

HUMANS IN SPACE & SPACE BIOLOGY

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The Earth is the cradle of mankind, but one cannot remain in the cradle forever.
-Konstantin Tsiolkovsky

Every age has its dreams, its symbols of romance. Past generations were moved by the graceful power of the great windjammers, by the distant whistle of locomotives pounding through the night, by the caravans leaving on the Golden Road to Samarkand, by quinqueremes of Nineveh from distant Ophir. . . Our grandchildren will likewise have their inspiration - among the equatorial stars. They will be able to look up at the night sky and watch the stately procession of the Ports of Earth - the strange new harbours where the ships of space make their planetfalls and their departures.

-Arthur C. Clarke

Preface

Inevitably, members of the human species will again walk on the face of the moon and ultimately establish a permanently occupied lunar base. Also, inevitably, humans will venture to the planets within the solar system, most likely beginning with Mars or the Martian satellite, Phobos. These missions will take place because the species that contemplates them is driven by an insatiable desire for knowledge and understanding and because the technical means to accomplish these objectives are possible. There is no question that humans will establish outposts on Earth's moon and make interplanetary journeys. The only uncertainties concern when and how these expeditions are to be made.

Just as a 90- or 120-day tour onboard an international space station is fundamentally different from a brief space shuttle mission; a one-year lunar base tour or a two- or three-year mission to Mars will be unique. Despite superficial similarities to other space missions and analogues, the extended durations and astronomical distances involved in lunar and Martian missions will make these activities far more difficult and dangerous. Crowded conditions, language and cultural differences, logistics problems, radiation concerns, communications lag times, workloads, and a variety of additional issues will conspire to impair the performance

and affect the behaviour of long duration crew personnel. Above all stressors, however, the durations of the missions will impose the greatest burdens and extract the most severe tolls on the humans involved. On long-duration space missions, time will be the factor that can compound all issues, however trivial, into serious problems.

Introduction

Worldwide peaceful cooperation in space

Human space flight started as a race between the two super powers of the world; however, already during the Cold War, human space flight became emblematic that peaceful cooperation was possible (Soyuz-Apollo, Shuttle-Mir mission). Today, human space flight is characterized by a worldwide cooperation by many countries. Future human space flight endeavours will be worldwide cooperation efforts, maybe including emerging space-faring countries (China, India), and this for several reasons: political, financial, technological and scientific.

The International Space Station (ISS) is today the catalyst of the human space flight activities worldwide. Through their cooperation, the ISS partners have reinforced their political, strategic and industrial cohesion, and optimized the use of their respective technical and operational know-how.

Space as a laboratory for the life sciences

Before humans went into space, animals were sent up in rockets as surrogates to help us understand if a living being could withstand and survive a journey beyond the Earth's protective environment. The first successful space flight for live creatures came on 20 September 1951, when the former Soviet Union launched a sounding rocket with a monkey and eleven mice inside the nose cone of the rocket. This was not an orbital flight, but instead, an up-and-down rocket flight (similar to a very fast elevator ride up and down), and the animals survived. A few attempts to fly animals had been made previously (in fact, since 1948), but something always went wrong. These attempts were made with one purpose: to study the effect of exposure to solar radiation at high altitude, and to determine the effects, if any, of weightless flight.

The legacy of space life sciences research

Orbital flight then began in 1957 (October 4) when the Soviets sent the Sputnik 1 satellite into space. This was an unmanned flight, but before the year's end, on 3 November 1957, a second satellite, Sputnik 2, was launched carrying the first living creature into orbit, a dog named Laika. Laika was carried in a pressurized compartment in the satellite, but after a few days she died. Sputnik 2 reentered the Earth's atmosphere on 14 April 1958.

While these animals were in space, instruments monitored various physiological responses as the animals experienced the stresses of launch, reentry, and the weightless environment. As scientists gained more experience with these flights, animal space travellers were able to return to Earth in healthy condition, refuting predictions that some vital organs

might not function in the low-gravity environment. This experience with animals paved the way for human expeditions.

On 12 April 1961, Soviet cosmonaut Yuri Gagarin became the first human to orbit the Earth. He rode Vostok 1 around the Earth (24,800 miles) and experienced weightlessness for 89 minutes. After one orbit he reentered the atmosphere and landed safely. Then on 6 May of that same year, astronaut Alan B. Shepard, Jr., rode in his Freedom 7 Mercury spacecraft for a 15-minute suborbital flight and was picked out of the water some 300 miles downrange. After the astronauts returned safely, medical scientists dismissed many of the concerns about the frailty of the human space explorer. However, the Mercury flights made it clear that the body undergoes some real changes during and after space flight, such as measurable weight loss and fluid redistribution.

Astronauts completed a more complex set of inflight medical studies during the Gemini missions, which served as precursors to the lunar missions. All the life sciences studies that had been carried out up to this point were important in preparing the space suit and equipment needed for survival on the first U.S. space walk, which occurred during Gemini 4 on 3 June 1965. Doctors observed additional physiological changes such as minimal loss of bone and muscle density, but discovered no substantial health problems that would prevent humans from travelling to the moon.

A total of 11 manned Apollo flights were launched between October 1968 and December 1972. Twelve astronauts worked on the lunar surface after Neil Armstrong first walked on the moon on July 20, 1969, during the Apollo 11 mission. The Apollo missions showed that astronauts could work quite productively on the moon in only one-sixth the gravity of Earth. While the Apollo missions included simple inflight physiological observations, doctors examined crew members primarily before and after each flight. During the flights, crew members reported a few minor physiological problems, such as space motion sickness, but once again humans were able to live and work effectively in space without experiencing any major physiological problems.

During these early missions (Mercury, Gemini, and Apollo), scientists began to learn about human responses to microgravity; however, the small Mercury, Gemini and Apollo spacecrafts had little room for research equipment. All this changed in 1973 with the U.S. Skylab programme, the United States' first space station. At last, scientists were able to make more detailed measurements during three missions lasting 28, 59 and 84 days, each involving three human subjects. The most important contribution of these missions was the proof that people can live and work in space for several months.

The Russian Mir space station and the American Space Shuttle provided the next generation of experiences that humans would have with the space environment. The Space Shuttle and Mir have provided space life scientists with a more regular opportunity to conduct experiments aimed at a deeper understanding of the human body.

What is gravity?

In 1665-1666, Sir Isaac Newton first developed the universal law of gravitation and the laws of motion, which form the basis for our understanding of planetary motion and spaceflight. The universal law of gravitation states that the attractive force between any two bodies is given by:

$$F_g = G_u \frac{Mm}{d^2}$$

where m (of any object) and M (of Earth) are the masses of the two attracting bodies, d is the distance between their centres of mass and G_u is the universal gravitational constant ($6.67 \times 10^{-8} \text{ cm}^3/\text{g}\cdot\text{s}^2$) (Pace, 1977). In other words, the force of gravity is directly proportional to the product of the masses and inversely proportional to the square of the distance between them. Each time the distance between the centre of two masses doubles, the force is cut to 1/4 of the previous value. Microgravity (10^{-6} G) requires a significant distance between the two masses (~ 1000 earth radii or $6.37 \times 10^6 \text{ km}$). Low Earth orbit is only about 300 km above Earth. How, then, can we state that microgravity is found in low Earth orbit? The next paragraph explains this apparent discrepancy.

A force is defined as equal to the mass of an object times its acceleration (i.e., $F=ma$). Equation (1) can be rewritten as:

$$a = G_u \frac{M}{d^2}$$

Thus, an object of any mass at the surface of the Earth will accelerate toward the centre of the Earth at approximately 9.8 m/sec^2 . This gravitational acceleration is referred to as 1-G. A spacecraft orbiting Earth produces centrifugal acceleration that counterbalances Earth's gravitational acceleration at that vehicle's centre of mass. The spacecraft is therefore in "free" fall around Earth with the two opposing acceleration forces producing momentary resultant gravitational forces that range between 10^{-3} and 10^{-6} G . Gravity *per se* is reduced about 10% at the altitude of low Earth orbit, but the more relevant fact is that gravitational acceleration is essentially cancelled out by centrifugal acceleration.

Weight is a factor driving numerous chemical, biological and ecological processes on Earth. Given these facts, one should not be surprised that a lack of gravity could produce important changes to life, as we know it, even though it is the weakest of the physical forces of nature.

What happens to life when gravity changes?

Gravitational acceleration has been constant throughout the nearly 4 billion years of biological evolution on Earth. Gravity interacts with environmental forces to produce today's Earth. As species evolved from water to land, they had to develop systems for fluid flow and regulation, postural stability and locomotion that would allow them to function and thrive under a 1-G force. Without gravity, there is no "falling down", no need for 1-G structural support, no convective mixing, no up and down, no separation of air and water, etc., and life evolving without or at different levels of gravity may be very different.

As we seldom are exposed to gravity levels other than 1-G for any length of time, we have developed a "1-G mentality". A 1-G mentality means that we use gravity in our daily life without even thinking about it and have difficulty comprehending the appropriate design of space habitats and the complexity of ecological systems exposed to altered gravity. To answer the question "Can terrestrial life be sustained and thrive beyond our planet?", we need to understand the importance of gravity on living systems and we need to develop a multi-G (i.e., gravity levels both below and above 1-G), rather than solely a 1-G, mentality. According to NASA, approximately 40% of equipment flown in space for the first time does

not work, often due to heat build-up from lack of convection, lack of dissipation of air bubbles or habitats based on designs more appropriate for Earth.

The science of gravitational biology took a giant step forward with the advent of the space programme, which provided the first opportunity to examine living organisms in gravity environments lower than could be sustained on Earth. Organisms ranging in complexity from single cells through humans, are or appear to be responsive to Earth's gravity and its effects on ecology; thus, such organisms most likely would be affected also by a lack of gravity. Plants, including crop communities, require gravity for water management, soil characteristics, and other environmental factors. Many systems change, transiently or permanently, when gravity is altered.

