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An Overview of Gravitational Physiology

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SUMMARY

This paper reviews the main findings from the American and Soviet programs of gravitational physiology, dating back to the first spaceflights about thirty years ago.

Although the main focus is on the response of human subjects and experimental animals to the weightless condition obtained aboard orbiting spacecraft, the data from on-the-ground g load manipulation (by centrifugation, immobilization or clinostat rotation) are also summarized.

It is evident after many hours of human spaceflight that humans, who have already conquered environments as hostile to life as the polar regions and the bottom of the oceans, can also withstand the drastic changes in gravitational loads imposed by space travel. Nevertheless, the data suggest that about half of the space travelers exhibit vestibular reactions similar to those related to motion sickness, which may impair their performance. Further, the microgravity linked cardiovascular deconditioning, bone calcium changes, and muscle atrophy might pose a threat to the health of space crews, especially to their ability to readapt to normal gravity on return to Earth after such long duration missions as a trip to Mars. This justifies intensive research to understand the pathogenesis of the "weightlessness syndrome," which, as noted elsewhere, has a symptomatology akin not only to the manifestations of disuse atrophy but to the effects of premature aging as well.

Most space physiology research has directly addressed the elucidation of the mechanisms responsible for the debilitating effects of zero g on human subjects and the development of countermeasures. In addition to the research on the physiological and pathological responses to altered g, numerous experiments of a more fundamental nature have been attempted to clarify the cellular and molecular effects of hypergravity and weightlessness and gain information on the role played by gravity in shaping the structure and function of animals. The data, although still preliminary, suggest that weightlessness is not mutagenic and that the fundamental processes of mitosis, cellular differentiation and embryonic development are not directly influenced by microgravity. On the other hand, at higher levels of biological organization, i.e., at the organ and organism levels, both microgravity and hypergravity trigger a variety of physiological responses (e.g., disorientation, impaired locomotion, bone and muscle loss) which, because of their metabolic cost, may influence processes such as development and aging that are modulated by the rate of oxygen utilization.

INTRODUCTION

Although only with the recent advent of spaceflight has it become possible to expose animals, including humans, to the whole range of gravitational forces (from near weightlessness to high-g loads), a great deal of information on the effects of altered gravity has already been obtained. However, some studies are only available in technical reports issued by the National Aeronautics and Space Administration (NASA) of rather limited circulation or in the Russian language in Soviet publications. Further, although a vast amount of experimental data have been gathered, very seldom is an attempt made to provide a unifying hypothesis on the effects of high and low gravity. In our opinion, much of the controversy surrounding the cellular and molecular responses to gravity and the physiological effects of very long duration spaceflights might be cleared up if we assume that most reactions of metazoans to altered gravity are linked to two general responses, namely disorientation and bioenergetic modulation (because of higher or lower functional demands).

In support of the above view, we present here the most salient data from the American and Soviet programs of gravitational physiology, followed by a discussion of our hypothesis on the relative insensitivity of genetic mechanisms to gravity changes, and on the key role of disorientation triggered behavior (and concomitant metabolic adaptation) in the response of metazoans (from insects to humans) to altered gravity.

Our focus will be on the most novel aspect of gravitational physiology, i.e., on the response of humans and animals to the effects of the near weightless condition obtained aboard orbiting spacecraft. However, since gravitational physiology is concerned with the whole range of g-loads, we will also summarize the most important data from exposure of animals to altered g levels obtained by centrifugation, rotation in clinostats, immobilization and so forth. We emphasize the general mechanisms of the "altered gravity syndrome(s)" rather than the technical details. Therefore, the reader interested in comprehensive coverage of individual topics is referred to the monographs and articles cited throughout the review.

This paper is specifically addressed to the newcomers to the field of gravitational physiology that originated about thirty years ago with the flight of the dog Layka aboard Sputnik-2. The paper includes a summary of the main accomplishments of the pioneering gravitational physiologists and an assessment of how much more work needs to be done in order to understand the biological role of gravity and the mechanisms responsible for the myriad effects resulting from its nullification or augmentation.

HISTORICAL PERSPECTIVE

The subject of the biological effects of gravity has attracted the attention of some of the greatest theoretical scientists. More than 300 years ago Galileo (ref. 1) recognized that when gravitational loading exceeds the cohesive forces that determine the strength of materials, a limit is reached for the size of living organisms.

The role of gravity in shaping the structure of plants was recognized by Darwin, who a century ago used the term "geotropism" and devoted a great part of his "Power of Movement in Plants" to this subject. As pointed out by Soffen (ref. 2), other examples of early recognition of the physiological effects of gravity were the realization that changes in gravitational vectors influence the cardiovascular system and that the vestibular system of vertebrates plays a gravity-sensing role.

In the last quarter of the 19th century the Russian mathematician Konstantin E. Tsiolkovsky (ref. 3) wrote a treatise entitled "The Free Space," which is the first scientific paper on the possibility of using rockets for manned flight. Tsiolkovsky was interested not only in the engineering aspects of flight but in the biomedical problems as well, and his predictions of the effects of weightlessness were amazingly accurate: "We shall not have weight, only mass. We can hold any mass in our hands without experiencing the slightest weight... Man does not press himself against anything... There is no top or bottom." This farsighted scientist did not limit himself to theoretical speculations. He carried out centrifugation studies on insects and chickens and showed that "the fivefold increase in their weight produced no harmful effect on them." By contrast, he predicted that the anatomy and physiology of animals and plants might be modified as a result of exposure to a weightless environment. At the turn of the 19th century, Tsiolkovsky rounded out his accomplishments as an astronautic pioneer by proposing two methods for simulating the weightless state on the ground: free fall and immersion in a fluid.

As reviewed elsewhere (ref. 4), gravitational physiology research was spurred by the development of high performance aircraft (ref. 5). Since then, considerable attention has been paid to the study of the physiological adaptation and pathological reactions occurring in humans and experimental animals as the result of exposure to high-g fields produced by linear acceleration and centrifugation (refs. 6 and 7). These studies had a practical reason, since high accelerations could be life-threatening, as shown by the "gray-outs" and "blackouts" occasionally experienced by fliers performing sharp turns during early airplane races.

Before the start of the spaceflight programs of the U.S.A. and the Soviet Union, the effects of brief periods of weightlessness were explored by exposure of experimental subjects to free fall (ref. 8) and to parabolic flight on jet aircraft (ref. 9).

The initial investigations in space gravitational physiology consisted of a series of suborbital flights in which mice, rats, and monkeys were launched in the nose cones of ballistic missiles and were exposed for very short periods of time to a number of stresses including weightlessness (ref. 10). In the period 1948-1961 a total of 17 primates, starting with the Rhesus monkey "Albert" and ending with the chimpanzee "Ham," were sent aloft in a program of spaceflight that was started under the support of the U.S. Armed Forces and was later transferred to the newly created NASA.

At about the same time, the Soviets had initiated a vigorous program of space physiology, which used dogs as experimental animals (ref. 11). From 1951 until the end of 1960, an impressive total of 25 dogs had been used in these flights. And, in 1957, another dog named "Layka" became the first traveler in an orbitting artificial satellite, in its flight aboard Sputnik 2. Shortly thereafter, the spaceflight of Yuri Gagarin in Vostok 1 had a tremendous impact on world opinion and awoke interest in the conquest of space for military and civilian use as well as in the biomedical research needed to ensure the safety of the crews (ref. 12).

As could be expected, the first animal flights were performed in rather small and primitive vehicles. Subsequently, animals were sent into space by Soviet space biologists in their unmanned but highly effective Cosmos biosatellites and, as fellow passengers of the cosmonauts, in manned vehicles such as the small Vostok and the roomier Soyuz (fig. 1) and Salyut (fig. 2).

The American manned spaceflights, from the Mercury program to the highly successful Apollo moon flights, and especially the Skylab missions, provided a wealth of information on the response of human subjects to weightlessness (refs. 9, 12, and 13–22). However, in comparison to the Soviet program, there has been a relative lack of fundamental biology experimentation (tab. 1) in the earlier NASA flights, since on few occasions have animals accompanied human crews aboard American spacecraft.

The NASA program of space physiology relied on the use of automated satellites, a few flights of which took place in the sixties (refs. 10 and 23). Later, in the seventies and eighties, a wealth of data was obtained as the result of a joint U.S./U.S.S.R. Biological Satellite Program (ref. 24). Under the auspices

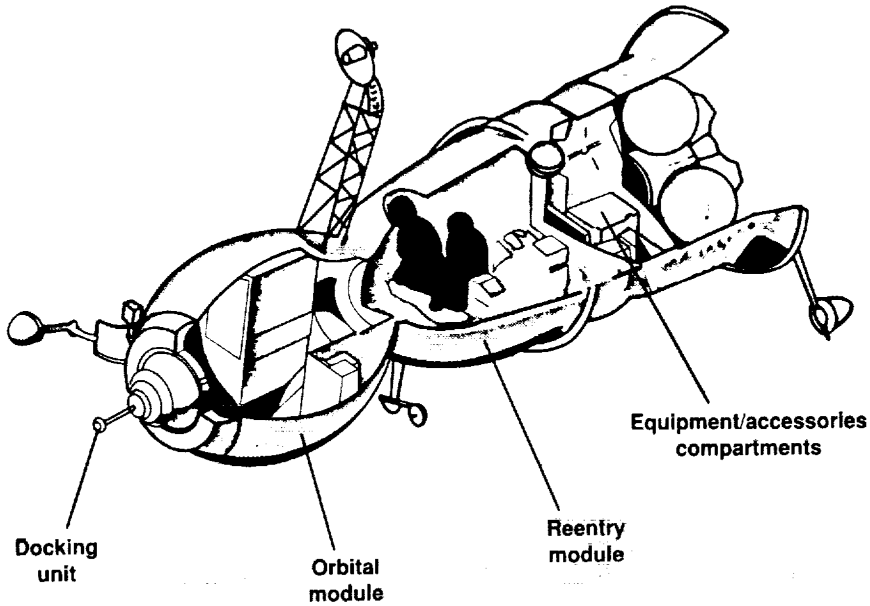

Figure 1. Soyuz vehicle. (Reproduced from ref. 16.)

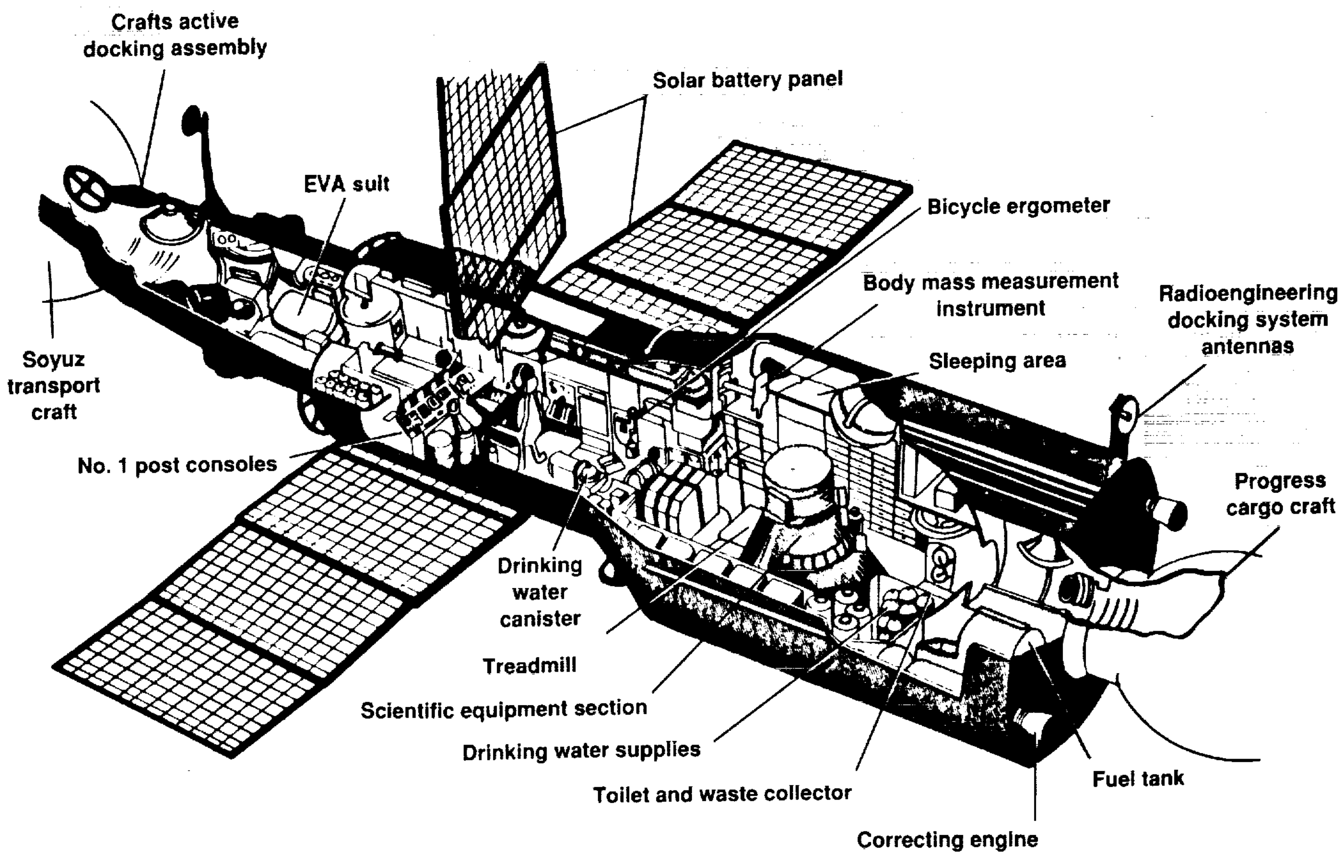

Figure 2. Salyut-6 space station. (Reproduced from ref. 16.)

