

One of the principal aims of research on the vestibular system that can be carried out in the Shuttle is to determine whether the basic operating characteristics of the peripheral end organ are altered under zero gravity conditions. It is reasonable to expect that both otolithic and canal mechanisms will remain sensitive to linear and angular head acceleration respectively even in the absence of gravitational force. What remains to be determined is how the loss of constant linear acceleration (gravitational force) alters the spontaneous activity and the dynamic response characteristics of primary vestibular afferent neurons. Those neurons constitute the principal input to the central vestibular system and their activity and responses will reflect changes in hair cell receptor functions.

A large body of information has been accumulated on the behavior of primary vestibular afferent neurons in monkeys. The work on squirrel monkey, although the most comprehensive, has all been done on acutely prepared anesthetized animals. Techniques exist for recording from that species; however, they have not been applied to any great extent in studies of the eighth nerve neurons. At least four separate laboratories, including those of such investigators as T. Raphan, Mt. Sinai Medical School; F. Miles, the NIH; L. Kimm, formerly University of Washington, now NIH; E. Keller, University of California, Berkeley, have conducted studies on vestibular primary afferents in unanesthetized, restrained rhesus monkeys. Therefore, the methodology for invasive recording from intact preparations in repeated experiments may be considered well established for this species. A derivation of those methods can be envisioned for use in a spacecraft experimental environment.

The first order of priorities is to apply those methods for recordings from animals under restraint conditions to obtain data on physiologically identified canal and otolith primary afferents. This will require no less than two hours per session of hands-on dedication to the experiment by the payload specialist. On earth, graduate students and medical students have been trained in these techniques requiring no more than two weeks to become sufficiently skilled to carry out the type of data acquisition required for these studies. Once an individual neuron has been characterized to determine its classification as innervating the otolith organs or semi-circular canals, sufficient data on its spontaneous firing rate can be acquired in a period of no more than two minutes. All primary afferent neurons exhibit spontaneous activity at rates that are characteristically an average of 90 to 100 impulses per second. These data should provide new information concerning the functional status of a good statistical sampling of primary afferent neurons. They may be compared with data obtained in previous earth-based experiments thus giving some preliminary indication of whether significant alterations have occurred in the mechanism that sustains spontaneous activity, implicating gravity in that function.

The next stage of experimentation requires an investigation of the response of vestibular afferent neurons while the animal is subjected to a time-varying acceleration separately stimulating the semicircular canals or the otolith organs. Since it is easier to control a stimulus for the canals, the first priority would probably be to devise simple instrumentation that will rotate the restrained animal about its vertical axis. The head of the animal must be restrained in order to place the

horizontal semicircular canals in proper orientation to the plane of acceleration. Engineering expertise exists within NASA for the development of such instrumentation especially among personnel that are affiliated with the Vestibular Research Facility (VRF) at Ames. The instrumentation should not be demanding either in terms of power or space requirements if the experimental design is restricted. Since an unanesthetized behaving preparation is to be used, an additional measure of vestibular function, i.e., the vestibular-ocular reflex, may be recorded in this species at the same time that recordings are acquired of neuronal activity.

The recommendation of the Working Group on Space Motion Sickness includes the suggestion that among vestibular and neurophysiological problems, studies should be carried out at the single neuronal (unit) level in normal, alert, chronic preparations; they gave as an example of an appropriate animal preparation chronically implanted monkeys. Several of the studies proposed by that group are particularly relevant to experiments that can be carried out in a large species primate preparation flown in the Shuttle. These questions would be directly addressed in later stages of development of the facility since they would require the on-board use of the multi-axis vestibular centrifuge under development in the VRF project at Ames. In anticipation of the inflight use of that facility, preliminary experiments on the spontaneous activity of primary afferent neurons is an appropriate antecedent. Finally, it is self-evident that these questions require the use of direct measurement from neurons which cannot be accomplished by non-invasive techniques and thus require an animal preparation.

3. **Musculo-Skeletal Physiology**

Objectives in the musculo-skeletal discipline require both short term and long term flight opportunities to study not only the initiating mechanisms of bone and muscle loss but also the adaptive responses of the homeostatic system. The objectives outlined here are primarily short term studies and provocative tests which would also be used in longer term flights to study the adaptive responses and responses to therapeutic intervention.

A. Calcium metabolism

The first objective examines the kinetics of bone response to zero g, from 0 to 30 days. This requires daily urine and feces collection, some blood samples, strict dietary control, and $^{46/48}$Ca. The hypothesis that will be tested is that bone destruction will be increased as a primary effect of reduced stress.

The second objective examines the kinetics of homeostatic response of Ca system to provocative tests. This requires urine collection at 6 hr intervals, frequent serum collection over 24-48 hrs, and injection of drugs to stimulate response. Treatments should be done preflight, within 48 hrs flight, then 7-30 days inflight and immediately upon recovery. The hypothesis that will be tested is that fluid shift and primary bone effects will cause differential response of calcium homeostatic system under zero g compared to 1-g. Provocative tests will elicit response of hormonal control mechanisms.