I. Overall physiological response to space flight

Protecting humans against extreme environments requires understanding the underlying physiologic changes resulting from the exposure and the degree of medical risk associated with that exposure.

Despite significant limitations, such as operational constraints, concomitant use of countermeasures, and large inter-subject variabilities in a highly select population, the data obtained so far point to the fact that humans do adapt to and can function usefully in the space environment if adequate medical support is provided.

The biggest problem that must be overcome for space missions of several years in duration is the harmful effects of weightlessness on the human body. These effects include loss of bone density, muscle mass and red blood cells, fluid shifting from the lower to upper body, cardiovascular and sensory-motor deconditioning and changes in the immune system. Such reactions by the body might be appropriate for zero-gravity flight, but are inappropriate for return to the surface of our planet or another planet.

Over the 40 years of human spaceflight experience, a variety of countermeasures have been developed, including saline "loading", intermittent venous pooling (using lower body negative pressure or LBNP), pharmacological manipulations and resistance training, but all have had only limited success (see NASA Task Force on Countermeasures, Final Report, May 1997). Indeed, despite extensive in-flight exercise, most astronauts experience problems with balance and orientation, fainting and risk of muscle tears and bone fractures for the first few days after landing. In the view of many, the purpose of a human Mars mission is not mere survival; we cannot afford to have astronauts in a weak physical condition on any part of the mission. Such a mission cannot be seriously considered until these problems can be overcome. The countermeasures currently adopted to counteract the effect of weightlessness conditions on board the International Space Station (ISS) and the Space Shuttle point at stimulating a particular physiological system: the exercising treadmill and cycle ergometer for muscles (and secondary bones), the LBNP and fluid loading for cardiovascular responses, etc. Artificial gravity represents a different approach to the problem of zero-gravity effects on the human body, because it simply simulates our natural 1-G environment. Consequently, all physiological systems are challenged: bone stress, antigravity muscles, the otoliths of the vestibular system, and the cardio-vascular responses. Artificial gravity is not going to solve the critical problems of radiation exposure or many of the psychosocial and environmental issues associated with extended confinement and isolation. However, it could very well deal

with the debilitating and possibly fatal problems of bone loss, cardiovascular deconditioning (including fluid shift regulation, orthostatic hypotension and loss of myocardial wall thickness), muscle weakening, sensorimotor/neurovestibular disturbance (including balance disturbance, oculomotor disturbances, and perceptual illusions), and space anaemia. For these reasons, artificial gravity can be considered as a multi-system or "integrated" countermeasure.

Living in space & the human body

Like every other living creature we know of, humans evolved at the bottom of a gravity well. We take the Earth's tug for granted, and so do our bodies. So it's not surprising that our bodies behave oddly in orbit. What is surprising is that humans turn out to adapt remarkably well to zero-G (more precisely, microgravity). After all, back in 1961, Soviet scientists were genuinely worried that any prolonged period of weightlessness might even be fatal, which is why they limited Yuri Gagarin's first space flight to just 108 minutes and a single orbit.

Since then, scientists around the world have had the benefit of years of data on the effects of long-term space living. (The record for a long-duration mission is still held by Russian cosmonaut Valeri Polyakov, who completed a 438-day tour of duty aboard the Mir space station in 1995.) The crews of the ISS are already making full use of that experience, and will certainly add to it.

Weightlessness itself is the most important and the most obvious influence on life in space. Most astronauts find their freedom from gravity exhilarating, especially as they adapt to their new environment. But weightlessness enormously complicates the business of daily life, from eating to sleeping. And space adaptation involves some very complex changes in the human body, both short-term and long-term. These changes can cause health problems both in space and on return to Earth.

There are other factors, too. Outside the protective shield of the Earth's atmosphere, astronauts have to contend with high radiation levels. Mostly, these have minor and long-term effects: a slight increase in the risk of cancer in later life, for example. But during occasional solar flares, the sleet of radiation from the Sun can be immediately life-threatening.

Human psychology plays an important part in the story, too. Life in space also means living with a distinct lack of space. The ISS is vastly larger than any previous space structure, but even so it is no mansion. Astronauts can enjoy the finest views imaginable, with the whole planet stretched out before them amid the starry immensity of the universe. But their living quarters are pretty cramped, and they must share them with their fellow crew members for months at a time.

Still, there is no shortage of applicants for astronaut positions, and virtually everyone who has had the chance to live in space is keen to return. Besides, as our knowledge increases and space medicine develops throughout the 21st century, the men and women in orbit - and hopefully beyond - should have a more comfortable time in the future.

Microgravity & human physiology

Space flight is associated with many environmental stresses that influence biologic systems. The most remarkable and consistent feature, however, is the relative absence of

gravity. The omnipresence of gravity has shaped the evolutionary process of all biologic systems on Earth. Growth, development, structure, function, orientation and motion have all evolved features to cope with and take advantage of gravitational forces.

Gross structural changes have been observed in space. For example, astronauts typically are slightly taller during flight and tend to assume a fetal body-posture in weightlessness. Fluid shifts provide additional substantiation for the profound effects of weightlessness. Some evidence exists for cellular-level changes in the elastic forces within body tissues. Presumably, some of the endocrine³ and metabolic alterations observed in flight are related to changes in the mechano-transduction processes in the body in the absence of gravitational force.

Although weightlessness is the primary contributing factor to the observed physiologic changes, it probably is not the only one. Launch and re-entry into Earth's atmosphere entail exposure to increased G-forces and vibrations that may have distinct physiologic effects.

There may be two to three major groups of individuals who respond differently to the space environment:

- a) The first group makes the transition from Earth to space and back with no apparent difficulty and no significant deterioration in performance or health;
- b) The second group responds with significant early physiological shifts associated with symptomatic responses during the first week of exposure; this group reaches a reasonably steady state later in flight;
- c) It is possible that there is a small third group of individuals who do not reach equilibrium in the space environment, and who will continue to show progressive pathological⁴ deterioration despite extensive use of countermeasures.

1. The Vestibular System

We take our ability to stand upright just as much for granted as we do the force of gravity that holds us to the Earth. In fact, the human sense of balance depends on an extremely sophisticated sensor system that provides a constant stream of information to the brain. The key motion sensors are the subtle organs of the vestibular system inside the inner ear. These function as super-sensitive accelerometers feeding the brain with a steady stream of signals that indicate motion and direction. There are also pressure receptors in the skin and in muscles and joints. Our senses of sight and hearing complete the data stream. Without having to think about it, we usually know everything we need about our body's posture and state of balance.

In the absence of gravity, signals from the vestibular system and the pressure receptors are wildly misleading. The effect usually leads to immediate disorientation: many

³ Hormones that circulate in body fluids and produces a specific effect on the activity of cells remote from its point of origin;

⁴ Pathological: altered or caused by disease

astronauts suddenly feel themselves upside-down, for example, or even have difficulty in sensing the location of their own arms and legs.

This disorientation is the main cause of so-called Space Motion Syndrome (SMS), which one astronaut wryly described as "a fancy term for throwing up". Half or more of all space travellers suffer from space sickness, which brings with it headaches and poor concentration as well as nausea and vomiting. Usually, though, the problems disappear within a few days as astronauts adapt.

It is their brains, not their stomachs that do most of the adapting. The confusing signals from the inner ear are largely ignored and vision becomes the prime source of "balance" information. In space, "down" is where your feet happen to be.

When they return to Earth, astronauts have to re-adapt just as painfully. Back at the bottom of the gravity well, most have difficulty maintaining balance - and if they close their eyes, they are very likely to fall over. Because of the effects of weightlessness on bones and muscles, they may have difficulty standing at all. But disorientation itself usually only lasts a few days, and there seem to be no long-term effects.

There is one re-adaptation that can take somewhat longer to accomplish, although the consequences are more likely to be amusing than crippling. Several long-duration Russian cosmonauts have reported that months after their flight, they still occasionally let go of a cup or some other object in mid-air - and are quite disconcerted when it crashes to the floor.

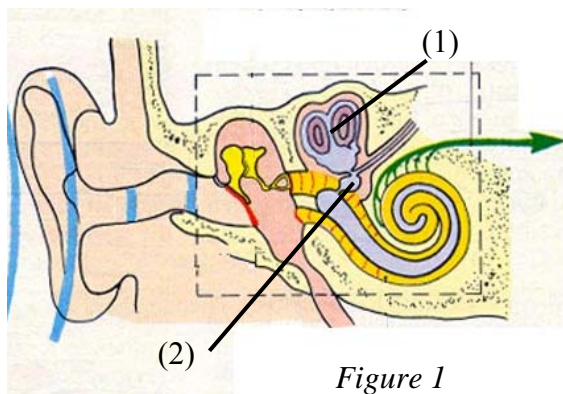
Correct transduction and integration of signals from all the sensory systems is essential for maintenance of stable vision, spatial orientation, eye-head coordination and postural and locomotion control. Central nervous system (CNS) plasticity allows individuals to adapt to altered sensory stimulus conditions. The microgravity⁵ environment of orbital flight represents such an altered sensory stimulus state.

Exposure to microgravity rearranges the relationships among signals from vestibular, visual, skin, joint and muscle receptors. Until some level of adaptation to the novel sensory conditions encountered in the weightlessness environment of space flight is achieved, astronauts and cosmonauts often experience the following: 1) Illusory self and/or surround motions; 2) Space motion sickness (SMS); 3) Eye-head coordination impairment; and 4) Equilibrium control disturbance. Many of the same types of disturbances are observed during a re-adaptation period following return to Earth. The magnitude and recovery-time-course of these neuro-sensory, sensory-motor and perceptual disturbances tend to vary as a function of mission duration.

For spatial orientation, people depend on the interaction of virtually every sensory system in the body. Our perception of location and position are a result of the brain's ability to integrate *visual* and *auditory* signals with *vestibular* input (from gravity- and motion detecting organs in the inner ear) and *proprioceptive* information (from motion, pressure and temperature sensors in the tendons, muscles, joints and skin).