Table 1. First exposure of mature members of animal species to microgravity aboard orbiting spacecraft (S: Soviet flight. A: American flight). (From refs. 10, 11, 63, 245-247.)

Mission	Year	Duration, d	Animal
Sputnik-2 (S)	1957	7	Dog
Space-Satellite (S)	1960	1	Guinea pig
			Rat
			Mouse
			Fruit fly
Biosatellite-2 (A)	1967	2.5	Wasp
Cosmos-211 (S)	1968	5	Tortoise
Biosatellite-3 (A)	1969	8	Monkey
Zond-8 (S)	1970	7	Flour beetle
OFO-1-A (A)	1970	6	Bull frog
Skylab-3 (A)	1973	59	Spider
Soyuz-19 (S)	1975	7	Fish
Apollo-17 (A)	1975	12	Pocket mouse
Shuttle OSS-1 (A)	1982	5	Honey bee
			Moth
			House fly
Shuttle STS-5 (A)	1982	5	Sponge
Shuttle STS-7 (A)	1983	6	Ant
Shuttle STS-51 (A)	1985	7	Brown planaria
Shuttle STS-61 (A)	1986	7	American dog tick

of this international venture, a variety of animals and other biological species were exposed to periods of up to 20 days of microgravity aboard unmanned Cosmos biosatellites. It is expected that the Shuttle, with its relatively large laboratory facilities (figs. 3 and 4) will allow better controlled experiments on the biological effects of weightlessness than have been possible in earlier research. Moreover, we can expect a steady Soviet effort in the areas of human and animal gravitational physiology using the permanent space station Mir. It is of particular interest from the viewpoint of this review that this station will contain dedicated laboratory modules, including one for biomedical research (Medilab), which may be operational in the early 1990s (ref. 25).

The increasing international collaboration in space research under the auspices of NASA, the European Space Agency (ESA), and the Soviet Union promises a bright future for gravitational physiology research.

DEFINITIONS AND MODELS FOR PRODUCTION OF ALTERED GRAVITY

As pointed out by Pace (ref. 26) the term "gravitational physiology" was coined at the 1971 meeting of the Committee on Space Research (COSPAR), because "it was becoming clear that the study of the

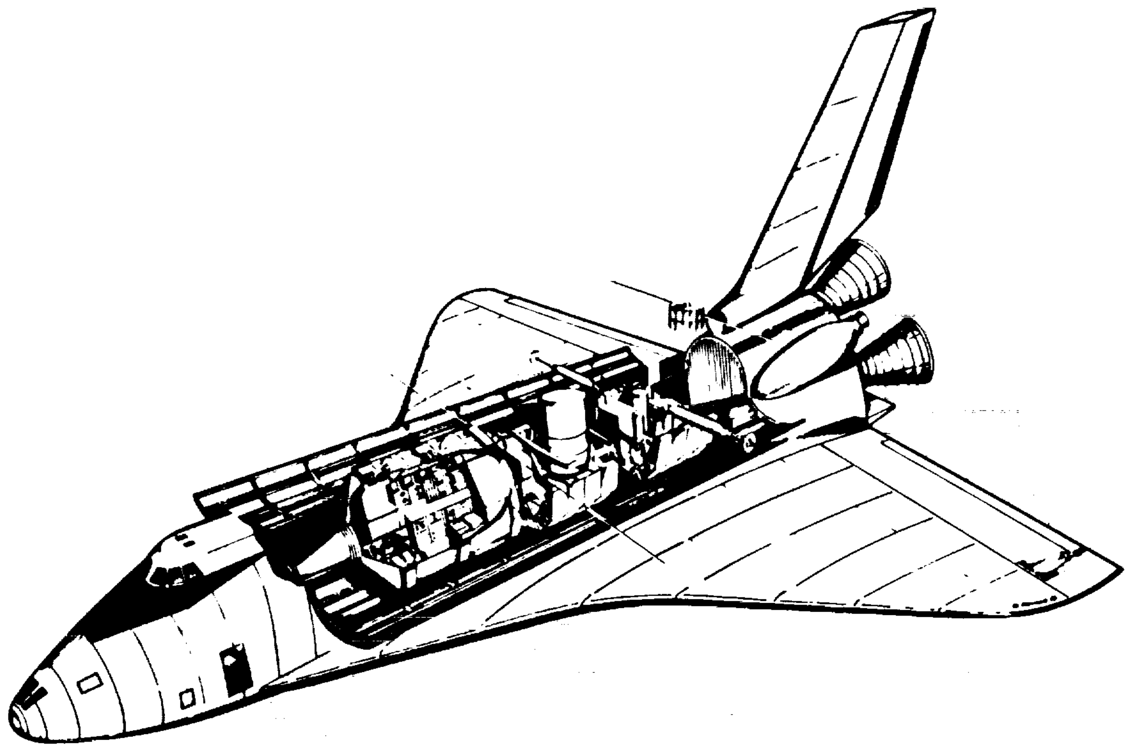

Figure 3. Drawing of the present American Space Shuttle showing the Spacelab. (Reproduced from ref. 16.)

effects of the space environment on Earth organisms was both feasible and valid scientifically as a branch of environmental physiology." (See also refs. 135 and 136.)

More recently, H. Bjurstedt (ref. 27) pointed out that "gravitational physiology encompasses the functions of living matter in response to the full range of gravitational forces both above and below the force of gravity exerted on stationary objects on the surface of the Earth." He further notes that "one can look at gravitational physiology in terms of problems belonging to three interconnected areas, viz., those dealing with man's health and survival in space, the use of weightlessness in spaceflight as a tool for studying fundamental issues in biology and medicine, and ground-based research aimed at simulating the effects of gravitational forces greater or smaller than the norm of Earth gravity."

The physical factors involved in the production of weightlessness are discussed in detail by Smith (ref. 28) who points out that from the physicist's point of view, a body could be weightless only in the absence of accelerative forces, which, by the Law of Universal Gravitation, is theoretically impossible. However, weightlessness can be simulated by free-fall (unrestrained movement under the influence of the ambient forces) in diving airplanes, in the flight maneuver known as "Keplerian arc" (performed by high performance aircraft), and in orbiting satellites (where the centrifugal force counteracts the pull of the Earth). In Smith's words: "It is obviously conducive to progress to adopt a generic term weightlessness to cover these varied conditions without demonstrable weight and their effects." This meaning of weightlessness without reference to its component physical factors has been recommended by NASA (ref. 29), which provides the following two criteria for the weightlessness state: (1) A condition in which no acceleration, whether of gravity or other force, can be detected by an observer

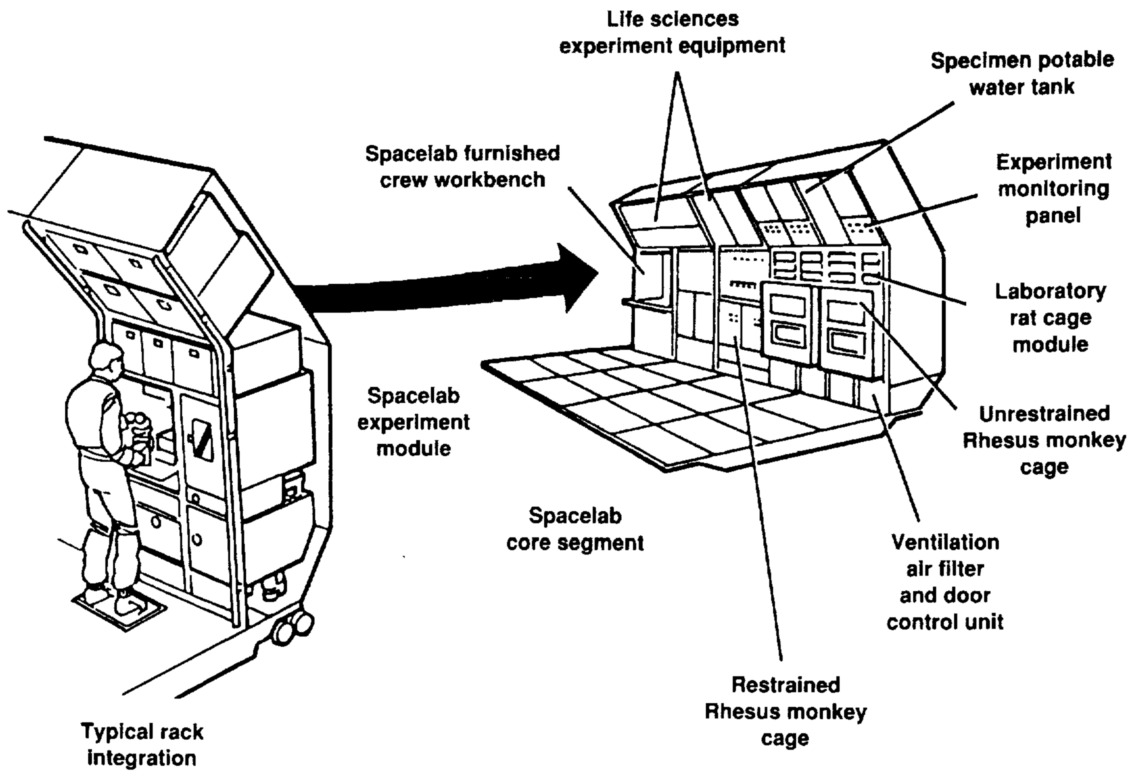

Figure 4. Sketch of Spacelab showing a typical set of Spacelab racks with integrated equipment.

within the system in question. (2) A condition in which gravitational and other external forces acting on a body produce no stress, either internal or external in the body.

No experimental procedure achieves total nullification of the gravitational and acceleration force. Therefore, hypogravity or microgravity are more correct denominations of the above-mentioned states than weightlessness or 0 g. In the present review all these terms are considered as synonymous.

The acceleration loads to which an animal or human subject is exposed are expressed as fractions or multiples of g, which indicate the number of times that the weight of a body has been increased by a given acceleration in comparison to the normal terrestrial gravitation, in other words, as the ratio of the dynamic weight to the static weight.

Gravitational physiology research has taken advantage of a number of experimental devices such as bed rest and water immersion for human subjects (refs. 21 and 30–43), and body suspension and immobilization for animals (refs. 44–56), which, because of the associated hypokinesia and hypodynamia, simulate at least some of the effects of space weightlessness. Horizontal rotation in clinostasts (a procedure widely used by plant physiologists to reproduce the effects of weightlessness on leaf orientation) is also useful to study the effects of gravity nullification on cells and small animals (ref. 57).

The first experiment on prolonged exposure of mammals to hypergravity-like conditions was reported by Matthews (ref. 58) in 1953. This investigation, in which rats were kept for up to one year at fields of 3 g and 6 g, has been followed by a number of similar studies in the U.S.A. and elsewhere, and by the construction of large centrifuges, specially designed for long duration exposure to high-g loads of animals ranging in size from mice to dogs (refs. 59–61).

The study of the physiological responses to chronic acceleration are of obvious importance for identification of processes that are gravity sensitive and therefore worthy of study under weightlessness. Thus, chronic centrifugation studies not only provide a wealth of information on the physiological effects of the upper range of the gravitational variable, but also help to define which experiments are worth the investment in the considerable time and resources needed for development as an in-flight study (tab. 2).

BIOMEDICALLY ORIENTED RESEARCH

General Physiological Reactions in Human Subjects Exposed to Microgravity

Before the first spaceflights, there was speculation that lack of gravity might be very hazardous or even lethal to animals and humans. These misgivings were dispelled by the evidence that higher animals such as dogs, monkeys, and even humans could successfully resist all the stresses associated with ballistic and orbital flight. Thus, on the basis of the studies performed during and after the American

Table 2. Standard Soviet procedures for on-the-ground support of animal flight experiments. (Summarized from Ilyin, ref. 248.)