The third objective examines the mechanism of intestinal dysfunction (Ca, P, N, and other nutrients). This requires timed urine and feces collection fixed diet, diet tracers, injected tracers, and serum samples. Preflight, inflight, postflight, continuous and pulsed tracers will be utilized. Fecal water analysis would be useful. The hypothesis that will be tested is that fluid shift and perhaps other effects (such as shifts in organ position) of zero g will affect intestinal transport time, thus affecting utilization of dietary nutrients.

The fourth objective examines the response of kidney, viz. Ca and phosphate handling, and acid-base balance. This requires timed urine and serum collections, tracer injections, and serum and urine pH measurements. The hypothesis that will be tested is that the kidney dumps Ca in the first 48 hours as a non-specific response to Na excretion, followed later by a homeostatically-regulated response to the other Ca/endocrine changes which are taking place. Metabolic alkalosis or acidosis may enhance certain responses of bone to other minor effects.

B. Bone

The first objective in this section examines the cellular kinetics and appositional rates. This requires bone biopsies immediately postflight, and inflight tracer injections. The hypothesis that is to be tested is that zero g stimulates both production and activity of osteoclasts and reduces proliferation of osteoblasts.

The second objective examines marrow composition. This requires pre- and postflight biopsies (preferable) or noninvasive techniques to measure marrow elements. The hypothesis that is to be tested is that zero g may induce conversion of red marrow to fatty marrow as is seen in paraplegia, affecting bone precursor cell kinetics.

C. Muscle

The first objective in this section examines generalized atrophy of isolated skeletal muscles. This requires pre- and postflight noninvasive measurement of size and strength of muscle groups. Inflight conditioning of one limb may be required. This will provide primary documentation of microgravity induced changes.

The second objective examines enzyme activity in muscle tissue. This requires pre- and postflight muscle biopsies following exertion in conditioned and unconditioned limbs. Inflight biopsy could be done, but this is not a pressing requirement. Tracers may be used in this study. The hypothesis that is to be tested is that muscle atrophy in spaceflight may result in decreased capacity of muscle to perform work, evidenced by decrease in quantity or activity of specific enzymes.

4. Fluid and Electrolyte Balance

The primary objective is to characterize the fluid and electrolyte adjustments occurring in response to spaceflight using a large primate. There is a need to obtain detailed information on the hemodynamic, electrolyte and endocrine responses to microgravity especially during the first few hours and days. This will require frequent blood and urine sampling and hemodynamic measurements in a human surrogate that is larger than the squirrel monkey. These data will provide a baseline for subsequent interventive studies which would aim to dissect out the precise mechanisms of the reflex responses to microgravity stimuli and will make possible the development of preventive measures prior to their introduction to human subjects.

The mechanisms modifying the changes in renal function need to be examined in a systematic fashion. For example, what is the role of the central volume receptors on the low pressure side of the circulation in detecting the shift of body fluids; what is the magnitude of the shift of fluid; what are the cardiac and systemic changes that occur; and what are the efferent components of the loop which effect the renal function changes? Do they involve autonomic nervous innervation of the kidney, the renin angiotensin-aldosterone system, third factors such as atrial natriuretic factor, and what is the time course of these events? What changes occur in the perfusion of the kidney and glomerular filtration? All these issues will require a significant number of studies in a preparation which can be repeatedly flown.

The physiological impact of salt and volume replacement therapy at the end of and/or during the mission needs to be explored. What are the most appropriate strategies for such volume replacement and in what ways are the reflex adaptations to spaceflight modified?

5. Homeostasis and Circadian Physiology

Technical Objectives: This research effort will require the development of a primate system which measures a wide variety of physiological information from individually housed 8-10 kilogram male macaques. In addition, life support including controlled light, ambient temperature, airflow and pressure are required. Access to food and water must be available on an ad libitum basis to the animal, and also monitored. All waste materials must be isolated and/or collected such that they do not contaminate the animal or its food supply. Light and ambient temperature should be regulated at precise levels and controllable over a discreet range. To measure metabolic changes in these animals, gases should be contained in an airtight manner within the cage, or at least the upper portion of the cage. Input and mixed exhaust gases should be in lines such that incoming and exhaust air can be monitored by a mass spectrometer for composition of oxygen and carbon dioxide. To meet the requirements of exercising a restrained animal, a system which can be periodically activated at different load levels needs to be included.