⁵ Microgravity: a condition in space in which only minuscule forces are experienced: virtual absence of gravity; broadly: a condition of weightlessness

When environmental conditions change so that the body receives new stimuli, the nervous system responds by interpreting the incoming sensory information appropriately. In gravity, for instance, the interaction between the sensory, motor and perceptual systems enables the control of eye, head and body motions relative to Earth. In space, the free-fall environment of an orbiting spacecraft requires that the body adapt to the virtual absence of gravity. Input that the brain receives from the sensors stimulated by gravity is changed, prompting the nervous system to develop a new interpretation of the available data. Until this occurs, crew members may feel disoriented or experience *space motion sickness*, which often reduces their efficiency. Almost 2/3 of all veteran astronauts, in fact, have reported symptoms of space motion sickness: faintness, sweating, dizziness, nausea and/or vomiting.



The peripheral vestibular apparatus in the inner ear consists of two kinds of sensory receptors (Figure 1): (1) the *Semicircular Canals* signalling rotatory head movements, and (2) the *Otolith Organs* that sense linear forces, including gravity, acting on the head. The angular accelerometers (1) are liquid-filled

tubular loops arranged in three orthogonal planes. In each loop is a swelling, the ampulla, within which sensory hair cells translate movement of the fluid into neural signals. The linear accelerometers (2) are calcium carbonate concretions embedded in gelatinous material and resting on sensory cells, the utriculi and saccule. These, together with the canals, are embedded in bone on each side of the head. There, in conjunction with the fluid-filled cochlear organ of hearing, they are known as the labyrinth, or inner ear.

The neural signals produced under acceleration are integrated in the brainstem with signals from proprioceptors reporting the relationships of position among limbs, trunk and neck. There, or at higher level, signals from skin pressure receptors, visual system and stored intellectual information are integrated to coordinate movements of the limbs, head and eyes.

The activity of the otolith organs is altered in microgravity (because stimulation from gravity is absent during space flight, interpretation of the gravireceptor signals as tilt is meaningless; therefore, during adaptation to weightlessness, the brain reinterprets all gravireceptor outputs). The activity of the semicircular canals is not affected.

Microgravity encountered during space flight offers an opportunity to study the relative role of two kinds of vestibular organs as well as the adaptive mechanisms the brain uses to adjust to the altered force and motion environment.

Spatial orientation

Spatial orientation is the relation established between the body and the external reference frame. It results from the integration of sensory signals from the visual, vestibular, tactile and proprioceptive systems, and from a comparison between them and the copy of the motor-command signals arising in the brain.

In weightlessness, the otolith organs can no longer serve their usual graviceptive role of indicating static head position to gravity. As a result, visual information on the direction of the vertical or horizontal, which normally interacts with graviceptive information on Earth, becomes increasingly dominant in establishing spatial orientation in weightlessness. Tactile information such as pressure on the soles of the feet (when strapped to the floor) continues to promote a sense of the vertical.

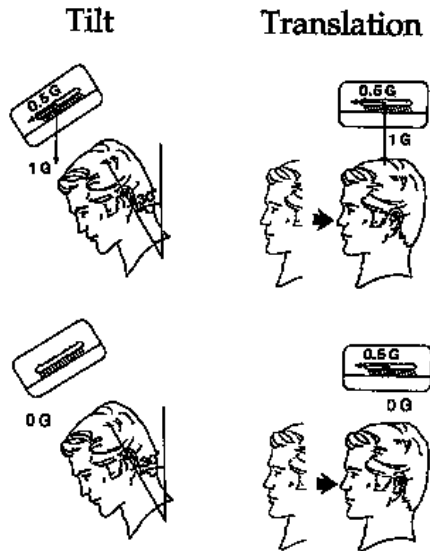


Figure 2: Displacement of the otoliths during tilt and translation on Earth and in space:

On Earth, gravireceptor signals from the otoliths can be interpreted either as linear motion (translation) or as tilt with respect to gravity. Because stimulation from gravity is absent during orbital flight, interpretation of the gravireceptor signals as tilt is meaningless. Therefore, during adaptation to weightlessness, the brain reinterprets all gravireceptor output to indicate translation, and otolith-mediated responses such as postural reflexes, eye movements and subjective responses would alter accordingly. This is the so-called Otolith Tilt Translation Re-interpretation (OTTR) hypothesis.

It is hypothesized that in microgravity the nervous system comes to reinterpret signals coming from the otolith organs. After return from space, the brain interprets the otolith signals as arising from translational head movements, rather than from a combination of such head movements with changes in attitude with respect to the vertical (Figure 2). As a result, immediately post-flight, the threshold of detection of linear acceleration may change, and visual influences on orientation appear stronger than before the flight. Also, tilting movements of the head may cause a sense of sudden linear translation in the opposite direction. In addition, several illusions and alteration of motor performance are also commonly reported, including a feeling of heaviness, a sense of disorientation when making sudden head movements, an inability to move about in the dark and an illusion of floor motion during vertical body movements.

Postural mechanisms

Since an important function of posture control is to coordinate muscular activity so as to maintain the orientation of the body with regard to gravity, significant changes are expected during adaptation to weightlessness. On Earth, it is well known that subjects maintain their equilibrium even during changing environmental conditions by using different combinations of fixed postural strategies, i.e., muscle activity and body segment motion. The strategy necessary to execute a given movement depends to a large extent on the configuration of support surfaces provided to the subject.

Voluntary pointing accuracy and perception of static limb position are impaired in microgravity, and naïve subjects, when asked to orient themselves vertically in relation to

visual surrounding and support surfaces, assume skewed⁶ postures. The postural reflexes under an otolithic control appear to be depressed in flight and may be enhanced for several days post flight. Returning crew members routinely experience difficulties in walking and standing with eyes closed, and in making quick turns. These symptoms occur even after missions of relatively short duration, where changes in muscular strength are minimal.

Space Adaptation Syndrome (SAS) and Space Motion Sickness (SMS)

Almost 67% [Moore et al; 1996] of astronauts and cosmonauts who spend time in orbit are subject to a form of motion sickness known as Space Adaptation Syndrome (SAS). This problem typically lasts for the first several days of weightlessness, and sometimes also occurs just after return to Earth, and includes symptoms such as *dizziness*⁷, *headache*, *cold sweating* and *fatigue* to *nausea* and *vomiting*. Consequences of this “space motion sickness” (SMS) range from simple discomfort to incapacitation, creating potential problems during re-entry and emergency exit from the spacecraft.

The primary cause of SAS is conflicts between the neurosensory inputs from visual and tactile⁸ senses and from the vestibular organs of the inner ear. However, the precise mechanisms of the conflict are not well understood, and an effective therapy has yet to be developed. There is also evidence from space experiments that neurosensory changes take place continuously during space flight, and even after landing, long after the acute symptoms of motion sickness have subsided. Symptoms are not significantly reduced on a re-flight. It has been observed that SAS is brought on or exacerbated by head movement (especially vertical head movement) and made better by rest. This suggests that activity arising in the vestibular system activates central mechanisms that produce the symptoms.

Today, the accepted method for preventing or treating the symptoms of SMS is the use of medications, usually scopolamine-dextroamphetamine sulphate (Dexedrine) or promethazine-ephedrine combinations. Such drugs, however, have strong central nervous system activity. For example, the space shuttle programme is using intramuscular injections of Phenergan. Additional approaches, such as the use of biofeedback⁹, mechanical devices to restrain head and neck movements and adaptation-training techniques, remain under laboratory investigation.

2. Cardiopulmonary System

It has been well known since the very earliest days of spaceflight that space travellers may experience dramatic perturbations in their cardiovascular function. The effects of spaceflight on this system are most apparent upon return to Earth when individuals are unable to stand without feeling dizzy, light-headed and may perhaps even faint. This phenomenon is called orthostatic intolerance (inability to maintain blood pressure on standing) and is thought to be due to cardiovascular deconditioning caused by exposure to microgravity. This could be a life threatening problem if emergency egress from the return vehicle is required or, in the case of the American Space Shuttle, where humans are required to pilot the returning craft.

⁶ Skew: to distort from a symmetrical form

⁷ Dizziness: having a whirling sensation in the head with a tendency to fall

⁸ Tactile: perceptible by touch

⁹ Biofeedback: the technique of making unconscious or involuntary bodily processes (as heartbeats or brain waves) perceptible to the senses (as by the use of an oscilloscope) in order to manipulate them by conscious mental control

There is concern that with prolonged exposure to microgravity, as might occur on a flight to Mars, the system may be severely impaired. In order to best understand what might happen in space, it will be important to understand how this system works in Earth gravity.

Heart, circulation and body fluids

Almost two-thirds of the average body weight is made up of water, in the form of intercellular fluid, blood plasma and the interstitial fluid between blood vessels and surrounding tissue. On Earth, all this liquid tends to settle downward in the body. Blood pressure at our feet, for example, is about 100mm of mercury (mmHg) higher than blood pressure in our chests. And the need to pump blood against the force of gravity requires the muscles of a big, powerful heart.

In space, there is nothing to pull body fluids down: there is no "down" to pull them to. The first effects are almost immediate. Without the restraint of gravity, fluids migrate from the legs to the head. Within a day, legs shrink by up to a litre in volume and faces puff up correspondingly. The extra fluid in the head also leads to blocked sinuses and noses - the "space sniffles" that astronauts generally have to live with throughout their mission.

Other effects are more serious. Blood plasma drops by about 20% and the red blood cell count falls similarly: returning astronauts usually suffer from a temporary anaemia. Without gravity to contend with, the heart has to do far less pumping work. Heartbeat slows down. Since the body no longer needs to maintain the powerful heart muscles needed on Earth, heart tissue begins to shrink.

Exercise is not enough to reverse the process, but it helps to minimize it and the exertion also provides some relief. Whenever possible, astronauts spend several hours a day on a treadmill or similar apparatus: the more exercise they can do in space, the less time it will take to recover on their return.