Stage 1	Development of flight programs and experimental protocols Selection of animal models and training methods Development of life support systems Development of scientific equipment Evaluation of mockup of flight units
Stage 2	Veterinary and physiological examination of animals Placement of animals onboard the biosatellite Final testing of life-support system and scientific equipment Prelaunch monitoring of capsule environment
Stage 3	Acquisition and processing of telemetric information Monitoring of the flight experiment Synchronous experiment in the biosatellite mockup Vivarium control experiment
Stage 4	Biomedical investigations at the recovery site in a field laboratory Transportation of animals and biomaterial to Moscow Laboratory investigations Analysis and discussion of results Preparation of reports

Mercury-3 flight, it was concluded that "No disturbing sensations were noted during weightlessness and astronaut physiological function appeared in no way to be impaired...Physiological responses were consistent with intact conscious performance during all of flight. Responses to 5 min of weightlessness were uneventful" (ref. 10).

Later flights of much longer duration, including the Skylab missions, and progressively longer Soyuz and Salyut flights clearly showed that space travel could be tolerated by humans but that weightlessness triggered a host of physiological adaptations and even some borderline pathological processes which might set a limit to the time that humans could safely stay in space (refs. 4, 11, 13–19, 43, 52, and 62–81).

Exposure to microgravity does not seriously impair performance (refs. 10, 82, and 83), since, as found out in the Skylab-4 mission, the astronauts were capable of normal motor-sensory activities during the flight. Of great interest as regards the ability of crews to perform in space was the observation that "None of the crewmen experienced any noticeable deterioration throughout the mission in performing tasks that required them to handle experiments and controls." Nevertheless, about 50% of the travelers experience a certain degree of malaise, similar to motion sickness. This is an extremely complex disorder of spatial analysis, which apparently builds up under the influence of disturbed impulses from the otolith (ref. 84) a decrease in skin and propioceptive reception and a relative predominance of afferentiation from the semicircular canals of the labyrinths (ref. 85). According to Simonov (ref. 22), humans can be divided into two basic groups according to the character of their reactions to weightlessness. The first group experiences sensations of falling and fear, suddenly replaced by euphoria. In this group, disorders of visual function may also appear. In the second group of subjects, the feelings of falling, fear, and euphoria are absent. On the other hand, these subjects experience spatial illusions of flying upside-down, accompanied by disorders of the motion sickness type. Usually, nausea and vomiting diminish after adaptation, although certain persons seem incapable to adaptation. Most space travelers evaluate the state of weightlessness as pleasant, if abrupt head movements are avoided.

One of the first observations from the space programs of the U.S.A. and the Soviet Union was that weightlessness results in a shift of fluid from the legs towards the torso and the head, which may cause some discomfort. This fluid redistribution is accompanied by a certain degree of cardiovascular deconditioning that may even include some loss of myocardial tissue and/or of intrachamber blood content (refs. 16, 17, and 20).

The effects of spaceflight on the heart and on body fluid distribution have been quantified by impedance measurements on four astronauts, during the Spacelab Mission D1. There was a fluid loss of about 2.5 liters per person, and cardiac output was increased over 30% of control values by the second day of flight, while on the fourth day its values were lower than preflight. The resting heart rate was below the normal preflight levels, which suggests that exposure to microgravity resulted in an enhanced parasympathetic activity (ref. 86).

The detailed Skylab studies confirmed observations from earlier manned missions that weightlessness induces a decrease of red blood cell mass of the order of 5 to 12%, through the first weeks of flight. This result of exposure to the space environment was not linked to intravascular hemolysis, and therefore splenic trapping fo the red blood cells seems the most likely mechanism although reduced cell formation may also occur (refs. 75 and 87).

Another interesting effect of spaceflight is a decrease of vital capacity which reverts to normal values after readaptation to Earth gravity and thus far has not had a significant impact on the health of astronauts or cosmonauts (refs. 10 and 13).

Exposure to weightlessness results in a host of adaptive changes in the musculoskeletal system that, although compatible with life in the weightless environment, might impair the ability for uneventful readaptation to normal gravity upon return to Earth. Among the most refined research performed on this problem was the electromyographic probe of skeletal muscle function performed during the "Apollo-Soyuz Test Project" (refs. 10, 16, and 74), which showed that, after nine days of spaceflight, both upper and lower extremity muscles suffered changes in excitability similar to those in pathological processes, such as myopathy, associated with random loss or reduced activity of muscle fibers. These effects of microgravity on muscle physiology are accompanied by postural changes (fig. 5), and an appreciable loss of calf muscle (which can be partially prevented by vigorous in-flight exercise), a negative nitrogen balance and an increase in the urine of nitrogen, magnesium, and calcium (refs. 18 and 19).

According to Whedon et al. (refs. 88 and 89) both muscle and mineral loss occurred despite the implementation of an exercise regimen on most flights. Thus, there seems to be a consensus among space physiologists that, unless protective measures can be developed, musculoskeletal function is likely to be impaired during long duration spaceflights, such as future missions to Mars.

The above NASA results are in general agreement with the observations of Soviet physiologists, including those performed on the cosmonauts who remained aboard the space station Salyut-6 for extended periods of time, ranging from 96 to 185 days. As summarized by Kozerenko et al. (ref. 74), "the major factor responsible for the pathogenic effects of weightlessness is the decrease of the weight-bearing loading on certain systems of the body due to the absence of weight and related mechanical tension." According to these Soviet authors, the cardiovascular system showed the most pronounced changes, including an increase in the pulse-blood filling of cerebral vessels, which returned to normal at

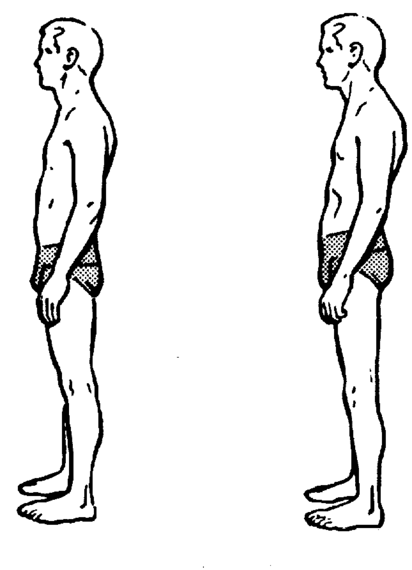

Figure 5. Schematic representation of postural changes due to spaceflight. (Reproduced from ref. 16.)

only 3-4 months after return to Earth. One of the most interesting effects of these long duration flights was that the postflight reactions to head-down tilt in a supine position were inversely proportional to flight time. Apparently, the increased tone of upper body vessels and their decreased distensibility (ref. 90) play a certain role in the mechanisms of adaptation to weightlessness-induced fluid shifts (refs. 91–93). There was a negative potassium balance (probably associated with muscle loss) and a decrease in the calcium concentration of the cosmonauts' bones, which after the 175-day Salyut flight reached the range of a 3.2-8.3% decrement. Interestingly, as ponted out in table 3 and figure 5, some of the reactions caused by microgravity are very similar to the effects of normal aging (see also refs. 94-96).

The subject of hormonal regulation in spaceflight of varying duration has been dealt with by Gazenko et al. (ref. 69). According to these Soviet authors, extensive biomedical studies carried out onboard the Salyut stations and in ground based simulations of weightlessness suggest that there are significant differences in the mechanisms of acute and delayed adaptive responses to microgravity. Apparently, after short term flights there is a stimulation of the pituitary-adrenal system and an adequate response of the hormonal homeostasis. By contrast, after long term flights (1-8 month duration), there is a greater production and metabolism of dopamine and DOPA, which do not produce an appreciable effect on the target organs but can compete with epinephrine and norepinephrine for the receptor binding sites, thus decreasing their functional activity. This results in important disturbances in carbohydrate and lipid methabolism, bioenergetics, aminoacid, and vitamin balance. In summary the specific homeostatic alteration of the microgravity syndrome could be linked to "a mismatch between a significant

Table 3. Similarity of the detrimental effects of normal aging and of exposure to space weightlessness. (From ref. 187.)

Cardiovascular system				
Reduction in cardiac output	S	C		
Increase in blood pressure	S	A		
Respiratory system				
Decrease in vital capacity	S	A	C	
Musculo-skeletal system				
Decrease in grip strength	S		C	
Decrease in lean body weight	S	A	C	
Decrease in muscle mass	S	A		
Collagen increase in muscle	S			R
Fat infiltration of muscle	S			R
Bone demineralization	S	A	C	
Adrenal cortical function				
Decrease in urinary excretion of total 17-hydroxicortico-steroids	S	A	C	

S = Changes found in human senescence.
A = Changes found in American astronauts.
C = Changes found in USSR cosmonauts.
R = Changes found in rats (exposed to weightlessness – 25 days in a COSMOS flight.

stimulation of the sympatho-adrenal system and an inadequate manifestation of the biological effects of catecholamines."

In her excellent review of the Soviet space program, Victoria Garshnek (ref. 64) concludes that the long duration cosmonaut flights, including the 326-day mission of Romanenko, show that "extended human spaceflight has become an operational reality, although physiological problems have by no means been eliminated." In addition to strenuous exercise, lower body negative pressure, fluid and electrolyte supplements and drugs have been used routinely by the Soviets to improve readaptation to 1 g upon return to Earth. Nevertheless, after long duration flights there is a great deal of orthostatic intolerance during readaptation to 1 g, which impeded the crews of the 237-day and 326-day flights to perform efficient work for several days after landing. Garshnek points out that these findings strongly support the need to provide countermeasures to the deleterious effects of spaceflight on humans if crewmembers are to be able to work productively on the Martian surface as well as upon return to Earth gravity.

In view of the variety of physiological responses resulting from microgravity, it is not surprising that a considerable effort has been addressed in both the U.S.A. and the Soviet Union to the elucidation of the mechanisms involved and to the development of protective measures for safe long-duration flights. For obvious reasons, which will be discussed below, a great amount of this work has been done on animal models.

Weightlessness Simulation in Human Research

Nicogossian and Parker (ref. 16) point out that, although it is not possible to produce zero gravity in ground-based studies, one can obtain a great deal of information relevant to the response of humans to weightlessness by using a variety of microgravity analogs. Since this subject has been covered in detail elsewhere (refs. 31, 33, 36, and 97), we will only offer a summary of the most important data from human exposure to microgravity simulation. Many of the physiological adaptations caused by the widely used bed-rest model of hypokinesia, such as bone calcium loss, are strikingly similar to those observed in human subjects during and after spaceflight. However, the deconditioning induced by prolonged bed rest in the horizontal position differs in some important aspects from that resulting from spaceflight microgravity. Thus, although vestibular deconditioning may be associated with some of the postural disturbances resulting from bed rest, this procedure does not lead to the full range of vestibular disorders linked to spaceflight (ref. 98).

Apparently, bed rest with head-down tilt (antiorthostatic bed rest) reproduces the early physiological response to microgravity more closely than the horizontal posture, especially as regards the cephalad fluid shifts that result in facial puffiness and in the subjective feelings of fullness in the head and nasal congestion (ref. 38). However, as shown by catheterization studies (ref. 39), the fluid shifts during bed rest are not accompanied by a persistent increase in intravascular pressure as it occurs during exposure to microgravity.

A joint U.S.A.-Soviet study on the effects of seven days of horizontal bed rest in comparison to seven days of $-6°$ head down tilt showed that, although both treatments have similar physiological effects, the head down tilt results in more evident cardiac deconditioning (ref. 67).

In a NASA study, periods of 10-15 days of bed rest were followed by centrifuge runs of up to 3 g as part of a program to simulate Shuttle flights (refs. 21 and 33). The main conclusion of this study was that tolerance to acceleration decreases following bed rest, primarily because of a reduction in plasma volume. Interestingly, the data suggest that older subjects have a better tolerance to centrifugation (after bed rest) than younger subjects.

While bed rest (in the horizontal position or with head down tilt) has been favored as the model of choice for microgravity simulation in cardiovascular research, water immersion has been chosen as a suitable analog of weightlessness by space physiologists interested in renal circulatory reactions (ref. 31). The reason is that immersion is quickly followed by an increased diuresis with concomitant loss of electrolytes and decrease in plasma volume, owing to an activation of cardiac mechanoreceptors.

Soviet scientists have developed a "dry" immersion technique (individuals float in water within a sheath of plastic) that, by preventing water induced skin maceration, allows longer treatments (ref. 99). This modified immersion procedure may be the most convenient analog of microgravity for human studies, since the physiological changes associated with the fluid shifts last longer in water-immersed than in bed-rested subjects (ref. 31).