Functional Objectives: This experiment is designed to examine the physiological responses of a variety of homeostatic systems to changes in gravitational loading of chronically prepared animals. In general, we will examine the thermoregulatory system (brain, body and skin temperatures, oxygen consumption and CO_2 production), circadian timekeeping system, sleep (polygraphic electrophysiological analysis and direct activity monitoring), feeding, drinking, performance and hormone levels. As an additional test, these systems will also be stressed with acute exposure to specific exercise paradigms. This test will also examine the cardiovascular responses and could be used to evaluate muscle and bone deadaptation. Exercise stress will be performed at least two times in the flight -- early and late.

The first experiments will be conducted in a light-dark cycle and subsequent experiments would utilize a change in the lighting conditions to either constant light or a phase shift of the light-dark cycle. The next experiment would involve changes in ambient temperature either acutely or for some significant period of the mission to look at changes in these systems to known physiological or environmental variables which are encountered on the ground. In addition to simply monitoring these parameters as a result of space flight, a provocative test, exercise, will be utilized to examine the response of these various systems. The type of questions that will be looked at include the following:

1) What are the homeostatic levels (steady state) of the various physiological variables to be monitored?

2) Are all variables rhythmic over a 24 hour period?

3) Do all variables still entrain to the light-dark cycle? If not, are they free-running and with what period and phase relationship to the other rhythm?

4) Is body temperature regulated at its normal levels and are the levels of heat production (oxygen consumption) and heat loss (skin temperatures) at normal levels? Further, do the brain and body temperature relationships exist as seen on the ground?

5) Is the efficiency of energy utilization during exercise in spaceflight modified?

6) Is physiological regulation during acute exercise or temperature stress modified in space flight?

7) What is the time course for each system to adapt to new steady state levels.

EVALUATION OF VARIOUS SPECIES FOR SPACE FLIGHT RESEARCH

As noted above, biomedical researchers have traditionally utilized many animal models. The most common animal species that have been used are rodents, rabbits, cats, dogs and monkeys. We have evaluated the various advantages and disadvantages of these species as models for space flight research. Our evaluation included generic issues that applied to various scientific disciplines, and also advantages and disadvantages that were relevant to specific research areas. Appendix II lists the major strengths and weaknesses of each of the species.

Rats are valuable animal models for many studies, but the usefulness of rats and other rodents is limited by their small size, and by postural and physiological differences from humans. Rabbits were excluded because of anatomical and physiological considerations and also because of their susceptibility to stress. While cats and dogs offer several advantages, the Soviets experienced problems in space with animals who eat and drink by lapping with their tongue. Because of their horizontal posture, the potential problem of food and water ingestion in space, and also public resistance to use of these animals in research, we did not recommend their use. While we recognized that NASA has already developed a primate research facility for squirrel monkeys, because of their small (1 Kg) size it was felt that a larger monkey was also necessary for research in several scientific disciplines which require more extensive bioinstrumentation or blood and tissue samples than are possible with squirrel monkeys.

We concluded that there is an important gap in the range of species available for biomedical research in space, viz. large primates. The rhesus monkey offers a good mixture of availability of baseline data, size, and appropriate anatomic and physiologic organization.

IMPLEMENTATION PLAN

Integrated experiments with large primates in space are sufficiently complex that there are numerous milestones that must be passed before the research facility is reliable. In ground based research, experiments can be repeated if necessary. However, opportunities for spaceflight experiments are, and will continue to be, infrequent. Consequently a goal of the development of the large primate facility should be not only the design and fabrication of the appropriate hardware, but also the development of the appropriate methods and procedures for working with the rhesus monkeys. Among the problems in spaceflight animal technology that need to be resolved are:

1. design and evaluation of the life support systems;
2. development and integration of bioinstrumentation;
3. agreement on animal conditioning methods and procedures for evaluating the monkey's progress through training;
4. identification of criteria for selection of flight animals;
5. definition of pre-flight operations.

These issues are intimately involved with hardware design and the overall engineering of the spacelab Large Primate Facility. The advisory committee contends that wherever possible, the design of the facility should provide optimum comfort and minimum stress on the monkeys, along with the maximal scientific capability. Thus the engineers need specific information from primate life scientists before the construction of the facility or life support subsystem can proceed. In order for this to proceed in a timely manner, scientists with experience both with large primates and also with NASA spaceflight procedures should be involved in the design, testing and evaluation of the spacelab Large Primate Facility. These points are discussed below in more detail.

1. Design and Evaluation of Life Support System

The design of the life support system includes environmental control, restraint, feeding, watering and waste management. This activity must involve both engineers and scientists. These issues must be agreed on in the beginning of the project before detailed design and construction of the facility can proceed. Consequently, it is necessary that the scientists involved have extensive experience with large primates and experience with spaceflight experiments. Considerable work needs to be done in this area especially in the design and verification of (1) the chair and restraint system to optimize animal comfort, minimize launch and reentry stress, and maximize compatibility with bioinstrumentation, and (2) other aspects of the life support system such as the urine collection system (design, evaluation of animal tolerance, reliability, etc.). We propose that the development and testing of these life support systems be done in laboratories that have expertise and experience in these areas.