The Cardiovascular System

Evolution has equipped us with a series of conducting tubes (blood vessels) and a pump (the heart) to circulate a fluid medium (blood) that brings the necessary materials (oxygen, glucose, amino acid) from the gut and lung and picks up the undesired by-products of metabolism (carbon dioxide, lactic acid) from the local environment and carries them to the organs of excretion (kidney, liver, lung). The primary function of the cardiovascular system is to deliver a flow of blood to the local tissues so that individual cells in that tissue can be maintained in optimal condition. In order for this to happen, the flow of blood has to be regulated according to need, as defined by activity level in that tissue. Thus, exercising muscles requires a high blood flow to bring in lots of oxygen and glucose to take away the lactic acid and carbon dioxide.

Control of blood flow

The flow of blood through a given tissue bed is directly proportional to the pressure gradient for flow across that bed and inversely proportional to the resistance encountered during transit:

$$F = (PA - PV) / R \quad R = 8 \eta L / \pi r^4$$

F = flow, PA = arterial pressure, PV = venous pressure, R = resistance to flow,
 η = viscosity, L = length of tube, r = radius of tube

If, as happens in health, the outflow pressure (venous) is so low as to be almost negligible, and arterial pressure is maintained constant, then the critical variable, blood flow, can be increased or decreased by altering resistance. In this consideration the primary determinant of resistance is the radius of the vessels distributing blood to the tissue in question. This size of the vessel opening is determined by the state of contraction of the muscle surrounding the vessels responsible for distributing flow (arterioles¹⁰) to the site of exchange (capillaries¹¹). If these muscles are contracted, radius is decreased, resistance is increased and flow is decreased. The state of contraction of this vascular smooth muscle is dependent on the tissue in question. Tissues whose blood flow is primarily controlled by the central nervous system (i.e., skin because of its role in temperature control) receive extensive nervous innervations to their vessel muscles. Tissues whose blood flow is dependent on local activity levels (brain, heart) are primarily influenced by changes in the local environment (pH, adenosine, oxygen tension, carbon dioxide tension). Many tissues (muscle) are subject to both control mechanisms. In all cases, varying resistance to change blood flow will only be possible if arterial blood pressure is maintained relatively constant.

Control of blood pressure

As with so many body systems, *feedback control* is critical to the regulation of blood pressure. The first step in a feedback control system is to measure blood pressure so that perturbations can be corrected. Signals “describing” blood pressure are constantly forwarded by nerves to the brain from sensors (baroreceptors) located in both the arterial and venous side of the circulation. The cardiovascular control centre in the brain integrates all the incoming messages and initiates corrective actions to return blood pressure to the “normal” set point.

The “pressure” in the blood vessels is generated by the volume of blood which the heart pumps per unit time (cardiac output, CO) into a system of very elastic vessels (arterial tree), the runoff from which is determined by the state of resistance of all the final branches of this tree, the arterioles (total peripheral resistance, TPR). This can be expressed as follows:

$$P = CO \times TPR$$

Cardiac output is in turn a function of the volume pumped out of the heart (stroke volume) with each beat (heart rate, HR). As suggested above, TPR is the sum of all the individual resistances of each of the vessels responsible for distributing blood from the major arteries into the very smallest divisions, the capillaries.

When, for whatever reason, blood pressure falls (as happens when you jump out of bed in the morning and the blood volume that was resting in the large veins in your chest ‘falls’ into your legs), the brain can immediately counteract this by calling on any combination of $TPR \uparrow$, heart-contraction \uparrow , $HR \uparrow$, etc. to correct pressure back to its set point.

¹⁰ Arterioles: any of the small terminal twigs of an artery that ends in capillaries

¹¹ Capillaries: any of the smallest blood vessels connecting arterioles with venules and forming networks throughout the body

Typically, such corrections are brought about by a beautifully orchestrated combination of hormones and nervous signals simultaneously.

All of the above is true, of course, only if one has an adequate or *effective circulating blood volume*. That is, if you suffer from a serious bleeding and have a reduced blood volume, no amount of increase in TPR, HR, contractility, etc. can restore your blood pressure unless the volume of the system is restored. This is why an infusion is always started when a person's blood pressure is dropping due to loss of blood.

What happens in Spaceflight?

The effects of spaceflight on the cardiovascular system are almost immediately evident. Photographs document the puffed faces and astronauts report an immediate sense of sinus congestion, fullness of the head, often accompanied by headache – all in association with a noticeable decrease in leg girth (“bird legs”). What has happened?

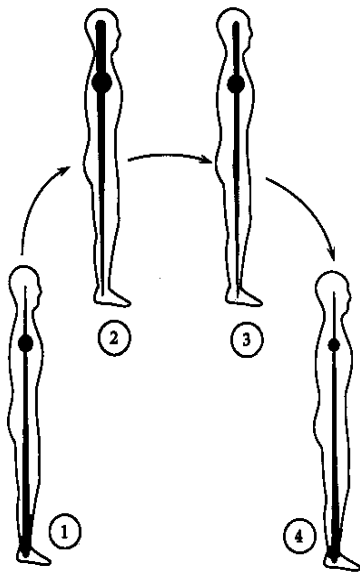


Figure 3 Diagrammatic representation of body-fluid distributions on Earth (1), upon entering weightless environment, before fluid loss (2) and after fluid loss (3), and back upon returning to 1 *g* (4). (Adapted from Charles and Lathers, 1991.)

We are quite sure that upon insertion into microgravity the blood that is normally pooled in the legs due to the pull of Earth's gravity moves to the point of least resistance, the large venous vessels in the chest. It is thought that the sensors located here perceive that the circulation is “overfilled” and signal a reflex response resulting first in an adjustment of the mechanical determinants of arterial pressure and then in excretion of this “extra” fluid by the kidneys in the form of urine (*diuresis*¹²↑). Evidence for this central movement of fluid includes the puffy faces, etc. noted above. Approximately 1-2 litres of fluid do actually move out the legs.

Interestingly enough, there seem to be little, if any, ill effects of these changes while in spaceflight. Indeed, one could argue that such changes are adaptive for microgravity. The only potential problem occurring during actual spaceflight may be the occasional report of *heart beat irregularity*, a phenomenon that we do not yet completely understand. As such irregularities seem to be especially prevalent during extravehicular activity (EVA), stress may be an important contributing factor.

The real problem comes with return to Earth (or other gravitational body). Many returning space travellers (around 50%) experience some level of *orthostatic hypotension*¹³ when trying to stand just after landing. This may range from a mild dizziness to actual passing out. In this transition, the body responds to gravitational pull by having blood pulled from the giant reservoirs in the central veins back into the leg vessels. This blood is then trapped here by gravity, so the “effective” circulating volume is considerably reduced. Perhaps even to the point that the system cannot adequately maintain blood pressure. Furthermore, evidence from post-flight testing shows that when the determinants of blood pressure are measured, only the

¹² Diuresis: excretion of urine

¹³ Orthostatic hypotension: abnormally low blood pressure when standing upright

heart rate is increased, suggesting that something may be wrong with the feedback control system. Recent evidence suggests that the nervous system no longer responds appropriately to a shift in pressure.

Countermeasures

Both the US and Russian space programmes have long used countermeasures assumed to prevent or delay the deconditioning thought to occur in space. Unfortunately, neither country has had the opportunity to study the body's response to microgravity in the absence of such countermeasures, as operational safety is too great an issue not to try and prevent adverse changes. Thus, returning space travellers are typically required to ingest (one hour before re-entry) about 1 litre of drinking water made isotonic by simultaneously swallowing an appropriate number of salt tablets. This volume will fill up the vessels when all the blood gets pulled down into the legs.

Returning space travellers also typically wear g-suits with inflatable leg bladders that can be activated if dizziness is experienced. In addition, space fliers typically exercise vigorously throughout the flight in the hopes of keeping the heart fully conditioned to the rigors of having to pump lots of blood and maintain blood pressure at the same time.

Cardiovascular changes seem to be completely reversed with time back on Earth, although this recovery may take months for long time space dwellers. However, the state of incapacity of many returning fliers is extreme and in the right circumstances (i.e., hydrazine¹⁴ leak or crash landing, requiring rapid egress) this could prove to be disastrous. Complete information can be gained only by critical, long-term observations in space.

3. Bone & muscle physiology

Bones are the scaffolding that holds the body against gravity. Our powerful skeletal muscles support that scaffolding - and of course move it around as required. Without gravity, bone and muscle alike lose their prime function. After even a short time in orbit, some strange things begin to happen. The first seems like good news: without the compressive force of gravity, the spinal column expands and astronauts grow taller, usually by between 5 and 8 cm. Unfortunately, the extra height can bring complications, which may include backache and nerve problems. More worrying than height gain, though, is the loss of bone and muscle tissue that becomes apparent from the first few days of a space mission.

Bone is a living, dynamic tissue. In normal life, new bone cells are constantly being made while worn bone is destroyed and its materials recycled. Bone regeneration is governed by a complex system, regulated by hormones and vitamins as well as physical stress (e.g. training) on various parts of the skeleton. In microgravity, the body has no need to maintain its skeletal structure to Earth-normal standards. So bone tissue is absorbed and not replaced: astronauts can lose up to 1% of their bone mass each month. The missing bone shows up as high calcium levels elsewhere in the body, which itself can lead to health problems - kidney stones, for example.

Microgravity bone loss stops soon after astronauts return to Earth, but so far, no one is sure whether the lost bone fully regenerates. The life science experiments planned for the ISS

¹⁴ Hydrazine: a colourless fuming corrosive strongly reducing liquid base used esp. in fuels for rocket engines

should help scientists learn much more precisely how bone loss comes about, and perhaps how to cure it. Since the problem is very similar to osteoporosis, a bone-wasting disease especially common among elderly women on Earth, astronauts will not be the only people to benefit from the research.