Research on Space-Flown Nonhuman Primates

Because of its anatomical and physiological similarity to humans, nonhuman primates are the animals of choice for study of microgravity-induced deconditioning (refs. 100–109).

A pioneering attempt by Adey and coworkers (ref. 23) to investigate the effects of weightlessness on the physiology of a heavily instrumented pigtailed monkey flown on Biosatellite III fell short of its goals because the monkey became sick and died shortly after recovery, following a nine day flight. Subsequent analysis indicated that the stress of restraint and invasive instrumentation rather than microgravity per se were the most likely reasons for the failure of Biosatellite III to meet its objectives.

Rhesus monkeys are suitable for microgravity research because during most of the day they adopt a vertical or semivertical position and have sensitive gravity receptors in the circulatory system and mechanisms of cardiovascular regulation similar to those of humans. This trait makes them excellent human surrogates for the study of altered gravity on the cardiac, vascular and other gravity dependent systems (ref. 102).

An interesting finding of Soviet research on monkeys flown on board Cosmos biosatellites in 1983 and 1985 was that blood flow linear velocity in the common carotid artery was not influenced by exposure of the animals to microgravity (ref. 102). This suggests that the edema of the face and neck and the nasal congestion that appear in astronauts during the first days in orbit are not linked to an increased blood flow to the head but may be caused by a decreased outflow of venous blood and cerebrospinal fluid. Moreover, microgravity may increase vascular permeability in tissues with a low interstitial pressure such as the soft tissues of the face and neck. In view of this, further studies on blood circulation and edema in space-flown monkeys seems advisable. Special attention should be paid to edema preventing mechanisms, since as pointed out by Hargens et al. (ref. 35): "It is possible that the smooth muscle tone of precapillary arterioles and lymphatic vessels in dependent tissues is lost during long term spaceflight in the absence of countermeasures." The work should include fine structural studies on the vessel walls, especially on the capillary basement membrane, which plays a key role in preventing excessive leakage because of gravity loads, as shown by the fact that the thickness of those membranes increases twofold from neck muscle to leg muscle of giraffes and humans (ref. 110).

As part of the NASA Ames Research Center, Life Sciences Payload Project for the Spacelab-3 mission, two unrestrained squirrel monkeys were exposed to microgravity during the Shuttle flight of April 29-May 6, 1985. This flight provided a striking demonstration of the interindividual differences in sensitivity to space sickness. While one monkey started normal feeding and eating behavior after a short period of adaptation to spaceflight and maintained its weight during the mission, the other animal did not eat for four days and showed the classical symptoms of "motion sickness," assuming a tucked, curled up posture. By the fifth day he seemed quite adapted to microgravity, starting to consume banana pellets at a normal rate (ref. 111).

It is apparent that monkeys will contribute a great deal to future progress in vestibular physiology in space, especially because more sophisticated bioinstrumentation can be used with them than can be used with humans.

Monkey Immobilization Studies

Occasionally, immobilization of animals by partial or whole body casting has been used for simulation of the effects of weightlessness on the cardiovascular system, muscle and bone. A study by Dickey et al. (ref. 101) has shown that primates maintained in horizontal body casts for two to four weeks suffer physiological changes similar to those seen in bed-rested or space flown humans, including a decreased plasma volume.

Another example of the use of monkeys in space-related research is the study by Savina et al. (ref. 106) on the physiological and pathological changes found in the organs of 12 Rhesus monkeys which were exposed to the weightlessness simulation procedure of immobilization with head-down tilt. Most interesting, because of its significance as a predictor of the probable effects of long-duration flight on humans, was the finding that the head tilt resulted in hemodynamic changes in the brain of the monkeys, with persistent congestion of small veins, greater permeability of vascular walls, and edematous perivascular spaces. This was accompanied by electron microscopic demonstration of hypoxic lesions in neurons and glia and of an increased number of pinocytotic vesicles and myelin bodies (resulting from mitochondrial breakdown) in endothelial cells. Savina et al. conclude that head-down tilt of monkeys is a suitable model for study of the reactions that occur during the acute stage of adaptation to weightlessness.

Sordahl and Stone (ref. 108) have studied the effects of hypokinesia in body-casted monkeys. The most important findings of this study were that immobilization results in a decreased respiratory activity in the mitochondria of the skeletal muscle, and that the mitochondria and the sarcoplasmic reticulum of the heart show a marked decrease in calcium transport. Thus, it seems that hypokinesia (and adaptation to weightlessness) are linked to altered calcium homeostasis, which may be a factor in cardiovascular deconditioning.

Stress and Adaptation in Rats Exposed to Microgravity and On-the-Ground Hypokinesia

General reactions

Because of the technical advantages associated with its small size and easy maintenance, the rat has been the animal of choice in many gravitational physiology experiments, both in biosatellites and in Earth-based laboratories. As a part of their Cosmos biosatellite program, the Soviets have exposed 60-85 day-old Wistar rats to microgravity periods for up to 22 days, which amounts to 1/50 of the animals' life span. The data obtained on the space flown rats were compared with the observations on rats kept in an animal colony and in a biosatellite mockup, where the complete flight profile, excluding weightlessness, was simulated. The postflight state of the animals was judged satisfactory. However, there was some decrease in motor activity on the first day after landing. According to Serova (ref. 112): "It looked as if the animals adhered to a sort of gentle regimen, i.e., functional hypokinesia, to alleviate their readaptation to Earth gravity after prolonged weightlessness." There were signs of activation of both catabolic and anabolic processes, with a predominance of catabolism, resulting in a decrease in muscle weight and an activation of proteolytic enzymes in the digestive tract. The activation of the metabolic processes manifested itself in a better assimilation of the diet and in a slightly increased oxygen utilization.

It was established by the Soviet physiologists that the stress factor responsible for the above changes was weightlessness and not other factors involved with spaceflight, since in a flight experiment in which artificial gravity was provided aboard the biosatellite by a centrifuge (ref. 113), the rats that were centrifuged in space showed less striking changes after landing than those exposed to microgravity. Thus, when tested on Earth upon recovery, they were more active than the noncentrifuged animals, readily overcame obstacles, stood on hindlimbs, moved with normal step and displayed few anatomical and biochemical differences from ground control animals.

Tables 4 and 5 present a summary of the general adaptive reactions of space-flown rats and of the specific effects of weightlessness on a number of organs, as described by American and Soviet space biologists. According to Gazenko et al. (refs. 69 and 114), their data suggest that the rats underwent various adaptive reactions during spaceflights of 18-22 days. Some structural and metabolic changes were directly caused by weightlessness while changes in the hypothalamus-hypophysis-adrenal system and the lymphoid organs were "the result of stress." The measured parameters returned to near normal values at 25 days after flight. Another observation of the Soviet authors was that the severity of the structural and metabolic changes in muscle and bone was directly correlated with their antigravity role under normal Earth conditions.

In summary, the extant data from American and Soviet research suggest that microgravity causes the following sequence of events: (1) Mild stress. (2) Adaptation to the space environmemt. (3) "A deconditioned state" when the animals are faced with the normal 1-g environment upon return to Earth.

Table 4. Effects of microgravity on rats flown on the Cosmos Biosatellites 605, 690, 782, 936, 1129, 1514, 1667, and 1887. All animals were sacrificed at times ranging from 4 hr to 2 days after landing. Flight duration was about 20 days, except for the flights Cosmos 1514, 1667, and 1887, which lasted 5, 7, and 14 days, respectively (Soviet studies).[a]

Body composition	Heart
↓ Total body water	↑ Glycogen and lipid
↓ Extracellular water in fat-free tissue	↓ Volume density of myocardial mitochondria
↓ Bone mineral content	↑ Number of myeloid bodies
Metabolism	↑ Catecholamines
↑ Food intake and oxygen utilization	↓ ATPase activity in myosin
Blood	↓ Number of mitochondria
↓ Mean red cell life span	Liver
↓ Levels of growth hormone	↑ Lipid and cholesterol levels
↓ Levels of osteocalcin	↑ Glycogen and triglycerides
↓ Number of lymphocytes	↓ Activity of diglyceride acyltransferase
↑ Cholesterol	Bone
↑ Triglycerides	↓ Breaking strength in femur and humerus
↑ Corticosterone	↑ Demineralization
Adrenal glands	↓ Number of osteoblasts
↑ Size	↓ Cytoplasmic volume of diaphyseal osteoblasts
Thyroid	↓ Alkaline phosphatase activity in tibial metaphysis and calvaria
↓ Production of T_3	↓ Periostium formation in the diaphysial area
Stomach	↓ Osteoid maturation
↓ Secretion of mucopolysaccharides	↑ Formation of collagen type III
Spleen	Osteoporosis of the spongy compartment of the metaphyses
↓ Number of hemopoietic stem cells	Weight bearing muscles
↓ Amount of nucleic acids	↓ Fiber diameter
Skin	↓ Atrophy of myofibrils
↑ Collagen type III	↓ Strength, elasticity and tolerance to fatigue
Immune system	↓ Amount of myofibrillar and sarcoplasmic proteins
↑ Number of necrotic cells in the inguinal lymph nodes	↑ Glycogen and lipid
↓ Sensitivity of bone marrow cells to colony stimulating factors	Degeneration of neuromuscular junctions
Pituitary gland	Membrane damage in vascular endothelial cells
↓ Content of oxytocin	Shift from the aerobic to the intermediate type of metabolism
↓ Growth hormone secretion	
Testes	
↓ Weight	
↓ Number of cells	

[a]Abstracted from references 54, 114, 115, 117, 126, 141, 170, and 249–277.

Table 5. Conclusions from the American study of rats flown on the Shuttle Spacelab 3 mission (April 29–May 6, 1985).[a]

- Stress reactions (not appreciable)
  - Normal growth
  - Normal adrenals
- Nutrition state (apparently normal)
  - Unchanged liver mass and appearance
  - Unchanged total body protein
- Immunological competence (decreased)
  - Inhibition of interferon production by spleen cells
- Endocrine system (altered function)
  - ↓ Size of thymus gland
  - Pituitary gland changes
    - ↑ Growth hormone producing cells
    - ↓ Prolactin producing cells
- Bone atrophy)
  - ↓ Bone mass
  - ↓ Bending and tensile strength
- Skeletal muscle (atrophy)
  - ↓ Mass
  - ↓ Number of antigravity and voluntary fibers
  - ↓ Amino acid pool
  - ↓ Krebs cycle enzyme activity

[a]Abstracted from references 117, 118, 129, 245, and 278.

Atrophic changes in bone

In addition to skeletal and cardiac muscle deconditioning, microgravity-induced bone alterations in animals has attracted a great deal of attention because of its practical significance for understanding the mechanisms of the similar changes seen in space travelers.

As shown by Morey and Baylink (ref. 115) there is a decreased rate of growth for space-flown rats in the weight-bearing bones of the leg. The resulting decrease in weight-bearing bone mass as compared to control groups was accompanied by an increase in marrow fat and by a decrease in the crush resistance of spinal vertebrae. The weight-bearing bones did not fully recover their normal characteristics by 29 days post-flight. The data suggest that three weeks of exposure of young, growing rats to space microgravity arrested growth of the bone forming cells (osteoblasts), while bone resorption by osteoclasts continued normally. As assessed by histological observation of bone (including tetracycline labeling) immediately after flight, the bone formation process stopped almost completely in the periosteal surfaces of the tibia. Further information on the cellular mechanisms responsible for the bone changes occurring at microgravity has been obtained by Roberts et al. (ref. 116), who showed a depletion of osteoblasts in the periodontal ligament, an osteogenic interface between tooth and bone. This preferential decrease of osteoblasts among the various cell types present in the bone-forming tissue suggests that weightlessness results not only in a block in osteoblast differentiation but also in a failure of bone cell division and/or enhanced cell death.

Although mechanical unloading is usually favored as the main cause of weightlessness-induced bone alterations, recent research spotlights the probable role of homeostatic changes linked to spaceflight. According to Dillman and Roer (ref. 117), recent evidence on the movement of fluid through bone lends support to the view that the cardiovascular perturbations induced by spaceflight may be a major cause of the mineral loss. Moreover, the negative calcium balance resulting from decreased intestinal absorption and renal resorption of calcium (due to hemodynamic shifts) may be a cause rather than an effect of bone calcium loss.

The hypothesis that decreased blood flow in the bone may play a key role in the weightlessness induced bone changes is in agreement with Doty's (ref. 118) views according to which the vascular system could control the level of extracellular calcium in the bone fluid compartment, with concomitant effects on osteogenesis in the weight bearing bones.