2. Effects of Restraint on Physiological Variables

The restraint system must not only provide life support but should also be designed and tested to determine how physiological measurements will be affected and accomplished. The advisory committee is concerned that the restraint system may have an impact on the physiological system that future users of the facility will be interested in measuring. For example, various restraint systems affect the resting heart rate, and probably other

physiological variables. It will be necessary to have life scientists from various disciplines verify that the restraint system is compatible with those measures that will probably be used in future space flights.

3. Development and Integration of Bioinstrumentation

There is an obvious core of techniques that will be necessary to evaluate the large primate facility during ground based and spaceflight testing. These techniques include cardiovascular monitoring, measuring various body temperatures, catheterization, sleep recording, and operant conditioning. Considerable expertise in these techniques is already available is some university laboratories and these resources should be utilized.

4. Animal Training and Evaluation

To prepare monkeys for spaceflight a training regime must be developed that includes objective methods for evaluating the animals' progress. Some of the training conditions that must be identified are: what is standard training environment (isolation, noise, vibration, etc.); do the monkeys need centrifuge training or exposure to simulated microgravity; how will the effect of various levels of bioinstrumentation be determined; etc. There are various criteria that can be used to evaluate a monkey's progress through training, including behavioral observations, food and water intake, heart rate, circadian patterns and corticosteroid levels. These evaluation criteria need to be objectively examined and agreed on so that they can be used for testing the life support system and the impact of various levels of bioinstrumentation. Further, studies need to be conducted to determine how long is required for monkeys to adapt to the restraint system. It is well known that even highly trained monkeys require acclimation time at the beginning of each restraint session before various physiological and behavioral indices reach "normal" levels. This information will be vital in animal selection and definition of pre-flight operations.

5. Selection Criteria

To identify the starting pool of animals and their suitability as spaceflight candidates, criteria need to be developed. These criteria include health, size, behavior and other issues which might affect pre-flight selection. The scientific advisory committee should be involved in this activity. The selection criteria also need to be integrated so that, for example, it is clear that the animal is normal in the physiological systems that are known to be sensitive to microgravity and flight stress. The advisory committee should identify these physiological normative criteria.

6. Definition of Pre-Flight Operations

It is important that pre-flight operational constraints be evaluated. The key issues are the number of animals needed, their permanent housing location, travel schedule, bioinstrumentation/surgical schedule, training schedule and ultimate flight selection criteria. These issues will affect hardware development, training and integration facility capability, and other issues.

As noted above, a major advantage of working with rhesus monkeys is that these animals can be used for integrated experiments involving multiple measures. If the research plan is properly organized, a true integrative study can be conducted in which the interaction of diverse physiological systems can be assessed. For example, the quantification and localization of the headward fluid shift and the neurophysiological responses to this shift will allow a much more sophisticated evaluation than measuring either fluid shifts or neurophysiology alone. Since physiology is inherently an integrative discipline, the advantages that accrue from joint use of research subjects by different disciplines can outweigh the disadvantages of small sample size. The model experiment that we have developed requires both chronic and acute cardiovascular and neurophysiological monitoring, blood sampling, waste collection and operant conditioning. It is important that an experiment of such complexity be developed so that individual techniques and systems can be accurately evaluated.

In order to support a wide variety of physiological investigations, the rhesus spaceflight research facility will be quite complex. Both U.S. and Soviet experience has shown that it is prudent to gradually develop and test such a complex facility. The committee proposes that the rhesus research facility be tested over a series of flights in which components of the facility are added after validation of the basic life support and waste management system. For example, if two monkeys were used in each flight the following sequence would allow a reasonable scientific return at each stage, but still permit evaluation of the various components of the facility.

Flight 1. Minimal instrumentation of both monkeys
- verify life support and waste management
- monitor feeding, drinking, activity, gas exchange, excretory patterns and vital signs (body temperature and EKG) with telemetry, and perhaps arterial pressure and operant conditioning

Flight 2. Objectives of Flight 1, plus verification of cardiovascular instrumentation on one monkey and neurophysiology instrumentation for sleep and vestibular function on the second monkey
- Monkey 1 - monitor carotid pressure and flow, arterial and venous pressure, and collect blood samples (perhaps automatically) via catheters
- Monkey 2 - monitor sleep, brain temperature, and eye and head movements

Flight 3. Objectives of Flights 1 and 2 plus verification of integrated cardiovascular and neurophysiology instrumentation
- monitor cardiovascular and neurophysiological parameters on both monkeys
- test removability of the facility and verify that the animal can be used outside of the rack for provocative testing (e.g. in a linear and/or angular acceleration vestibular test facility, or in a LBNP test facility, or in an exercise test facility)