Bone and mineral metabolism

Even in a mature skeleton, bone constantly undergoes breakdown and rebuilding on a regular basis. If this were not the case, we would never heal from a crack or break. In bones this remodelling process is in a balance between cells that break down bones (called *osteoclasts*) and those that lay down new bone (*osteoblasts*). Hormones control both processes.

Our bones perform two very important functions. Bones provide the rigid trusses that provide support to our body parts and the structural framework for our upright posture. Bone also serves as a reservoir of the mineral calcium. It derives its strength from the deposition of crystallized calcium salts onto a collagen¹⁵ fibre matrix. Calcium is a substance that is critical for many body functions, including muscle contraction, nerve conduction, secretory processes, blood pressure regulation and blood clotting. Because optimal functioning of these calcium-dependent processes depends on tightly controlled levels of calcium in the blood, anything such as space flight that might cause the bone to alter its calcium content would influence blood levels of calcium and, potentially, all of the calcium dependent functions mentioned above.

It has long been known that removal of muscle forces and weight from bones, as occurs in bed rest or having a limb in a cast, causes the loss of minerals, which is known as *disuse osteoporosis*¹⁶. Living in the weightlessness environment of space, which represents a form of musculoskeletal disuse, has been found to cause a loss of bone mineral. Early studies of bone mineral changes using X-ray densitometry suggest that large amounts of bone may be lost during relatively brief periods of spaceflight. Measurements from Gemini and Apollo crew members show an average post-flight loss of 3.2% compared with pre-flight baseline values. Data from Skylab, Salyut, and Mir show a *loss of 1% of heel bone density per month*. The weight bearing bones loose more substance than the non-weight bearing bones do. Flight data from Skylab show a monthly calcium loss for the average of crewmen of about 8 g, or about 25 g for the 84-day flight. This would mean a total calcium loss in 1 year of over 300 g, or approximately 25% of the total body supply. Loss of bone mineral, if allowed to proceed unchecked, could represent a limiting variable for long duration space missions. There is no evidence that the in-flight bone losses are self-limiting, and it is the current assumption that *calcium losses occur progressively throughout the flight*. The precise mechanisms underlying the loss of bone mineral during spaceflight are still not known. Studies of animals with immobilized limbs indicate that disuse produces a number of time-dependent changes in bone formation and resorption. It may be that a proportionally *larger increase in resorption* over formation is responsible for the loss of bone mineral mass, at least in immobilized subjects (in response to gravitational unloading). Also not known are the underlying physiologic processes – whether hormonal, neural, electrical or mechanical – that initiate these changes.

¹⁵ Collagen: an insoluble fibrous protein that occurs in vertebrates as the chief constituent of connective tissue fibrils

¹⁶ Osteoporosis: decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and fragility

The major health hazards associated with skeletal changes include signs and symptoms of *hypercalcemia*¹⁷ with rapid bone turnover, the risk of *kidney stones* from *hypercalciuria*¹⁸, the lengthy recovery of lost bone mass after flight, the possibility of irreversible bone loss, the possible effects of calcification in the soft tissues, and the possible *increase in fracture potential*.

At least two countermeasures, however, are considered to be potentially beneficial. The first countermeasure is *exercise*. An ideal exercise countermeasure programme represents the best possible compromise among efficacy, equipment size, ease of performance, and operational time requirements. 1 to 1.5 hours per day of walking or jogging under a 1g force applied by elastic straps is considered to be adequate to prevent disuse osteoporosis. A *pharmacologic countermeasure* has also been considered. Ground-based studies have shown that drugs such as diphosphonate can control the loss of calcium in subjects undergoing bed-rest over a period of many weeks. This approach has not been tried during a space mission but may offer a useful means of reducing bone demineralization during the weightless environment of an extended spaceflight.

Muscle structure and function

There are three major types of muscles in our bodies, all of which function by the coordinated contraction and relaxation of the individual units making up a given muscle. *Cardiac Muscle*¹⁹ is found only in the heart and works automatically, i.e., without conscious input from our brain, to pump blood through our blood vessels. *Smooth Muscle*²⁰ also works independently of our conscious thoughts to perform those basal, autonomic functions such as blood pressure regulation, digestion, and urinary flow. *Skeletal Muscle*, on the other hand, is usually active only when called to do so by our brain (walking, running, lifting, eating or standing upright).

The functional capacity of skeletal muscle, which constitutes nearly 40% of the volume of the human body, depends on its predominant fibre type and its motor innervation. Muscle fibre types are categorized as *slow-twitch* (ST) or *fast-twitch* (FT) depending on their contractile, metabolic²¹ and fatigue properties. FT muscle fibres are recruited for brief periods of high-intensity work, and ST fibres are recruited primarily for low-intensity work including maintenance of posture and activities requiring endurance. The plasticity of muscle fibres allows them to adapt to under-loading or weightlessness as they do to overloading or exercise. Studies from short duration flights show that *extensor*²² muscles suffer from atrophy²³ more severely than *flexor muscles*. Severe muscle atrophy can occur within a few days, in extensors more rapidly than flexors, and in slow contracting fibres more severely than in fast ones. Muscles that have an *antigravity function*, such as the calf and quadriceps muscles of the leg, hip-, back- and neck extensor muscles rapidly shrink during space flight. In contrast, arm and hand muscles are barely affected. Two distinctive phases in muscle deterioration have become apparent: 1) the first phase showed a 20-30% decrease in muscle strength during the first

¹⁷ Hypercalcemia: an excess of calcium in the blood

¹⁸ Hypercalciuria: an excess of calcium in the urine

¹⁹ Cardiac muscle: heart muscle

²⁰ Smooth muscle: Type of muscle responsible for involuntary actions

²¹ Metabolic: the turnover of energy

²² Extensor muscle: any of the muscles that increase the angle between members of a limb (e.g., straightening the elbow or knee)

²³ Atrophy: shrinking, reduction of size

weeks of flight when compared to pre-flight levels. 2) The second phase started 3-4 weeks after the beginning of a flight, and the magnitude of muscle deterioration was highly dependent on the level of physical exercise on board [Kozlovskaya; 1996].

The lack of motivation to activate large parts of the musculoskeletal²⁴ system in microgravity conditions derives from the absence of any ‘biological need’ to do so, and therefore this is one of the examples of how humans must work against an adaptation process which makes physiological sense in the given situation, that is to lose unnecessary muscle mass in weightlessness, but would have dangerous consequences when re-entering 1 G conditions, particularly after longer-lasting travels in space.

4. Hematology²⁵ & Immunology²⁶

Exposure to microgravity and the associated head-wards shift of fluids results in a series of compensatory mechanisms. A rapid, *significant reduction in blood volume* is followed by a *reduction in red blood cell (RBC) mass*. The decrease in RBC mass results from a depression of erythropoiesis²⁷, which is caused primarily by low erythropoietin²⁸ and the associated ineffective erythropoiesis. During long space flight, RBC mass apparently reaches an equilibrium that is optimal for the microgravity environment.

The immune system also seems to be affected by spaceflight or its associated stresses. *White blood cells* (cellular immune system) are *significantly reduced* after spaceflight. Changes in *immunoglobulins*²⁹ (antibodies secreted by lymphocytes and circulating in bodily fluids) also have been observed. The immune system functions seem to be impaired while at the same time the various bacterial colonies increase growth. These micro-organisms play an indispensable role in the recycling of elements and biomass on Earth. Very few known micro-organisms pose a threat to human health. However, a small number of pathogenic species are capable of causing discomfort or illness. In space, infectious pathogens pose an extra threat due to the confined quarters and recycled air of the spacecraft. If the human immune system is compromised in space, as some research has suggested, risk of illness would be increased.

Normal precautions can exclude most known pathogens from space habitats. However, under certain conditions, normal human endogenous bacterial micro-flora can cause infections. Such infections result from changes in the relationship between the host and its internal microbes, which normally live in a very delicate balance. Microbes can also contribute to food spoilage and the degradation of many materials, such as the rubber seals found in spacecraft.

Nevertheless, up to now no major problem relating to a malfunction of the immune system appeared during or after space flight. In-depth investigations of immune system adaptations to the conditions of space flight, including the effects of radiation, nutrition, low physical load and psychic stress, still need to be conducted in detail.

²⁴ Musculoskeletal: involving both musculature and skeleton

²⁵ Haematology: a medical science that deals with the blood and blood-forming organs

²⁶ Immunology: a science that deals with the immune system and the cell-mediated and humoral aspects of immunity and immune responses

²⁷ Erythropoiesis: the production of red blood cells from the bone marrow

²⁸ Erythropoietin: a hormonal substance that is formed esp. in the kidney and stimulates red blood cell formation

²⁹ Immunoglobulins: any of a large number of proteins of high molecular weight that are produced normally by specialized B-cells after stimulation by an antigen and act specifically against the antigen in an immune response

Time course of in-flight acclimatization

Microgravity affects just about everything in the human body, and usually for the worse. Fortunately, the effects are seldom more than temporarily disabling: humans are very good at adapting. And when astronauts return to Earth, they normally re-adapt very quickly to the customary, gravity-bound environment.