The bone rarefaction occurring in space can be better understood as a reaction of the animal body to an environment in which structural strength can be maintained at a lowered metabolic cost. As discussed by Morey-Holton and Bond-Arnaud (ref. 119), an absence of gravity requires less structural support and, hence, less skeletal mass and turnover. During prolonged spaceflight, the gut and kidney could become the major regulators of calcium metabolism. Although some adaptation is appropriate for the weightless condition, it could prove a hindrance to readaptation to the Earth gravitational field.

Skeletal muscle atrophy and cardiac deconditioning— For in-depth coverage of the subject of skeletal muscle changes induced by weightlessness and by a variety of immobilization and hypokinesia procedures the reader is referred to the articles cited in table 4. Here, the focus will be on the most important experimental findings and on some recent hypotheses on the pathogenesis of disuse alterations of skeletal and heart muscle.

As summarized by Oganov et al. (ref. 120), the main physiological effect of adaptation of skeletal muscle to microgravitry is a decrease in the strength of muscle contraction, a loss of elasticity and a decline in the tolerance to fatigue. At the cellular level, it seems that these changes are linked to a decrease in size and a partial rearrangement of the structure and function of the slow (aerobic) muscle fibers which makes them more similar to the glycolytic fast fibers.

Recently, Musacchia and coworkers (refs. 48 and 49) have shown that the above changes are associated with a 10-30% decrease in the total RNA content of the soleus and gastronecmius of both Shuttle-flown and of whole-body suspended rats. In addition, the muscles of rats exposed to weightlessness or hypokinesia show a raised glycogen content and mitochondrial changes (refs. 121–123) as well as a higher rate of protein degradation (ref. 124), which suggests that muscle atrophy is indeed accompanied by decreased cell respiration and raised protein catabolism. According to Soviet research on Cosmos-flown rats, the physiological changes occurring in skeletal muscle at microgravity are accompanied and probably induced by alterations in the biochemical and physicochemical properties of contractile and regulatory proteins (refs. 120 and 125). From an adaptational viewpoint, spaceflight may trigger not only atrophic changes in the slow antigravitational muscles but also a transformation of the phenotype responsible for the synthesis of contractile muscle proteins. This may cause a rearrangement of the functional profile of the muscles, since the slow antigravitational soleus acquires the characteristics of typical fast muscle while the fast brachialis muscle gains those typical of slow muscles. The change in the brachialis muscle is explained by the fact that in the weightless environment the animals may prefer the use of the highly developed forelimbs in order to be able to maintain body position while feeding, which is in agreement with the well-known fact that flexor muscles such as the brachialis are most actively involved in precise locomotor tasks (ref. 73).

The major mechanism involved in the above conversion of muscle fibers may be an alteration of the trophic effects of the nervous system set in motion by the propioceptors (ref. 120). This concept is supported by the finding that a decreased functional load induces degenerative changes in the innervation of motor end-plates. An alternative or synergistic mechanism of microgravity induced muscle changes could be a disturbance in the blood supply to the muscle tissue, linked to hemodynamic alterations and adaptive changes in the vessel walls (ref. 52).

There is some experimental support for the above views. After flights of about 21 days aboard the biosatellites Cosmos 605 and Cosmos 690, quantitative morphometric studies at the ultrastructural level showed a statistically significant diminution in the mean number of mitochondria and synaptic vesicles in cross sections of the axonal endings (ref. 121). This shift toward a less aerobic metabolism is similar to those resulting from experimental transection of nerves in experimental animals. Further, there is a reduction in the number of functional capillaries in the soleus and gastrocnemius of space-flown rats (ref. 126), which suggests that changes in oxygen and nutrient supply to the muscle may set in motion the above organelle and biochemical changes.

Not surprisingly, heart muscle of space-flown and immobilized rats shows changes similar to those seen in skeletal muscle, including mitochondrial degeneration (refs. 121, 127, and 128). Moreover, the myocardial cells of rats exposed to near-zero g for seven days aboard the Shuttle Spacelab SL-3 contained a lesser amount of microtubules (ref. 122), which suggests a decreased need for scaffolding of the heart in the weightless condition. Changes were also seen in the proteins that play the main role in the degradation of the myofibrils (ref. 129).

Despite the considerable amount of work that has been already done in this problem area, the authors agree with Rambaut et al. (ref. 80) that knowledge of the pathogenesis of the muscle atrophy of spaceflight is not yet sufficient for development of completely effective countermeasures to be applied to space travelers.

FUNDAMENTAL GRAVITATIONAL PHYSIOLOGY

As a complement to the above biomedically oriented research, both the U.S.A. and the Soviet Union have performed experiments of a more fundamental nature (refs. 130–133). Such studies are needed in order to gain information on the role of gravity in shaping the structure and function of living organisms (refs. 134–138). One emphasis of this space biology program is on the developmental process, which has been the subject of a NASA-sponsored workshop (ref. 139), which covered not ony the narrowly defined embryonic-developmental issues but also the related aspects of behavior, reproduction and life span. Following the format of the aforementioned workshop, we will deal separately with the effects of microgravity on the development and other biological parameters of mammals and other vertebrates, and of invertebrates.

Mammals

In referring specifically to mammals, Keefe (ref. 140) notes that development should be considered broadly as encompassing all aspects of the mammalian life span from initial germ-cell production through the complete life cycle to death of the organism. Thus, gamete production, fertilization, embryogenesis, implantation, fetogenesis, birth, peri- and postnatal maturation, and aging should be considered as stages of a developmental continuum relevant to space biology.

On the basis of ground-based studies of vertebrates' ontogenesis, Keefe suggests that the overall developmental process might be divided into a gravity sensitive early phase, probably including copulation, fertilization and initial cleavages, an orientation-independent phase (embryonic and fetal stages) and another gravitational dependent phase (postnatal maturation). These predictions have to be accepted with caution, since in the placental mammals the developing systems are either neutrally buoyant in an aqueous environment, or are difficult to expose directly to gravity changes without secondarily involving a complex support system. Accordingly, Keefe maintains that the potential for indirect influences of altered gravity on the developing or nuturing subjects (via modification of the maternal system involved at the time) is greater than the potential for direct gravity action at most developmental stages. Further, since the maternal-fetal system is so intertwined in mammals, differentiation of direct and indirect (or maternally induced effects) will be extremely difficult.

Thus far, the experimental data are in agreement with at least some of the above predictions. According to Serova et al. (ref. 141), pregnant rats which were exposed to weightlessness (aboard the Cosmos 1514 biosatellite) from the 13th to the 18th day of the gestational period exhibited a delay in the increase of the body mass (of the mother) and delivered a total mass of pups of about 11% less than the total mass delivered by the ground control rats. On the other hand, the calcium content of the space-flown offspring was about the same as that of those animals that developed on Earth. Nevertheless, skeleton morphometry of the space-flown fetuses showed a delayed development involving a 5 to 20% reduction of the ossified areas of virtually every bone. The Soviet authors conclude that these preliminary studies should be followed by breeding of animals aboard space vehicles, once they have adapted to the space environment.

A collaborative American-Soviet study on the same Cosmos 1514 mission dealt with the effects of weightlessness on the development of the sensory and motor functions of rat pups (refs. 142 and 143). This experiment showed that the development of vestibular function had proceeded normally, since normal responses were exhibited by the animals when examined, after landing, using standard righting, negative geotaxis, and rotation tests. In summary, the data suggest that mammalian embryogenesis during the last half of the gestational period is not critically dependent on gravitational forces; however, the effects of microgravity on fertilization and early development remains to be determined.

A relative lack of response of the postembryonic development of mammals to altered g would be in agreement with the centrifuge data from Oyama and Platt (ref. 144) and Oyama et al. (ref. 145) showing that both mice and rats were able to complete normal pregnancies during chronic centrifugation, and that the time when altered gravity may be more injurious to the mammalian organism may be at birth and during the period immediately after weaning.

Amphibians

The frog (ref. 146) was used for investigation of the effects of weightlessness on the key acceleration-sensor mechanism of vertebrates, i.e., the hair cells of the otolith organ. In this spaceflight study, two bullfrogs were used to record action potentials from vestibular nerve fibers of the inner ear. During the first few days of weightlessness, the otolith showed a fluctuation of activity at rest up to 20 times larger than that shown on the ground, at 1 g. There was also, during flight, an increased responsivity of the gravity sensors to hypergravity, during periodic in-flight centrifugation. The data showed that the otolith activity at rest returned to normal at 4 to 5 days after lift-off, but there was no trend toward normalization of the exagerated otolith response to in-flight centrifugation. These pioneering experiments suggest that the adaptation to microgravity of the fundamental mechanisms of gravity perception of vertebrates may be only partially successful.

Most gravitational research on amphibians has dealt with the effects of changes in the g vector on development. The theoretical basis of this work is Pfluger's (ref. 147) finding that, upon sperm penetration, the eggs orient spontaneously, so that the axis between the animal and the vegetal poles becomes parallel to the field of gravity. He also noted that the plane of the first division was parallel to the field of gravity even in eggs restrained in an abnormal orientation. Therefore, Pfluger concluded that gravity played a determining role in embryogenesis (see also refs. 148-158). However, later experiments suggested that the influence of gravity in the above phenomena is indirect, since egg rotation was caused by a turbulent rearrangement of yolk and cytoplasm as a result of their different densities. The first centrifugation studies of these eggs, done by Hertwig (ref. 159), showed that the development of amphibian eggs is not very sensitive to acceleration, proceeding normally in fields of up to 4 g and only becoming suppressed at about 9 g. In 1908, Konopacka (ref. 160) concluded that acceleration fields interfered with development by limiting the distribution of cytoplasmic material during cell division.

More recently, Earth-based work on *Xenopus* eggs exposed to high gravitational fields in a centrifuge suggest that though a primary embryonic axis may not immediately be established, when exposed to abnormal g fields, this may not be an obstacle to the achievement of normal development in weightlessness (refs. 153 and 154). Further, it appears that frog eggs that are rotated in clinostats (ref. 161) or immobilized shortly after fertilization under conditions which prevent the "rotation response" exhibit only a minor disruption of normal pattern formation. This suggests that rotation of the egg is not essential for establishment of normal bilateral symmetry and organogenesis and that amphibian development aboard space laboratories will not be strikingly hindered by the lack of gravity (refs. 162–165). However, the key experiment, i.e., fertilization and development in microgravity, has yet to be done.

As summarized below, the numerous experiments on amphibian development in space satellites have not provided any data contrary to the above views (refs. 166, 162, 163, 164, and 165). In the early 1960s, a frog embryology experiment was proposed by R. S. Young, with subsequent implementation on the U.S. Biosatellites 1 and 2 (ref. 164) and Gemini VIII and XII (ref. 167). Unfortunately, the technical constraints of these missions required that loading of the specimens occur 12-15 hr before launch, a period which precluded the fertilization of eggs in microgravity. Instead, eggs of *Rana pipiens* were fertilized on the ground, loaded into acrylic chambers, and held at 4°C to retard their growth until they reached orbit, whereupon they were warmed to 21°C so that development could take place. During the spaceflight, the embryos were fixed by automatic injection of glutaraldehyde at various stages of development and, after 2.5 days of exposure to microgravity, they were returned to Earth. Light and electron microscopic observation of the tadpoles failed to detect any morphological abnormality. However, these results should be considered with caution since, as pointed out by Souza (ref. 168): "subsequent experiments in ground-based laboratories indicated that the period between fertilization and first cell division was the most sensitive to perturbations of the gravity vector, exactly the period missed in the Biosatellite and Gemini experiments."

More recently, a series of Soviet experiments by Vinnikov et al. (ref. 169) explored the effects of microgravity on the development of the vestibular system of *Rana temporaria* and *Xenopus laevis*. Like their American colleagues, the Soviet biologists sent into space eggs which had been fertilized on the ground. The analysis of the embryos, which did not reach orbit before the blastula stage, did not show any significant change in the vestibular system, except for some utricular otolith enlargement and a tendency to greater asymmetry between the left and right otoliths in some larvae.

A similar experiment was conducted on the Space Shuttle/Spacelab D-1 mission to find out if the amphibian genome would be able to guide the normal development of the vestibular system in the absence of a normal gravity vector. This experiment had the same technical drawback as the previous U.S. and Soviet work, i.e., the eggs (from the clawed frog *Xenopus laevis*) had been fertilized before launch. The post-flight analysis of the specimens showed no difference between a flight group exposed to microgravity, a flight group provided with artificial gravity, and a ground based control group, except for a peculiar swimming behavior, i.e., the tadpoles swam in small circles. This abnormal behavior was not observed in the centrifuged population and took almost two days to fully disappear.

In summary, microgravity does not appear to have deleterious effects on the developing amphibian embryo, at least when the microgravity exposure begins at or after the first cell division. However, further research is needed, since the period between insemination and first cell division has not yet been examined under conditions of microgravity and it is this early stage that appears to be most sensitive to changes in the gravity vector.