Procedures and techniques that have been verified or corrected will be carried over to the next stage, thereby slowly building up the level of complexity. Problems which may arise with life support or data collection should be able to be localized and corrected. If there were 12 to 18 months between flights, then there would be sufficient time to evaluate the results of the previous flight and factor these data into the next flight. This schedule could be accelerated to 2 test flights if the U.S. and Soviet experience over the next five years indicates that this is prudent. At the end of the test sequence, flight support personnel and facilities would have developed considerable experience with this animal model. Further, a data base for essential physiological parameters would be established, and many basic parametric studies would not have to be conducted. Rather, the animal facility would be ready for research on the mechanisms of microgravity induced responses.
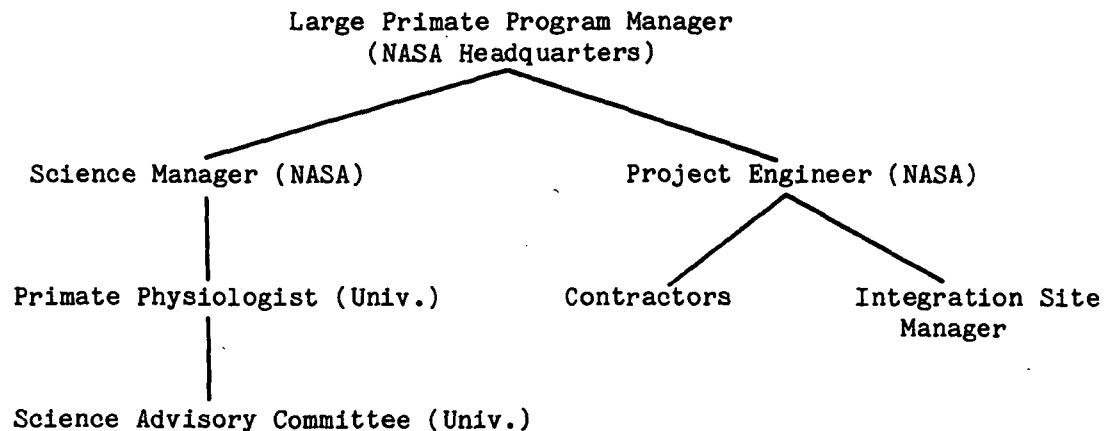
The facility which would be completed by the end of this implementation plan would be one which included both the necessary life support and waste collection systems for the large primate model, as well as the scientific apparatus necessary to conduct much of the physiological testing required by the various disciplines. Both the facility and this scientific support apparatus would thus be flight qualified. The design and engineering of the facility would have been done with an overall program in mind, so that the extension of experimental protocols to include long term spaceflight should require only minor modifications in the life support equipment. Most instrumentation to accomplish these scientific objectives of short term flight will also be used in longer term experiments, although new experimental objectives or inclusion of other disciplines may require a few experiment-specific hardware items. This approach will use the short-term capabilities of shuttle flights for development, flight qualifications and some scientific objectives while building toward the eventual goal of long-duration flight experiments.

MANAGEMENT PLAN

It is the impression of the Large Primate Advisory Committee that the Flight Experiment Program at NASA has considerable management and engineering expertise, but little expertise with large primates. As noted several times above, experience with large primates and NASA spaceflight procedures is essential for the timely development of this facility. There are numerous operational constraints that are associated with NASA flight projects that are not encountered in ground based biomedical research (eg. time lines, long lag time, extensive engineering, etc.). The significance of these constraints becomes apparent with experience in the system. Because of the time required for the engineering aspects of the project, important scientific decisions will have to be made in the near future. Prudent scientific advice will certainly be facilitated if both primate and spaceflight experience is present in the science advisory committee. In addition to providing advice, the members of the science advisory committee should also be involved in the development and testing of the animal technology areas. The laboratories and expertise of academic primate physiologists represent readily available resources that are not present in NASA or aerospace contractors. The involvement of academic physiologists in the animal technology areas is the most timely and efficient way to begin this effort.

The advisory committee feels that it is essential that in order to insure the maximum scientific potential from the rhesus facility, potential users should form an advisory committee that would be involved in the design, development and testing of this facility. The evaluations and recommendations of the reviewers should not only reflect their judgment and particular expertise; the reviewers should act as spokesmen for the scientific community in general and their research disciplines in particular. This will insure that the science done in the large primate facility is of the highest quality and of general interest. There are many research laboratories that have considerable expertise in these types of physiological monitoring. Utilization of this resource should lead to the most effective development of the large primate research facility.

Consequently, the committee proposes that the following organizational scheme be adopted:

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                      Large Primate Program Manager
                          (NASA Headquarters)


   Science Manager (NASA)                   Project Engineer (NASA)


   Primate Physiologist (Univ.)       Contractors        Integration Site
                                                              Manager


   Science Advisory Committee (Univ.)
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Science Manager: NASA individual with responsibility to oversee the science and animal technology implementation issues.