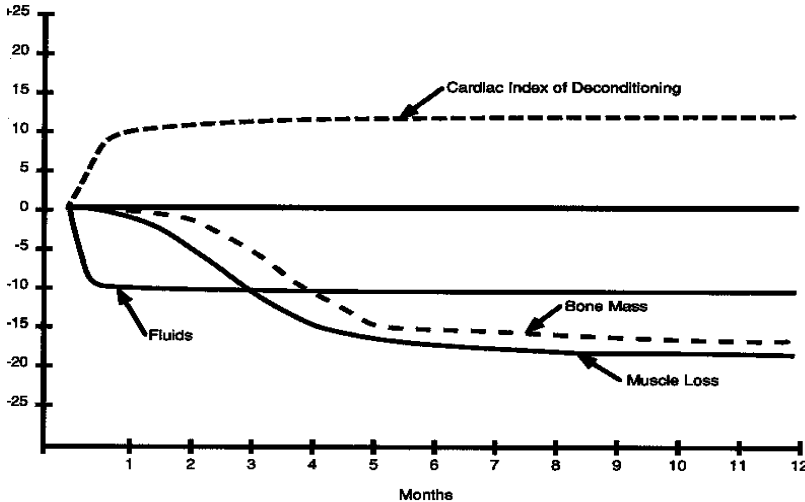


Figure 4: Time course of physiologic shifts during re-adaptation to 1 G in body systems in which the characteristics of re-adaptation are minimally dependent upon flight duration. Adequate post-flight data concerning calcium recovery have yet to be collected. [Nicogossian et al., 1994]

It is presupposed that all biologic systems are in a state of homeostasis at the beginning of the flight. Some susceptible systems exhibit changes almost immediately as the vehicle begins orbiting Earth. For example neuro-vestibular adjustments, and their associated symptoms, are likely to take place during the first hours or days in orbit; in contrast, decreases in RBC mass peak after 60 days in flight. Other physiologic functions do not seem to shift early in flight, but later undergo gradual and progressive changes. In particular, loss of calcium and lean body mass and possible effects from cumulative radiation seems to increase continually, regardless of flight duration or level of acclimatization achieved by other body systems. Most physiologic systems seem to reach a new steady state compatible with “normal” function in the space environment within four to six weeks. Complete acclimatization, however, may require a very long period of exposure to weightlessness, probably in the absence of countermeasures.

Re-adaptation to Earth’s environment

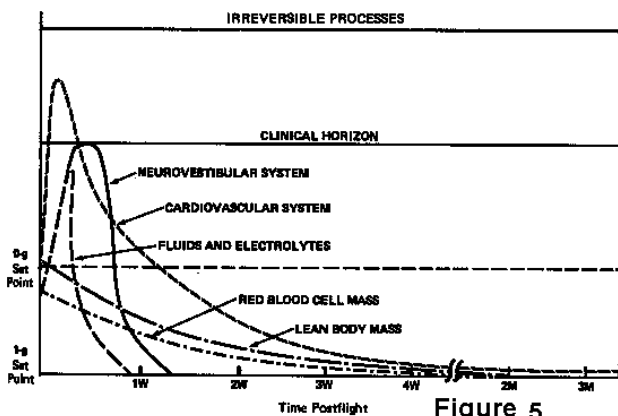


Figure 5 [Nicogossian et al., 1994]

Biomedical data collected from returning crews indicate that a compensatory period of physiologic re-adaptation to 1 G is required after each spaceflight. The amount of time necessary for re-adaptation and the characteristic features of the process vary greatly between individuals. Some differences can be attributed to variations in mission profile and duration, sample size, or in the use of countermeasures. Furthermore, different physiologic systems seem to readapt at varying rates. Nevertheless, preliminary

conclusions can be drawn concerning the time course of re-adaptation, especially for those systems that are affected only minimally by mission duration.

The return to Earth involves compensatory shifts in several physiologic systems, sometimes leading to obvious symptoms. For example, astronauts and cosmonauts consistently demonstrate *orthostatic intolerance*³¹ of varying severity upon landing because of body fluid shifts and associated reflex responses of the cardio-pulmonary neuroreceptors³².

**INCIDENCE OF ORTHOSTATIC HYPOTENSION³⁰
OF SPACE SHUTTLE MISSIONS THROUGH STS-50**

Before Egress	
% of missions	35%
% of crewmembers	9%
At Landing-Site Clinic	
% of missions	27%
% of crewmembers	6%
Number of missions	48
Number of crewmembers	261
Average mission duration	7 days

[Nicogossian et al., 1994]

The post-flight re-adaptation process in the neuro-vestibular system is usually heralded by difficulties in postural equilibrium; symptoms ranging from mild to severe illnesses. Most measured variables, however, including cardiovascular³³ function, fluid levels and erythrocyte³⁴ mass, return quickly to pre-flight baselines after landing. Longer space missions usually require more time for re-adaptation, especially for bone and muscle. For example, muscle strength seems to be restored after four to eight weeks, and bone mass probably recovers within about eight months, depending on the duration of the mission. However, the possibility of residual regional bone loss and atrophy in antigravity muscles exists even when countermeasures such as vigorous exercise are employed.

Despite these numerous shifts, humans seem to acclimate adequately to the environmental effects of spaceflight and recover after returning to Earth. Until now, astronauts have not shown residual pathology upon return to Earth. Wide variability probably exists in individual tolerance and ability to acclimatize to weightlessness and later to readapt to Earth's gravity.

³⁰ Hypotension: abnormally low blood pressure

³¹ Orthostatic intolerance: hypotension relating to, or caused by erect posture

³² Cardiopulmonary neuroreceptors: neural receptors in the heart and lungs

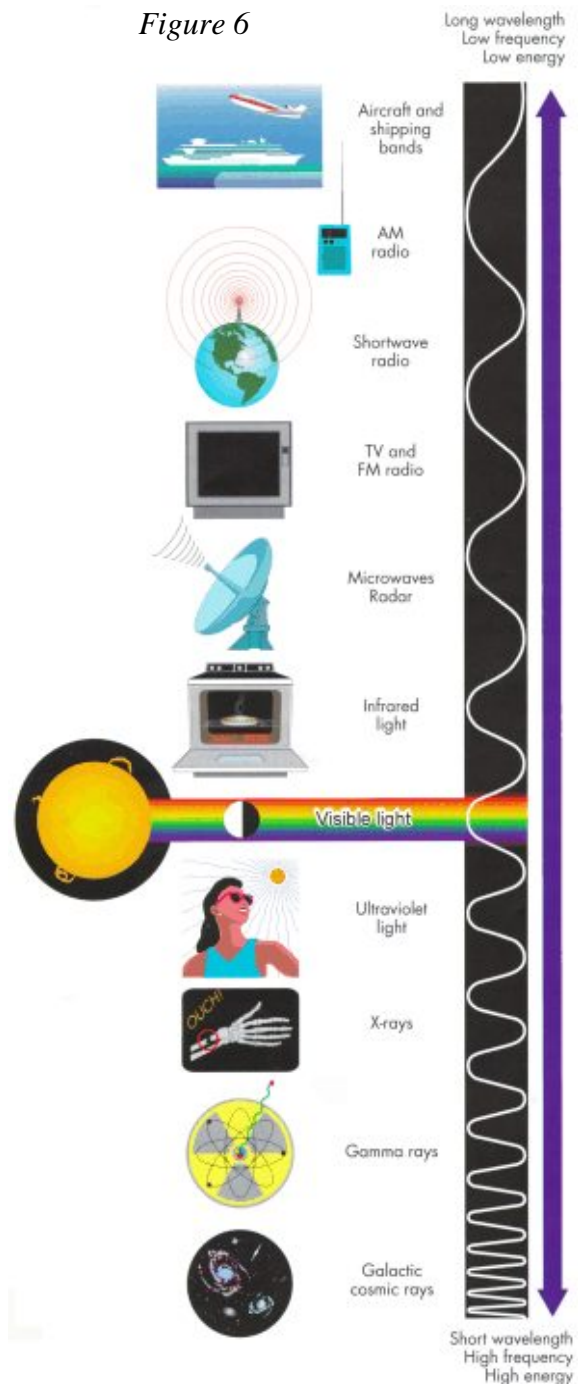
³³ Cardiovascular: relating to, or involving the heart and blood vessels

³⁴ Erythrocyte: red blood cell; any of the haemoglobin-containing cells that carry oxygen to the tissues and are responsible for the red colour of vertebrate blood

II. Radiation and Radiobiology

The electromagnetic spectrum

The Earth's atmosphere serves another very important purpose in sustaining life: it filters most of the Sun's ultraviolet (non-ionizing) rays that can be harmful to the body, and it protects us from the even more dangerous *ionizing radiation* of space. What is radiation, anyway? First of all, to radiate is "to spread," and the radiation that we are talking about here is energy. Therefore, radiation is energy that travels and spreads out along its path. Nearly everyone is aware of the fact that radiation can be dangerous, but, in fact, some radiation is an important part of our lives and is not dangerous at all. Visible light that "spreads" from a lamp in your house or radio waves that "spread" out from a radio station transmitter that you pick up on your stereo are both examples of harmless kinds of *electromagnetic (EM) radiation*. Other examples of EM radiation are microwaves, infrared and ultraviolet light, X-rays, and gamma rays (figure 6). The differences between the various types of EM radiation exist in the length of their waves and the number of wave cycles per second (frequency). Although we have described such EM radiation in terms of waves, it can also be described in terms of a stream of (massless) particles, each travelling in a wave fashion with the same velocity (speed of light) and each carrying a certain amount, or bundle, of energy. Each bundle of energy is called a *photon* and all EM radiation consists of these photons. The most abundant type of EM radiation in space is gamma rays that originate outside our solar system and are called *galactic cosmic rays*.



Another kind of radiation comes in the form of *particulate radiation* (consisting of particles with mass), which includes electrons and the fundamental nuclear particles (protons and neutrons). The particles in outer space are mainly protons, but there are also nuclei typical of the matter that is found in our galaxy, from helium to uranium. There is a peak in abundance at iron. This is presumably due to a large amount of iron present in the sources,

probably supernovae. There are also particles, mainly protons and electrons, trapped in "belts" or orbits around the Earth.

The term *ionizing radiation* can refer to EM radiation or to energetic nuclear particles that are capable of producing ions (charged atoms) directly or indirectly as they pass through matter. This process is called *ionization* (figure 8). Ionization occurs when atoms in a cell are bombarded by radiation and an electron is either added to or taken from the atom, thus giving the atom a charge. In the body, such ionization can rupture chromosomes and cause mutations that are responsible for certain cancers. Ionizing radiation is abundant in space. A rain of particles, along with the electromagnetic radiation, arrives at the top of the Earth's atmosphere from space. Most of it is filtered by our atmosphere. Radiation coming from outside our solar system is called *galactic cosmic radiation*. That coming sporadically from the Sun is called *solar particle radiation*. The solar particle radiation arrives over a period of several days in what are called *solar particle events*, or *solar flares*.