Fish and Birds

Fish have been used for some preliminary research on their response to space microgravity. According to the Soviet work summarized by Gazenko et al. (ref. 170), the viviparous guppy *Lebistes reticulatus* (the female of which stores the sperm and fertilizes the eggs on a continuous basis) stops this internal fertilization process during the period of spaceflight, with fertilization resuming after landing.

In the U.S.A., a Skylab-3 experiment dealt with 50 fertilized eggs of the killifish, *Fundulus*, which were exposed to spaceflight conditions from the late gastrula stage through hatching and early maturity (ref. 171). Development proceeded uneventfully, resulting in normal swimming behavior of the young fry, but several young adult fish which were flown alongside showed an uncoordinated behavior similar to that of vestibularly deafferentiated fish. This was characterized by abnormal swimming in tight circles, and frequent looping sideways, with their backs facing the light source. The frequency of the looping declined slowly after the third day of flight until normal swimming prevailed. It was concluded that weightlessness acts as a permanent vestibular stimulus until long term habituation occurs. Further, this appears to be the result of a central active inhibitory process and not of fatigue or receptor adaptation alone.

Two additional fish studies were performed on the "Apollo-Soyuz Test Project" (ref. 172) and as a joint U.S.A.-U.S.S.R. experiment on the unmanned Soviet biosatellite Cosmos 782 (ref. 173). These technically sophisticated experiments, in which five developmental stages were chosen for their relevance to vestibular system development, showed that differentiation proceeded normally, if not more rapidly than under normal gravity, probably because of a lack of stratification (and more uniform distribution of the gases) within the aquaria. Further, hatching rates were highest for the spaceflown specimens on the Apollo-Soyuz study. Although no significant alterations in vestibular morphology were reported by the U.S. investigators, the Soviet space biologists found marked changes in otoconial membrane morphology as the result of spaceflight (ref. 174).

Numerous data have been obtained on the reaction of hens to hypergravity (refs. 28, 175, and 176). By contrast, studies on the response of birds to space microgravity are practically nonexistent. A Cosmos 1129 experiment dealt with the effects of microgravity on the development of Japanese quail eggs (*Coturnix* species). Sixty fertilized eggs were flown inside an incubator that, unfortunately, failed to maintain an adequate humidification during the latter half of the mission, resulting in the death of the specimens. Some interesting data were obtained, nevertheless, since it was established that there was a normal development of the embryos in the microgravity condition up to the point of incubator failure (ref. 142). Chicken eggs were recently carried on the Shuttle (STS-29). Two age groups were flown, eggs that were five and nine days old at launch. Preliminary results indicated that the entire group of the youngest eggs died early in the flight. The principal investigator, John Vellinger, believes that microgravity may have had a deleterious effect on early embryonic development (personal communication). Soviet investigators have recently flown Japanese quail eggs on the Mir station. They reported that although the newly hatched chicks appeared normal, they had an impaired locomotive ability.

Earth-based work suggests that gravity may play only an indirect role in the early development of chicken eggs, by maintaining optimum separation among the various components of the egg. This is suggested by the marked reduction in hatchability of hen eggs maintained on the ground in an inverted position, i.e., with the small end up (ref. 177).

Insects and Other Invertebrates

Because of their small size and simple housing and feeding requirements, insects are ideal experimental animals for spaceflight research. This has been recognized by Soviet space biologists who have often used *Drosophila melanogaster* in their program of research aboard unmanned and manned satellites. As far back as 1960, fruit flies were exposed to the space environment for 24 hr in an unmanned Soviet "Spaceship-Satellite" and, in 1961, larval cultures and imagoes of *D. melanogaster* accompanied the first cosmonaut Yuri Gagarin in his orbital flight aboard "Vostok" 1 (ref. 11).

Space microgravity and Drosophila genetics

Early spaceflight research by both Soviet (refs. 81 and 178–180) and American geneticists (refs. 181–184) suggested that microgravity or cosmic radiation, or an interaction of both, caused an increase in insect mutations. However, a more critical analysis of the data as well as the results of other pioneering flight experiments from the Soviet Union lend support to the view that deviations from normal g do not increase the frequency of *Drosophila* mutations of the determinant lethal type. Nevertheless, some data suggest that weightlessness increases the effects of ionizing radiation, which for flies exposed to heavy particles from the cosmic flux may lead to disturbances in the ability of chromosomes to separate correctly (ref. 185). On the basis of studies in which *Drosophila* was irradiated in space, the Soviet geneticist Parfenov (ref. 180) concludes that "radiation in spaceflight causes genetic effects that differ from effects on the Earth."

More recently, the Soviet biologists have reinvestigated the genetic effects of spaceflight on *Drosophila* maintained aboard the Salyut 6 Orbital Station (ref. 186). The data of this study show that, although flight-associated vibration and acceleration increase the frequency of chromosomal nondisjunction and recombination, their role in inducing these genetic effects is minor in comparison to the mutagenic influence of the heavy ions from the cosmic flux, to which *Drosophila* was exposed during flight.

Effects of microgravity on Drosophila reproduction, development and aging

Though there have been early reports of morphological abnormalities in fruit flies which had developed in space, it could not be established that these abnormalities were the result of microgravity instead of vibration, abnormal temperature, faulty nutrition, or other poorly controlled factors present during spaceflight (ref. 180). Our own observations on fruit flies that were conceived, developed, and eclosed in space aboard the Cosmos 936 biosatellite support the view that microgravity does not exert a detrimental effect on the processes of cell growth, division and differentiation which are involved in normal morphogenesis (refs. 187–190).

The first experiment ever performed in the area of animal reproduction in space took place in 1962 aboard the manned satellites Vostok 3 and 4, with the assistance of the cosmonaut crew. In their report of that pioneering experiment, Antipov et al. (ref. 191) commented that, "While planning these experiments one could expect that weightlessness would affect processes of copulation and laying of eggs." The fruit flies proved to be more adaptable than expected since they were able to mate and lay eggs in the microgravity environment. However, the data obtained were only of a qualitative nature and do not allow an accurate determination of such quantitative parameters as duration of the developmental period, percent of viable embryos and body weight of the imagoes which developed in weightlessness.

In contrast to the relative insensitivity of the genetic and developmental processes of *Drosophila* to the lack of gravity, the experimental data suggest that higher physiological processes such as those involved with tropisms, reproduction, flight and aging (tables 6 and 7; appendix A) may be influenced in a negative way by the lack of gravity. Our studies in collaboration with G. P. Parfenov (of the Institute of Biomedical Problems of Moscow) dealt with exposure of several hundred *Drosophila* to microgravity for about 20 days in two Soviet biosatellites of the Cosmos series (refs. 189, 190, and 192). This research showed that, although the developmental process was not altered by spaceflight, flies that were exposed

Table 6. Effects of microgravity on *Drosophila* and animal cells maintained in vitro: summary of the results of experiments performed on the ESA Biorack Facility–German Spacelab D1 mission (30 October–5 November 1985).[a]

Experimental material	Effects	Principal investigator
Paramecium aurelia	↑ Growth rate ↑ Cell volume	Planel
Human lymphocytes	↓ Mitogen induced cell activation	Cogoli
Drosophila melanogaster	↓ Rate of hatching ↑ Size of embryos ↑ Number of embryos laid ↓ Life span of males	Marco

[a]Abstracted from references 197, 198, 210, and 279–282.

Table 7. Pioneering observations on the effects of weightlessness on the life cycle and behavior of animals.[a]

Animal	Observation	Principal investigator	Mission	Year
Dog	Successful adaptation	Chernov	Sputnik-2	1957
Fly, *Drosophila*	Ability to reproduce	Antipov	Vostok 3-4	1962
Beetle, *Tribolium*	Normal development	Parfenov	Cosmos-605	1973
Fish, *Fundulus*	Disturbed swimming	von Baumgarten	Skylab-3	1973
Spider, *Araneus*	Abnormal web threading	Mills	Skylab-3	1973
Bee, *Apis*	Inability to fly	Nelson	Shuttle STS-3	1982
Fly, *Drosophila*	Accelerated aging	Miquel	Cosmos-936	1977

[a]Abstracted from references 81, 179, 202, 171, 10, 205, and 190, respectively.

to microgravity from the 7th to the 27th day of their adult lives suffered a shortening of their life span (fig. 6). This was accompanied by a significant decrease in the "fitness" of the space-flown insects for negative geotaxis and mating ability, when tested upon return to Earth. As discussed elsewhere (refs. 187, 188, 190, and 192), our working hypothesis is that flies which are exposed to microgravity after completing maturation on the ground cannot control their flying behavior in the absence of the usual gravity cues. This results in a disordered motor activity, with concomitant increase in metabolic rate, which, in agreement with the rate-of-living and oxygen radical theories of aging (refs. 193–195), causes an acceleration of senescence. Since life shortening was not as marked in flies that eclosed as adults during the flight, we assume that those imagoes could adapt or "learn" to control flight in weightlessness during the first hours of adult life, when the insects may be more receptive to the function-molding inputs from the environment. This adaptation should result in a less wasteful utilization of oxygen and,

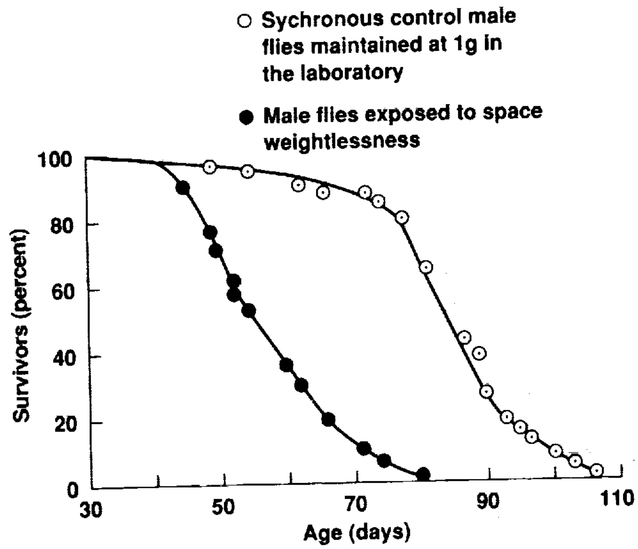

Figure 6. Effects of weightlessness on the life span of *Drosophila melanogaster*.

therefore, in a *Drosophila* life span at microgravity similar to that found under normal 1-g conditions. This interpretation of the Cosmos data is in agreement with the finding that exposure of fruit flies to continuous rotation in horizontal clinostats results in increased locomotion and flying, and significant life shortening (ref. 196).

More recently the response of *D. melanogaster* to microgravity has been reinvestigated by Marco (ref. 197) and by Vernos et al. (ref. 198) in the Shuttle D-1 mission. In this experiment the flies were flown for six days in the Biorack facility of the European Space Agency and studied upon return to Earth. No significant accumulation of lethal mutations was detected, as evidenced by the male to female ratio in successive generations arising from the space-flown *Drosophila*. In agreement with the previous data from Parfenov (ref. 180) and Miquel and Philpott (ref. 190), the D-1 experiment suggests that microgravity does not exert any drastic influence on the developmental processes. However, spaceflight induced a host of developmental disturbances (such as a decreased proportion of hatching of embryos in space and of the oogenesis rate of females), probably caused by weightlessness-induced changes in the mothers. Further, in agreement with our previous Cosmos results, exposure of flies to weightlessness in the Shuttle flight resulted in male life shortening. According to R. Marco (private communication) a preliminary analysis of the videorecordings of the fly containers in the Biorack indicate that at least some of the flies showed an accelerated type of movement suggesting that "the increased energy utilization in microgravity hypothesis of Miquel may be at least in part responsible for the decrease in life span in space."

Effects of hypergravity and clinostat rotation on *Drosophila*

A complete understanding of the role of gravity in invertebrate biology cannot be obtained without exposure of these animals to high gravitational fields. Again, the most comprehensive studies on the effects of high-gravity loads on growth and development of invertebrates have been carried out on *D. melanogaster*. Fruit flies were chosen because they are ideally suited for refined quantitative determination of the efficiency of growth, since they show an almost perfect linear correlation between the logarithm of their volume and the passage of time. Wunder (ref. 199) took advantage of this fact for a demonstration that, though growth was possible in fields as intense as 5000 g, both the rate of growth and the final size attained were below the values in larvae maintained at 1 g. The growth rate decreases as the field activity increases beyond 1000 g. Paradoxically, at fields of 500 g there is a 25% increase in growth rate. This phenomenon was accompanied by a decreased oxygen utilization, which suggests that, following exposure to high-gravity loads, the bioenergetic processes supporting growth became more efficient.