Project Engineer: NASA individual with responsibility for hardware construction, Spacelab integration and the NASA rhesus integration site.

Physiologist - A university physiologist with experience with large primates and space flight procedures who will coordinate the activities of the Science Advisory Committee.

Science Advisory Committee: A group of U.S. physiologists with primate and spaceflight experience. Their responsibilities will be to advise on the scientific capabilities of the Spacelab Large Primate Facility. Additionally, individuals in this group will play an active role in development and testing of the animal technology areas (eg. training procedures, urine collection, catheterization, etc.).

Integration Site Manager: An individual (NASA or contractor) that will manage the NASA site where the pool of flight animals are housed, and where integration of engineering development activities and animal technology (training, bioinstrumentation, etc.) will be done.

ACKNOWLEDGEMENT

APPENDIX I

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APPENDIX II

EVALUATION OF VARIOUS SPECIES FOR SPACE FLIGHT RESEARCH

RAT/RODENT

GENERIC

Advantages:
- small size (large N)
- readily available
- genetically defined disease states
- popular laboratory animal
- uniform populations available
- space flight facility already exists

Disadvantages:
- small size (limits instrumentation)
- horizontal posture
- weight distributed on 4 limbs
- small blood and urine volume limits sample size and frequency

CARDIOVASCULAR

Advantages:
- much known about rat CV system

Disadvantages:
- AIBS Scientific Review Group for Shuttle CV Sciences said the rat is an inappropriate model for studying CV responses to weightlessness, with the exception of studies on microcirculation
- dissimilarity of rodent and primate CV system
- small hydrostatic column
- horizontal posture
- big tail and caudal blood flow
- high resting heart rate (>250 bpm) (implies little vagal input)
- high heart rate and small size present severe limitations on instrumentation

VESTIBULAR

Advantages:
- much ground based data on anatomy
- flight data

Disadvantages:
- lateral eyes give differences in vestibular-ocular reflex
- orientation of vestibular apparatus
- little ground based data on vestibular physiology
- different vomiting reflex from higher mammals
- small size restricts instrumentation

MUSCULO-SKELETAL

Advantages: - genetic uniformity
- good data base
- there are flight data

Disadvantages: - classified as juvenile modeling M/S system
- horizontal system for load distribution
- differences in calcium and phosphate metabolism
  (the hypocalcemic rat does not become tetanic)
- small blood and urine volume

FLUID AND ELECTROLYTE

Advantages: - some ground base studies on fluid shifts (suspended
    rat model)
- popular model for renal physiology
- genetic strains provide important models (e.g.,
   Brattleboro strain)

Disadvantages: - size (small blood and urine volume)
- posture
- nocturnal

OTHER DISCIPLINES

Advantages: - a large number of subjects can be flown in a small space
- considerable data base on physiological regulation

Disadvantages: - nocturnal circadian rhythm organization
- thermoregulatory control different from primates
  (eg. surface to volume ratio means small thermal
  mass and large heat loss)
- small size presents problems for chronic
  instrumentation

RABBIT

GENERIC

Advantages:
- popular in immunological research
- Soviets have flown rabbits in space
- good size
- large Soviet literature on immobilized rabbits and morphology changes
- availability

Disadvantages:
- very susceptible to stress

CARDIOVASCULAR

Advantages:
- reasonable data base on CV physiology and neural control of circulation
- an accepted model for arteriosclerosis research

Disadvantages:
- CV reflex exaggerated (eg. bradycardia in stress)
- some gaps in current understanding of CV regulation (eg. few studies on CV regulation and exercise)
- distribution of CV output with stress
- large ear blood volume
- instrumentation and size limitations
- relatively small hydrostatic columns (better than rats, but still limiting)

VESTIBULAR

Advantages:
- extensively used in vestibular research

Disadvantages:
- do not have smooth ocular pursuit mechanisms (different from primates)
- questionable data base on first order vestibular response
- laterally placed eyes
- not used much as an alert preparation in neurophysiological research

MUSCULO-SKELETAL

Advantages:
- better than rat in that it has the equivalent of an adult remodeling phase
- data on immobilization in limb denervation preparation

Disadvantages:
- little known about calcium metabolism and endocrine regulation
- not a generally used model for musculo-skeletal research

FLUID AND ELECTROLYTE

Advantages: - modest gravity loading and urinary response data base
- popular model for isolated nephron research

Disadvantages: - questionable data base
- poor urine concentrating mechanism
- alkaline urine
- not a good model for human renal function

OTHER DISCIPLINES

Advantages: - used routinely in research on febrile thermoregulatory
response
- data base on gravity loading responses
- large head -- good for instrumentation

Disadvantages: - little data on sleep, circadian rhythms and other
areas of integrative biomedical physiology
- large ears and blood volume may play a role in gravitational
responses