While we may occasionally become sunburned after several hours outdoors at the beach or elsewhere, the atmosphere shields and protects us from the worst effects of the Sun's radiation. It is true that, even on Earth, overexposure to the Sun can and will occur without adequate additional protection from lotions or creams manufactured for that purpose. Skin and other cancers due to radiation are a risk faced by everyone on Earth. However, can you imagine how much more dangerous the Sun's radiation would be with no protection from the atmosphere at all? That is the situation in space, but protection against non-ionizing radiation is relatively simple. The real problem is created by the ionizing radiation of space, which can produce major biological damage.

A special unit of radiation that describes the amount of energy that is deposited by ionizing radiation in the body is *absorbed dose*. All of us are familiar with the use of the word "dose" in connection with the medicine we must take when we are sick. There are several different ways that scientists describe a dose of ionizing radiation, and such a description depends on two things. First, a dose measurement obviously must depend on the radiation exposure level, or the amount of radiation present. The basic unit of measurement for the amount of radiation is the *roentgen*. Second, a dose measurement depends on the medium the radiation is penetrating. The *medium* is the material receiving the radiation. For instance, the medium may be a human being, a spacecraft, or a house here on Earth. Each medium's reaction to radiation differs based on its physical structure and what it is made of. In the past, scientists have described radiation exposure to humans in units of *rem* (*roentgen equivalent, man*). More recently, a special unit has been developed to describe the biologically effective radiation to humans, and it is called the *sievert* (*Sv*). The relationship between rem and sievert is: $1\text{ Sv} = 100\text{ rem}$

The findings from radiation research carried out in studies here on Earth, as well as on previous and planned space missions, will help medical scientists determine what steps must be taken so that human beings can safely undertake long-term space voyages, such as a flight to Mars. Also, and perhaps of even greater importance, these findings will aid in determining the tolerance of humans to the ever-present radiation from natural sources, such as ultraviolet rays, and from industrial, scientific and medical sources now being encountered on Earth.

So far, we have discussed two main differences between the environments of Earth and space. The first difference is that space has no atmosphere. This means there is virtually no pressure, very little gas molecular activity and extreme temperature variation. Human

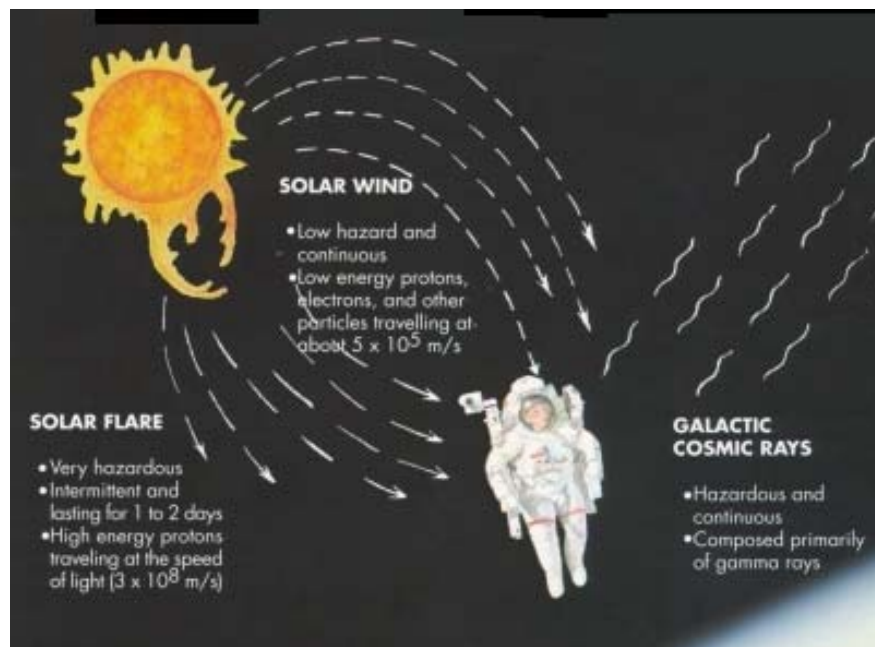
beings could not survive under these conditions without taking their own atmosphere and temperature control system with them. The second difference is that space does not have an atmospheric filter to help shield and protect humans from the dangers of radiation exposure. A human being could not survive without adequate protection from the radiation of space. The third shield is the Earth magnetic field that protects us on the ground from particle radiation. Because the particles are electrically charged, all but the most energetic are deflected by the Earth's magnetic field, and what does get through is absorbed by the upper atmosphere.

Radiation constitutes the most dangerous hazard for humans during long-term space flight, particularly those outside the Earth's magnetic field. Radiation protection is therefore mandatory to safeguard the well-being of astronauts and to limit the occurrence of later damage, such as cancer. Passive shielding is practical only to a certain extent, both because of obvious mass limits and physical reasons related to the very high energy of the particles in galactic cosmic radiation (GCR). Space radiation has been called the primary hazard associated with orbital and interplanetary spaceflight (Petrov et al., 1981). Human exploration of space will subject crew members to greater amount of natural radiation than they would receive on Earth. Radiation carries both immediate risks from acute effects, and long-term risks from delayed effects. Understanding the dynamic nature of radiation, the extent of health risks and the means of providing appropriate protection are all important aspects of ensuring mission success, particularly as human space exploration extends farther from the protection of Earth's atmosphere.

Radiation protection in space is not only an issue for manned missions; it is also a concern for electronic equipment. Electronic circuit structures are nowadays so small that they are comparable to the dimensions of chromosomes and bio-molecules.

The Space Radiation Field

In general terms, the space environment presents radiation conditions which cannot be found anywhere else. It is not uniform, however, but depends on parameters like altitude, geographical latitude (in low earth orbits) and the activity of the Sun. Data from past space missions show that the most important variable that determines the average dose rate is flight altitude (for Earth orbital flights in Low Earth Orbits).



A. Galactic Cosmic Rays (GCR)

They consist of atomic nuclei from hydrogen to iron ranging in energies up to 10^6 MeV per nucleon! GCR constitute an important hazard both to biological and electronic systems because of the very high local energy deposition.

For near-Earth orbits, interactions of GCR with the magnetic field and the upper atmosphere have to be taken into account. Since our planet is a magnetic dipole there is a variation of particle fluxes with geographical latitude, being highest near the poles and lowest near the equator. Less energetic ions are either deflected or trapped in the radiation belts. In low Earth orbits, spacecraft and crew are better protected against this radiation compared to free space (outwards of the Earth magnetic field).

B. Solar cosmic rays (SCR)

The sun is also an important source of radiation. In contrast to GCR, the intensity is not constant but depends on solar activity. SCR consist mainly of *protons*, and partly also of *helium ions*. Proton energies are considered lower than in GCR with a maximum of about 200 MeV.

A typical characteristic of SCR is their variability in time. They are classified as ordinary and anomalously-large events. The latter can be a very important hazard since they build up in very short times with a sudden enormous increase in particle intensity. Within one anomalously-large peak flux, very high peak fluxes have been measured. They result in doses which may even cause acute radiation damage. During the last few years, considerable effort has been devoted to the measurement of solar flares and to find ways for their prediction and the assessment of possible hazards.

Reliable ways for prediction are not in sight because of the essential stochastic behaviour of solar flares. They are linked to an 11-year solar cycle, having a higher probability particularly towards the end of solar maximum but neither the time of occurrence nor the strength can be foreseen.

C. Trapped radiation

As mentioned above, charged particles may be trapped in the Earth's magnetic field, a process which forms the *radiation belts*, which consist of *electrons*, *protons* and very few heavier ions. The electrons are found in two zones, an inner (1 to 2.8 earth radii) and an outer zone (from 2.8 to about 12 earth radii). Since their penetration power is rather low, they do not give cause for concern because they are stopped by the wall of the spacecraft. They may, however, produce *Bremsstrahlung* which is penetrating and may add to the total radiation burden, though only to a minor degree.

Protons are considerably more important. They cannot be associated with clearly defined zones but extend from about one Earth radius to more than 4 Earth radii. Their energies and fluxes vary with altitude and geographical latitude. Protons not only do penetrate the shielding material appreciably, but they also give rise to secondary radiations. In the present context it is important to note that the magnetic dipole is not co-linear with Earth's axis but is offset by about 11° and is also displaced so that the radiation belts extend to rather low heights at certain locations. The most important is the South Atlantic (South Atlantic Anomaly) where even low orbits cross the extension of the radiation belts. Consequently, the

highest dose contribution is received when a spacecraft crosses this area. As already mentioned, the interaction of primary and trapped radiation with atmospheric atoms may lead to the production of secondary radiation to which neutrons make the most important contribution. They play a significant role also in air travel at high altitudes.

D. Secondary neutron flux

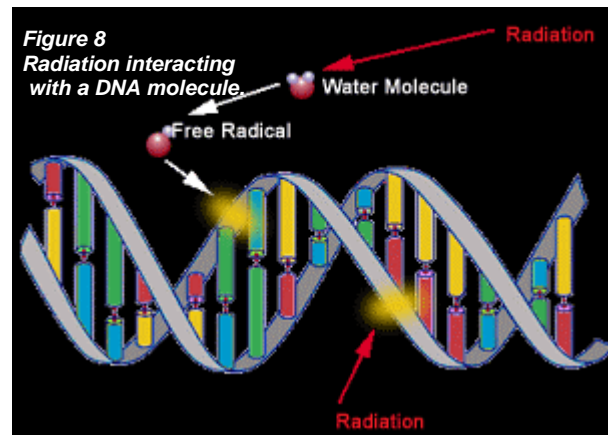
Neutron flux is created when matter (like a spacecraft wall or planetary soil) is bombarded by Galactic- or Solar Cosmic Rays.