Preliminary research on the effects of *Drosophila* rotation in clinostats has yielded interesting results. It should be noted that clinostats do not provide an exact replica of the microgravity environment of space. Nevertheless, we are of the opinion that rotation about the horizontal axis using clinostats, with continuous change in the direction of the gravity vector, may result in a disorientation phenomena akin to those occurring in microgravity. This view is supported by the finding that flies show an increased locomotion and decreased life span when kept in the clinostat from eclosion to death (ref. 196). Further, there was a delayed eclosion of the offspring of flies in our NASA Ames laboratory which mated while being rotated in horizontal clinostats. This interesting effect may be due to a disturbed behavior (with delayed mating in the parent population) and/or to a direct effect of altered g on the larvae.

Spaceflight experiments on Tribolium

After *Drosophila*, the flour beetle *Tribolium confusum* is the most often used invertebrate in the biological flight experiments of both the United States and the Soviet Union. A pioneering experiment by Buckhold et al. (ref. 200) and Slater et al. (ref. 201) dealt with the effects of microgravity and the combined effects of microgravity and gamma radiation on mutations and wing development in beetles exposed to the space environment aboard the U.S. spacecraft Biosatellite II. The results suggested that microgravity did not affect survival of the insects. On the other hand, pupal period, wing abnormalities, and mutations were significantly increased. it was concluded that some factor in spaceflight, probably microgravity, was responsible for the effects observed, though a temperature drop occurring before retrieval of the flight capsule could have played a significant role.

Further research on the effects of microgravity on the biology of *Tribolium* was performed on the beetles flown in the manned space station Salyut 6 (ref. 202). In this long-duration experiment, *T. casteneum* completed its developmental cycle, from fertilization to the eclosion of the mature imagoes of the next generation, in a normal way. There were no significant genetic changes (ref. 202). This lack of response to altered gravity is in agreement with a clinostat study showing that rotation on this instrument did not result in genetic changes or abnormal development of *Tribolium* (ref. 203).

Very recently, house flies have been exposed to microgravity aboard the Shuttle (ref. 204). No life span shortening could be observed, but the space-flown females showed a decrease in egg laying as compared to controls kept at 1 g. Since this decreased fertility was not seen in later generations of flies, it seems that, while microgravity may influence the rate of ovarian development, this effect is not genetically transmitted.

Insect flying behavior in microgravity

In 1982 the Shuttle STS-3 mission carried an insect flight experiment designed by Todd E. Nelson (a high-school senior from Adams, Minnesota), which exposed three species of insects to microgravity, in order to explore flight behavior (ref. 205). The experimental animals were house flies (*Musca domestica*), velvet bean caterpillar moths (*Anticarsis gammatalis*) and worker honey bees (*Apis mellifica*). The insects were observed and filmed at microgravity during a period of 25 min. At launch time, all bees were in their adult stage (about 6 days old), whereas the flies were loaded into the housing units as puparia, "scheduled to emerge prior to the experimental observations, during space flight." Further, the moth population included both adults and pupae.

In the weightless condition, the bees were unable to fly: "Brief attempts at flight resulted in unstable paths, tumbling about their axes and floating with little or no wingbeat." On the other hand, the flies limited themselves to walking on the walls of the housing unit, with their flight periods lasting less than 4 sec although the flies were apparently able to control their motion in all three of their body axes (pitch, yaw, and roll), the moth population which was at the adult stage prior to launch showed some impairment of flight control with occasional tumbling in pitch. Interestingly as regards insect "learning" ability, the young adults which emerged from pupae during the mission seemed to avoid active flight; instead they floated without wing beat, for periods of up to 3 min.

Upon return to Earth, it was noted that the number of eggs laid per female for the flies that were exposed to microgravity was lower than for the flies maintained on the ground. Moreover, the moths did not mate in space but were able to mate upon return to Earth.

The above findings on the flight behavior of moths in microgravity are in agreement with a previous study by May et al. (ref. 206) in which insects were exposed to brief periods of microgravity on a Learjet flying parabolic paths: "...at zero g, moths very occasionally spread their wings and floated for a few seconds. At zero g moths retained control of rolling and yawing movements but stability of pitch was greatly reduced or absent."

As discussed by Nelson and Peterson (ref. 205), the flight of an insect at 1 g requires development of a force to counteract gravity. An insect is propelled in a direction and at a velocity determined by the resultant of three forces: (1) reaction to thrust generated by wingbeats, (2) resistance offered by the air to the passage of the insect through it (drag), and (3) the downward pull of gravity. Since in space the downward pull of gravity is absent, insect flight velocity will increase unless the insect reduces the aerodynamic output (frequency and/or amplitude of wingbeat). Difficulties in flight control may be linked to disproportionate increases in flight velocity with normal wingbeat output. It seems that the insect flight mechanisms are endowed with a certain degree of adaptability to altered gravity, since as noted by May et al. (ref. 206), and confirmed by Nelson and Peterson (ref. 205) in research on moths, exposure to microgravity led to occasional reductions in the amplitude of wing beat and/or interruption of flight.

Insects differ in the degree of sophistication of their flight mechanisms. Thus, bees have two pairs of wings and lack halteres, while house flies and other *Diptera* have only one pair of wings the other pair being transformed into gyrostat-like halteres. This refinement of the flight apparatus may give the flies a more accurate perception of the accelerations sustained during flight (and a better postural control) than is available to bees and other four-winged insects. In the case of moths, the large ratio of wing area to body weight and their more gliding style of flight may play a role in the preservation of flying ability in weightlessness.

We feel that these preliminary data justify the study of the flying behavior at microgravity of insects that are exposed to this condition in space after developing on Earth, and of insects exposed to 0 g after eclosion in space. The hypothesis to be tested is that insects which develop and mature in space may control flight in microgravity better than those exposed to microgravity after completing their development under the influence of normal gravity (appendix A).

Flight experiments on other invertebrates and protozoa

Cysts of the crustacean *Artemia salina* and adult parasitic wasps *Habrobracon juglandis* were exposed to microgravity in the 2.5 day flight of the U.S. Biosatellite II (refs. 10 and 207). In these experiments no conclusive microgravity effects on the development process could be shown. An earlier experiment on sea urchin eggs (*Arbacia punctulata*) was flown in the Gemini 3 mission, but no data were obtained because of a technical failure of the housing unit (ref. 166).

Only one flight experiment on *Arachnida* has been performed to date, that of high school student Judith Miles, showing that cross spiders (*Araneous diadematus*) spin finer threads at microgravity (in Skylab 3) than on the ground (ref. 10). As is the case for flying behavior of insects, the netwebbing of spiders may be a behavior worth studying on animals developed in space.

The problem of the direct cellular effects of microgravity has been investigated by Planel et al. (refs. 137, 208, and 209) on cultures of *Paramecium tetraurelia*, in flight experiments performed both aboard the Soviet orbital station Salyut 6 and on the Biorack facility of the Shuttle Spacelab. These studies suggest that "exposure to spaceflight factors resulted in a higher cell growth rate associated with an increase in cell volume. This last response was observed in interphasic and mitotic cells." Interestingly, measurement by X-ray microanalysis showed changes in the intracellular electrolyte content, for calcium (Salyut 6 flight) and magnesium (Spacelab D-1) (ref. 210). According to Planel et al. (ref. 209), the effect of microgravity just described may be linked to a facilitated motion of the paramecia in the microgravity environment. The energy requirements for ciliary movement would be reduced and more ATP would become available for cell proliferation.

THEORETICAL ISSUES IN GRAVITATIONAL PHYSIOLOGY RESEARCH AND RECOMMENDED TOPICS FOR FUTURE FLIGHT EXPERIMENTS

Although the practical relevance of biomedically oriented gravitational research has never been questioned, doubts have occasionally been raised on the fundamental scientific payoff. Nevertheless, even if future experiments confirm our tentative conclusion that weightlessness is not mutagenic and that developmental processes do not seem to be directly influenced by microgravity, we will see below that study of long term exposure of individual animals to microgravity is not devoid of scientific justification.

Mass-Related Effects of Gravity; Role of Gravitational Forces in Molding the Bone and Muscle and Influencing the Rate of Aging

Experimental simulation of hypergravity and microgravity has allowed testing of a cluster of theoretical concepts linking the weight of terrestrial animals and the size of the bones needed to support this weight. Galileo (ref. 1) noted as far back as 1638 that, as animal species become larger, the bones must become disproportionately thicker in relation to their length in order to avoid breaking as the result of the increased load. As pointed out by Galileo, the strength of a material to resist breaking is directly proportional to its cross section while the loading force is a function of its volume or mass. Therefore, a large body size requires use of stronger materials or a disproportionate thickening of the supporting structures. Galileo pointed out that this "scale effect" was a response to gravity since it was not present in aquatic animals.

Further studies on the scale effects were performed by Thompson (ref. 211), who noted that "Man cannot build a house nor nature construct an animal beyond a certain size without altering the design of materials." Similar views on the structural response to gravity were offered by Wolff (ref. 212) who in 1892 pointed out that "bone responds dynamically to a change in loading by a change in architecture (see also ref. 213). More recently it has been shown that, among terrestrial species, skeletal size increases proportionally to the 1.15 power of body mass (ref. 214).

An interesting development in the field of theoretical gravitational physiology is the recent formulation by Economos (reference 215; see also related concepts in (refs. 216 and 217)) of an equation that correlates body mass (m) with gravitational tolerance (G max):

$$\text{Gmax} = 4\text{m}^{-0.14}$$

On the basis of this power law, Economos estimates that the largest land mammal that has existed weighed about 20,000 kg.

Recently, Smith (ref. 175) has presented data supporting the concept that gravity influences body and organ size in animals with a body mass larger than 2 kg (fig. 7).

Spaceflight data provide information on the relationships between gravity and bones, since during exposure to microgravity there is an adaptation in the opposite direction, i.e., the bone strength diminishes (through calcium loss) to the reduced values that are sufficient to support motion in weightlessness. One of the most pressing questions to be answered by future spaceflight research is to determine if decalcification will proceed indefinitely or if skeletal bone will reach a steady state commensurate with the reduced dynamic demands of life in space.

From an adaptation-physiology viewpoint, skeletal muscle atrophy is very similar to bone loss, since both phenomena are manifestations of disuse atrophy in the musculoskeletal system, a system that has been shaped to a considerable degree by Earth gravity (ref. 218). Before the advent of spaceflight, the exquisite malleability of the muscle to the functional demands imposed on it was already evidenced by the hypertrophy caused by physical exercise and the atrophy associated with prolonged inactivity. These changes in organ size induced by altered gravity are known to influence the relation between

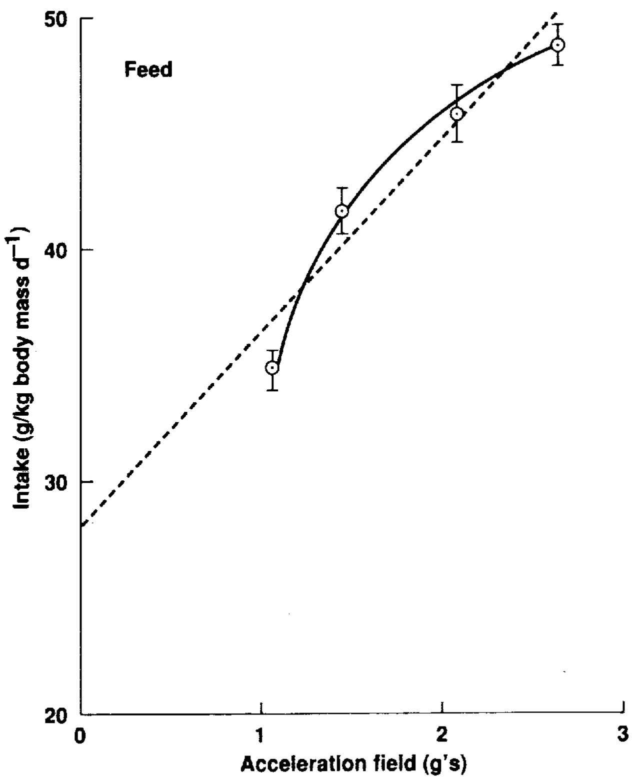

Figure 7. Influence of chronic acceleration on the caloric maintenance requirements of chickens living in an animal centrifuge. (From ref. 28.)

metabolic rate (MR) and total body mass (TBM). According to the classic studies by Kleiber (ref. 134):

$$MR = K \times TBM^{3/4}$$

In agreement with Kleiber's equation, in the absence of gravitational loading the scale relationship of metabolic rate to total body mass should tend to shift from the three-fourths power toward the one-half power of body mass. Conversely, the scale relationship should shift toward the first power of body mass if gravitational loading is increased as in chronic centrifugation of animals. Evidence in favor of these concepts has been provided by ground-based centrifugation studies and it is expected that the Shuttle Spacelab program will provide the opportunity to confirm the predicted effects of microgravity on the scaling of metabolic rate on body mass in a variety of mammalian species of different body size (refs. 215 and 216).