CAT

GENERIC

Advantages: - good size
- popular for neurophysiology
- available

Disadvantages: - problem with ingestion by lapping in space
- poor in prolonged restraint
- respiratory diseases common
- horizontal posture
- public resistance

CARDIOVASCULAR

Advantages: - popular for study of neural control
- many anatomical pathways known
- tolerate instrumentation well

Disadvantages: - little or no hemodynamic data
- there are some species peculiarities
- little known about exercise physiology

VESTIBULAR

Advantages: - frontal placement of eyes
- species of choice for many studies on vestibular
  and vestibular-oculomotor systems
- susceptible to motion sickness
- good size

Disadvantages: - limit to ocular range of motion
- pharmacologically peculiar - some questions
  on drug responses, i.e. sedative dosage of
  morphine produces hyperactivity

MUSCULO-SKELETAL

Advantages: - remodeling system
- large size

Disadvantages: - limited data base

FLUID AND ELECTROLYTE

Advantages: -

Disadvantages: - genetic renal dysfunction (prone to kidney stones)
                - small data base
                - poor circadian rhythms

OTHER DISCIPLINES

Advantages: - tolerates chronic instrumentation
             - common animal model for many neural studies - esp.
               sleep

Disadvantages: - crepuscular with erratic sleep-wake cycle
                - poor circadian rhythms
                - little data base (other than neurophysiology)

DOG

GENERIC

Advantages:
- large size for instrumentation
- good restrain tolerance
- ease of handling
- commonly used in drug studies on earth
- good data on immobilization

Disadvantages:
- Soviet experience showed feeding and drinking problems with dogs in space (ingestion by lapping with tongue)
- quadrapedal
- public resistance

CARDIOVASCULAR

Advantages:
- the most commonly used animal for CV studies and therefore there is a substantial data base
- large enough size to give hydrostatic column effects in zero gravity
- basic understanding of human CV physiology based on work with dogs

Disadvantages:
- circulatory reflex control in exercise is different in dogs and humans
- distribution of cardiac output is different in dogs and humans
- dogs have more coronary collateral circulation
- dogs have a conical chest configuration

VESTIBULAR

Advantages:
- frontally placed eyes
- has been used in research on motion sickness

Disadvantages:
- substantial interindividual neuroanatomical variations
- very little data available on vestibular physiology

MUSCULO-SKELETAL

Advantages:
- large data base, including immobilization
- skeletal system responses similar to humans in many cases

Disadvantages:
- small data base on calcium metabolism
- horizontal posture
- some susceptibility to orthopedic problems

FLUID AND ELECTROLYTE

    <u>Advantages</u>:   - dogs popular for research on fluid balance and renal
                            regulation

    <u>Disadvantages</u>:   - poor circadian rhythms
                            - posture gives reduced fluid shifts in zero gravity

OTHER DISCIPLINES

    <u>Advantages</u>:   - good for bioinstrumentation
                            - used in exercise physiology (esp. thermoregulation)

    <u>Disadvantages</u>:   - thermoregulatory differences with humans
                            - poor circadian rhythms
                            - small data base on many physiological systems

SQUIRREL MONKEYS

GENERIC

Advantages: - small size (approximately 1 KG) permits large number
                per unit space.
             - restraint tolerance
             - primate and therefore anatomical and physiological
                similarities to humans
             - space flight facility already exists
             - circadian rhythm like humans

Disadvantages: - small size makes some bioinstrumentation difficult
                  and limits biological sampling
               - large tail is an important anatomical difference
                  from higher primates

CARDIOVASCULAR

Advantages: - upright posture gives hydrostatic column effects

Disadvantages: - high resting heart rate implies primary role of
                  sympathetic regulation
               - too small for CV instrumentation
               - little known about neural regulation
               - more prone to systemic infection than rats and dogs

VESTIBULAR

Advantages: - best data base on primary vestibular afferents
             - some good data on vestibular-ocular reflex
             - susceptible to motion sickness (seen in ground studies
                and parabolic flights)
             - consistent stereotaxic uniformity

Disadvantages: - unlike humans, there is idiopathic positional nystagmus
               - small size limits number of brain penetrations

MUSCULO-SKELETAL

Advantages: - nutritional similarities with humans (but high protein
                requirement)
             - adult bone remodeling phase

Disadvantages: - differ from humans in vitamin D metabolism
               - no data base
               - small blood and urine volume limits experimentation

FLUID AND ELECTROLYTE

Advantages:
- good data base including upcoming space flights
- restraint tolerance permits accurate urine collection
- renal responses to fluid shifts comparable to humans
- diurnal circadian rhythms

Disadvantages:
- small blood volume limits blood sampling

OTHER DISCIPLINES

Advantages:
- valuable size for scaling studies
- good data base on thermoregulation and circadian rhythms

Disadvantages:
- some (minor) circadian rhythm differences from humans
- very reduced sweating response
- some minor difference from humans in sleep patterns

RHESUS MONKEYS

GENERIC

    <u>Advantages</u>:   - large size permits substantial bioinstrumentation
                      - excellent physiological and anatomical similarities to
                         humans
                      - availability -- domestic breeding colonies exist
                      - trainable and restrainable
                      - data base from Soviet biosatellite
                      - upright posture

  <u>Disadvantages</u>:   - difficult to handle
                      - susceptible to Herpes B
                      - large size reduces the number of individuals that
                         can fly on a mission

CARDIOVASCULAR

    <u>Advantages</u>:   - data from Soviet biosatellite
                      - reasonable data base from ground studies on hemodynamics
                      - thorax to lower limb ratio approximately similar to humans
                      - like humans, and unlike most other species, cerebral blood
                       flow is primarily via the internal carotid.

  <u>Disadvantages</u>:   - little information on neural control
                      - more prone to systemic infection than rats or dogs

VESTIBULAR

    <u>Advantages</u>:   - at least 4 different labs currently studying primary
                       vestibular neurons
                      - vestibular-ocular reflex similar to humans
                      - instrumentation for CNS recording developed
                      - large brain allows multiple sampling

  <u>Disadvantages</u>:   -

MUSCULO-SKELETAL

    <u>Advantages</u>:   - reasonable data base for normal and immobilized
                       preparations
                      - metabolic kinetics similar to humans
                      - easy to biopsy
                      - established hormonal assays

  <u>Disadvantages</u>:   - some differences in Vitamin D metabolism

FLUID AND ELECTROLYTE

Advantages: - size means good blood volume
- some water immersion data suggesting similar responses humans
- aldosterone control system almost identical to humans
- renal handling of volume load similar to humans

Disadvantages: -

OTHER DISCIPLINES

Advantages: - good circadian rhythms
- good system for chronic CNS instrumentation
- popular animal model for physiology and behavior
- female reproductive physiology similar to humans
- large behavioral repertoire
- good size animal for biological scaling

Disadvantages: - not a large data base on circadian rhythms

HUMANS

GENERIC

Advantages:
- primary object of biomedical and clinical studies
- ability to select healthy or "normal" subjects
- subject cooperation
- number of potential subjects available

Disadvantages:
- medical and legal concerns, especially for techniques involving invasive instrumentation and biopsies from healthy people
- any experiment will take time away from operational objectives
- problem with informed consent (conflict between agreeing to serve as subject influencing selection for flight)
- potential risk of long term consequences from research procedures
- difficulty in monitoring cerebral spinal fluid
- interindividual variations

CARDIOVASCULAR

Advantages:
- ability to conduct limited invasive studies on circulation (eg., sample blood, measure arterial and venous pressure, cathaterize venous system, and infuse drugs)
- there are non-invasive measures available for blood pressure, flow and distribution

Disadvantages:
- cannot study basic mechanisms using non-invasive techniques
- almost all indirect, non-invasive measures have limited resolution and substantial statistical variance, and may not be able to detect subtle changes
- inability to biopsy many sites and directly test some tissue (eg. myocardial biopsy)
- cannot study response to various drug infusions (eg. alpha and beta blocking agents and their agonists)

VESTIBULAR

Advantages:
- humans provide ability to interact and conduct assigned tasks
- tremendous data base
- ease of psychophysical measurements
- introspective reporting can provide new insight, especially on visual-vestibular interaction (eg. reports on movement illusion and other changes in perception)

Disadvantages:
- vomiting can lead to aspiration pneumonia
- loss of operational time resulting from sickness
- almost all measures of the central nervous system must be indirect
- no ability to monitor pathways
- not possible to directly measure vestibular sensory function

MUSCULO-SKELETAL

Advantages: - can obtain data on muscle strength non-invasively
- CAT scan and NMR technology will be available for bone and muscle studies
- metabolic balance studies can be conducted in space

Disadvantages: - need biopsies of bone and muscle to obtain information on morphology (fiber type, bone cells, etc.)
- impossible to obtain direct information on osteoblasts and osteoclasts
- impossible to directly measure bone strength
- poor tolerance for experimental diets

FLUID AND ELECTROLYTE

Advantages: - long term neurohumoral regulation can be monitored by intermittent blood sampling and urine collection
- provocative tests available for studying regulation (eg. LBNP and LBPP)

Disadvantages: - not able to open control loops in humans
- cannot directly test central nervous system influences
- fluid shifts and volume changes hard to determine quantitatively

OTHER DISCIPLINES

Advantages: - cooperative subjects greatly facilitate experimental measurements
- great deal of data available

Disadvantages: - long life span makes it difficult to detect aging effects
- limited access to subject for continuous metabolic gas monitoring
- difficult to control 24-hour environment precisely
- difficult to instrument for multiple continuous simultaneous physiological measures
- invasive measures (e.g. brain temperature) not available