The scaling effect is of considerable interest in relation to the testing of current theories of aging (ref. 219). As shown in table 3, the musculoskeletal changes and the other effects of microgravity are strikingly similar to the physiological alterations usually found in aging experimental animals and human subjects. Particularly, the muscle atrophy and calcium loss induced by exposure to zero g are similar to the atrophic changes occurring during human senescence. Moreover, the fact that metabolic rate can be modulated by changes in the gravity load (ref. 220) makes exposure to hypergravity and microgravity an ideal tool for testing the concept that senescence is a byproduct of aerobic metabolism. Our work has shown an acceleration of aging in centrifuged rats (ref. 217), which is in agreement with the predictions of the "rate-of-living" theory of aging and with more recent ideas on the senescence-causing role of the oxygen radicals released in the cell as the side effect of mitochondrial oxygen utilization (refs. 193 and 194).

Vectorial Effects of Earth Gravity: Orientation Mechanisms

As discussed in detail elsewhere (refs. 17, 85, and 138), the contribution of weightlessness experiments toward the understanding of orientation mechanisms (refs. 169 and 221–224) cannot be overestimated. Since all but the most primitive organisms are gravity-responsive (posturally and in locomotion), the state of weightlessness alters locomotion, with concomitant metabolic effects. Indeed, as noted above, extant research has already shown striking responses to the absence of perception of the gravity vector and body weight. A variety of organisms from human subjects to fish and insects may be disoriented and unable to engage in normal locomotion in the microgravity environment. Comparative studies, like the previously mentioned investigation of the flight pattern of *Diptera*, *Lepidoptera*, and *Hymenoptera* aboard the Shuttle, may throw light on the role that gravity has played in the evolution of orientation, propioception and walking and flying behavior and on the development of gravity and acceleration-sensing devices of lower animals such as the crustacean statocysts, and the propioceptors (ref. 225), hair plates (refs. 226 and 227) and halteres (ref. 2) of insects. Not only insects, but also more highly evolved flying animals such as birds and bats should be used aboard orbiting space laboratories in order to increase our understanding of orientation mechanisms.

The ongoing research on human disorientation in the weightless condition has, in addition to its practical relevance, considerable scientific interest, since, as stressed by Graybiel (ref. 85), "transition into weightlessness abolishes the stimulus to the otolith organ in an elegant and harmless manner. . ." and "it is not an overstatement to say that the opportunities to study the vestibular system aloft constitutes a major historical landmark in the advancement of knowledge not only in the vestibular but also in related areas."

Adaptation to Microgravity of Animals Born or Hatched in Space

One of the questions to be solved by future space research is whether animals which are exposed to microgravity during postembryonic maturation are better able to adapt to microgravity than those exposed to that condition after reaching the mature state in the normal 1 g environment. A comparative study of the adaptation ability of reproductive and locomotion behavior of phylogenetically different animals exposed at different stages of their life cycle should be specially rewarding. It has already been shown that fruit flies eclosed into the adult stage aboard a Soviet Cosmos biosatellite may have been less disturbed (as shown by their normal life span) than flies which were sent into space as young or old imagoes (both of which populations suffered a significant life shortening) (refs. 190 and 192).

Animals reared at 0 g from the time of their conception should be studied to learn whether they can adapt satisfactorily when brought to the normal 1-g environment, and whether the abnormalities present in these animals are mainly functional or also structural. As pointed out by Bjurstedt (ref. 228), if postnatally acquired malfunctions occur, the animal may or may not be able to learn by experience the appropriate movement patterns and locomotor orientation. This may shed new light on the old issue of heredity versus learning. Further, an investigation of the pathways and mechanisms of readaptation to Earth gravity of animals of phylogenetically different species will make a significant contribution to the theory of evolution, the general principles of adaptation, and exobiology.

Yet another question of fundamental importance is whether multiple generations of animals and plants are possible in the absence of normal gravity. Although we now know that many stages of plant and animal ontogeny proceed normally in microgravity, multiple generations have been achieved only with single celled organisms.

Does Microgravity Exert Direct Cellular Effects?

The present literature on the effects of microgravity on cells maintained in vitro abounds in conflicting findings, the details of which are beyond the scope of the present review (refs. 229–235). A relative insensitivity of most cell types to change in g-loads would be in agreement with a number of theoretical concepts. As far back as 1896, Crookes (ref. 236) pointed out that gravity will exert minimal influence on very small objects. Further, as discussed by Cook (ref. 237), although gravitation is a very pervasive and constant force, it provides only a very weak field, since the gravitational attraction between two protons is only 10^{-36} as intense as their electrostatic repulsion. Therefore, it is not surprising that at the submicroscopic and microscopic level of organization, structures remain generally insensitive to forces on the order of Earth gravity. For instance, according to Dawson (ref. 100) forces of about 1000 g are needed to displace the subcellular organelles of animal cells, and about 100,000 g are needed to separate large biomolecules such as proteins.

Another theoretical analysis by Pollard (ref. 238) concluded that, although in a mammalian cell 10 μm in diameter gravity could play a role in the distribution of mitochondria, the potential effects of gravity would be very small in comparison to the convective streaming induced by metabolic activity and the concomitant changes in local density caused by the uptake of adjacent molecules. Therefore, Pollard concluded that lack of gravity would not significantly influence the statistical distribution of organelles. Further, Went (ref. 239) proposed a critical dimension on the order of 1 mm above which gravity and mass-related phenomena predominate, and below which forces of molecular origin exert control (see ref. 240).

On the basis of these speculations and of his own data from the Soviet flight experiment program, Parfenov (ref. 218) states that "all unicellular free-living organisms are gravity independent. This implies that. . .weightlessness cannot influence these organisms."

In our opinion, the above would be accurate only as regards genetic effects since the data suggest that microgravity may trigger physiological responses, because of its effects on cell motility (with concomitant metabolic modulation) and on cell-medium interfaces, which are influenced by disturbed convective flows. Similar conclusions have been reached by Menningman and Lange (ref. 241), according to whom: "From these experiments, which admittedly are rather limited in number, it may be deduced that gravity exerts opposing effects on free living motile organisms and on not-actively motile cells."

A BEHAVIORAL-METABOLIC VIEW OF THE EFFECTS OF NORMAL AND ABNORMAL GRAVITY ON MULTICELLULAR ANIMALS

The ultimate goal of gravitational physiology, as of any other scientific discipline, is to provide unifying concepts and laws, which will facilitate predictions. This state of knowledge has not yet been reached in gravitational physiology, since, as noted by Vorobyov (ref. 242), "there is no single theory interpreting the relationship between a living body and gravity." Nevertheless, some concepts can be found in the recent literature which are beginning to unravel the chain of cause-and-effect relationships in the animal responses to normal and abnormal gravity. In Parfenov's (ref. 218) words: "The genetic, morphological and physiological state of organisms is a result of the effects of gravity, that plays three different but closely related roles, i.e., as a creator and transformer of the abiotic environment, as a factor of natural selection and as a physiological stimulus producing mechanical stresses. These gravity effects are addressed to various structures and realized via various mechanisms."

The main task of gravitational physiologists is the identification of those structures and systems which are sensitive to gravitational loads and of the mechanisms involved in the response(s) to altered g (appendix B).

It is apparent that two types of cells will be especially sensitive to changes in g. The first cell type is the main component of the organs which have evolved to support body locomotion (overcoming the pull of gravity). The second cell type is present in the orientation devices, statocysts, otoliths, and so on, which "sense" the direction of the gravity vector. These cell types are widely recognized. However, since general physiologists tend to concentrate on those effects of gravity that are related to mass (and metabolic adaptation) and vestibular physiologists focus on the disorientation reactions to the lack of gravity, it is not usually realized that both responses may be interrelated (fig. 8). This explains why metabolism and respiration-dependent rates of aging of *Drosophila* (which because of its small size should be insensitive to the mass effects of gravity) are changed by exposure to weightlessness or clinostat rotation.

An awareness of the relationship between disorientation effects on behavior and on bioenergetic metabolism throws a new light on the controversy surrounding the issue of the stressful effects of hypergravity and weightlessness. This requires a statement of the precise meaning of "stress" in a gravitational physiology context. It is clear that exposure to high g loads in a centrifuge, which can cause sickness and even death, may induce classic stress reactions (refs. 243 and 244), with neuroendocrine involvement

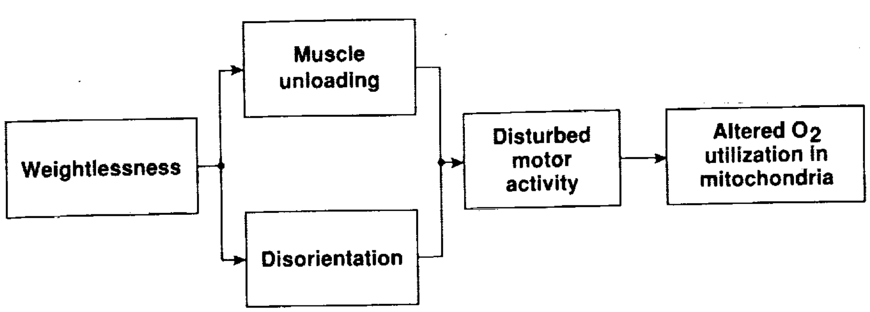

Figure 8. Preliminary integration of the hypothetical main pathways by which microgravity alters the physiology of metazoa as phylogenetically diverse as insects and mammals.

and gastric mucosa ulceration. However, if stress is defined according to Simonov (ref. 22) as "a state of high working capacity," i.e., as a metabolic activation reached in order to meet environmental threats, even relatively low g loads (of the order of 2.4 g, which lead to increased metabolism (ref. 220) and life shortening (ref. 217)) may be considered stressful. It could be argued that extended periods in space might cause decreased "metabolic stress" in humans because of the hypodynamic condition associated with weightlessness. However, this view is contradicted by the finding of high caloric requirements in rats maintained in weightlessness aboard cosmos biosatellites. On the other hand, rats flown on SL-3 had slightly lower food intake but maintained the same growth rate as ground controls (P. X. Callahan, personal communication). Most probably, mammals, like *Drosophila*, also experience difficulty in controlling body position and locomotion in the absence of the normal gravity cues. This results in disordered motion, "waste" of bioenergetic resources and "metabolic stress," with indirect effects on processes, such as aging, which are modulated by the rate of oxygen utilization (fig. 6; refs. 193 and 194). Postembryonic development is also probably influenced by microgravity, at least as regards the maturation of behavior in which orientation and body posture play a role.

Finally, as for most other environmental parameters which both support and set limits to life, deviations from the normal 1 g field toward higher or lower values may jeopardize long term population survival.

APPENDIX A

EXPECTED RESULTS FROM FUTURE SPACEFLIGHT EXPERIMENTS ON INSECTS

Development may be slowed down in microgravity because of disturbed larval behavior, with resulting decrease in food intake.

In the weightless environment there will be a decrease in mating competence and female fertility.

Insects eclosed in space will be more capable of controlling flight than those tested in space after eclosing on the ground (because of adaptation to microgravity during the first hours of their imaginal life).

Insects showing geotactic responses may lose these responses following development and eclosion in space.

Insects which have developed in microgravity may show altered behavior (locomotion, flight, and mating) when tested afterwards in Earth-based laboratories.

Development of invertebrate gravity-sensing systems may not occur normally in microgravity.

APPENDIX B

TENTATIVE CONCLUSIONS ON THE RESPONSE OF ANIMALS TO MICROGRAVITY

Sensitive Processes and Functions

Orientation
Locomotion (especially flight)
Mating
Geotactic drives
Cardiovascular system
Musculoskeletal system
Postnatal behavior and maturation

Insensitive Processes

Genetic replication
Cell growth, division, and differentiation
Embryonic development (except through the effect of microgravity-induced homeostatic disturbances in the maternal organism)

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The focus of this review is on the response of humans and animals to the effects of the near weightless condition occurring aboard orbiting spacecraft. Gravity is an omnipresent force that has been a constant part of our lives and of the evolution of all living species. Emphasis is placed on the general mechanisms of adaptation to altered gravitational fields and vectors, i.e., both hypo- and hypergravity. A broad literature review of gravitational biology was conducted and the general state of our knowledge in this area is discussed. The review is specifically targeted at newcomers to the exciting and relatively new area of space and gravitational biology.

14. SUBJECT TERMS
Space biology, Gravitational biology, Hypergravity, Microgravity, Hypogravity, Weightlessness, Zero-g

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