Mechanisms of biologic damage

Ionizing radiation can kill a cell outright, damage its genetic material and, in some instances, induce cancer. The primary biologic effect of low and moderate radiation doses, such as those found in the space environment, is damage to the genetic material, deoxyribonucleic acid (DNA). The mechanisms giving rise to mutations are complex, involving physical energy transfer, free radical formation and alteration of the molecular structure of DNA.

There are two major ways that radiation can damage cells (Figure 8):

1) The water in the organism (e.g., a person's body) absorbs a large portion of the radiation and becomes ionized to form highly reactive, water-derived radicals. The free radicals then react with DNA molecules causing the breaking of chemical bonds or oxidation. 2) The radiation collides with the DNA molecule directly. In either case, the DNA molecule breaks.



By far the most dangerous components of cosmic rays, and of particular concern, are the heavy high-energy particles, or Galactic Cosmic Rays (GCR); with high mass and high energy, found only in space, especially at geosynchronous orbit or during deep-space manned missions. These are fast atomic nuclei travelling along close to the speed of light. If they run into denser matter - like the wall of a spaceship or the flesh of a human body - the particle will shatter itself and its target, and create a cascade of secondary particles. It is like a bullet ploughing into a wall, shattering and leaving a trail of debris. Secondary particles also present a hazard. GCR can penetrate tissues and kill cells that are in the particle's path by acting essentially as microneedles. These micro-lesions pose a special risk to non-dividing cells such as neuroblasts³⁵ that must migrate to the cerebral cortex during a specific point in embryonic development, and to proliferating gametes³⁶.

³⁵ Immature nerve cell

³⁶ Germ-cell

A. DNA³⁷ Damage

Much experimental evidence exists to indicate that nuclear DNA is the target molecule responsible for cell death from radiation. Organisms with higher DNA content (e.g. mammals) are more radiosensitive than those with low DNA content. (e.g. bacteria); i.e., mammalian cells can be killed with a lower dose of radiation than can bacterial cells.

Radiation can damage DNA by *changing* or *deleting bases*; by *breaking hydrogen bonds* between the two strands; by *breaking one or both strands*; and by *creating cross-links*, either with the helix, to other DNA molecules, or to protein. A change in the base can potentially give rise to *mutation*³⁸.

Most single-strand breaks can be repaired or rejoined by *repair enzymes* in normal cells. Repair kinetics seem to be first-order, with half-time between 10 and 40 minutes depending on cell type and temperature. [Ono and Okada, 1974; Koch and Painter, 1975].

Irradiating DNA molecules also can cause double-strand breaks. Sections of DNA can become separated when each strand has a break less than about 3 nucleotides³⁹ apart, which can occur either when 2 single breaks come into juxtaposition⁴⁰ or when a single particle with higher linear-energy-transfer (LET) breaks both strands.

Non-rejoining strand breaks are probably the most important lesions in terms of cell death. For a given absorbed dose, high-LET heavy ions can induce more non-rejoining strand breaks than low-LET radiation. Moreover, as the LET increases, the rate of rejoining slows substantially down.

The production of complex, irreparable DNA strand breaks may relate to the track structure of high-LET radiation. Heavy ions can produce high-density ionization tracks having a diameter larger than that of several genes. A single heavy ion, therefore, can produce a cluster of damage in several continuous genes⁴¹.

B. Chromosomal Damage

Irradiating cells at any stage of their mitotic cycle⁴² can induce structural changes in chromosomes⁴³ or their component chromatids⁴⁴. *Single breaks* in a chromosome are frequently rejoined such that no lesion is visible. Mammalian cells rejoin up to 99% of single breaks. If the break doesn't heal, the end portion remains a chromosome fragment (*deletion*).

³⁷ DNA [deoxyribonucleic acid]: any of various nucleic acids that are the molecular basis of heredity, are localized in cell nuclei and are constructed of a double helix held together by hydrogen bonds between purine and pyrimidine bases which project inward from two chains containing alternate links of deoxyribose and phosphate

³⁸ Mutation: an alteration in the genetic material of a cell that is transmitted to the cell's offspring. May be spontaneous (copy error) or induced by external factors (e.g. electromagnetic radiation).

³⁹ The nucleotides are of great importance to living organisms, as they are the building blocks of nucleic acids, the substances that control all hereditary characteristics.

⁴⁰ Juxtaposition: placing two or more things side by side

⁴¹ Gene: unit of hereditary information that occupies a fixed position (locus) on a chromosome. Genes achieve their effects by directing the synthesis of proteins.

⁴² Process of cell division to form new cells

⁴³ Chromosome: the microscopic part of the cell that carries hereditary information in the form of genes

⁴⁴ Each chromosome is formed of two identical chromatids which are linked by the centromere

Broken ends from different chromosomes also can rejoin to form dicentric structures or deletion. Radiation induced chromatid aberrations include terminal deletion, dicentric-, and ring-chromatid formation. If breaks in the chromatids of different chromosomes are involved, *interchanges* may give rise to *translocations*. High-LET heavy ions can be several times more effective than X- or gamma rays in causing chromosome aberration .

Health Effects

The health effects of space radiation are usually considered in two categories: *early (acute) effects* and *late (delayed) effects*. Early effects are manifested within hours, days or weeks after high-dose whole-body exposure, such as that delivered by a solar particle event. Late or delayed effects usually appear months or years after exposure and include *tissue damage, impairment of fertility, lens opacification of the eye, cancer induction, heritage effects* and *developmental abnormalities*. Of these delayed effects, most attention has been focused on cancer induction. Crews will be exposed unavoidably to low-dose-rate galactic cosmic rays and may also be exposed to high-dose-rate solar particle events during flight.

The principal sites of biological action of ionizing radiation are the *proliferating*⁴⁵ *cells* of renewing tissue and body organs, particularly the bone marrow, lymphopoietic tissue, intestinal epithelium, the male gonadal tissues and, to a lesser extent, the female gonadal tissues. Delay and inhibition of cell division, fractional cell population killing, cellular depletion of vital tissues and organs, organ malfunction, serious illness and possibly death occur sequentially in the increasingly heavily-irradiated individual.

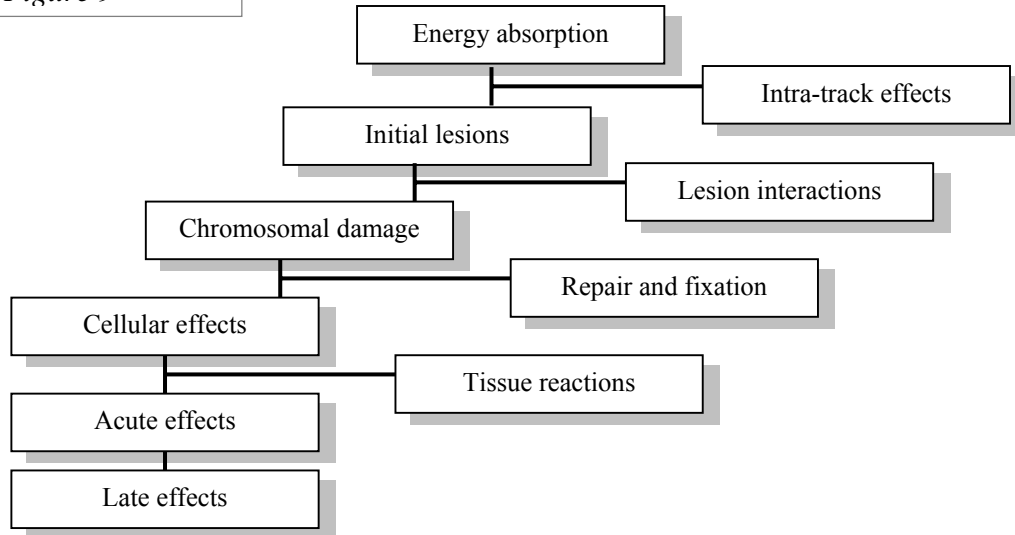
Understanding the concept of dose and dose equivalent is useful in quantifying radiation, assessing the effects of radiation exposure on health and setting appropriate exposure limits. Absorbed dose is defined as the mean energy imparted by ionizing radiation per unit mass. *Absorbed dose* is expressed in Gray units (1 Gy = 1 J/kg of absorbed ionization in any material) or in rad (100 rad = 1Gy). *Dose rate* is the dose expressed per unit time interval. Biologic doses are expressed in terms of *dose equivalents*. It describes an amount of radiation that can produce the same ‘health decrement’ as an equivalent amount of low-LET absorbed dose. Dose equivalents are expressed in Sievert or in rem (1 Sv = 100 rem), and are equal to the dose received in Gy (or in rad) multiplied by a quality factor Q. The quality factor is based on the relative biologic effectiveness (RBE) of different types of radiation.

RELATIVE BIOLOGIC EFFECTIVENESS (RBE) VALUES	
Radiation	RBE
Gamma-rays	0.5-1
Electrons (e-)	1
Protons (p+)	2
Neutrons (n)	2-10
Helium-Nuclei (α)	10-20

Radiation effects start from the primary absorption of energy which takes place within about 10^{-12} to 10^{-16} s, although ultimate effects may be seen as late as after many generations, as in the case of genetic damage to the germ cells.

⁴⁵ Proliferate: to grow by rapid production of new cells

Stages of biological radiation effects.
Figure 9



The development of radiation damage does not proceed in a linear unidirectional manner, but is modifiable in a number of ways. The most important process in this respect is the ability of cells to recognize genetic alterations and to repair them. Whether this actually occurs depends not only on the properties of the system under consideration, but also on the molecular nature of the initial lesions. It is determined by the spatial distribution of energy deposition, i.e. radiation quality. Environmental factors may also intervene. Whether microgravity plays a role here is still an open, and interesting, question. It has been suggested several times that microgravity might change the repair capacity of cellular systems.

Radiation damage can lead to: DNA lesions; chromosomal aberrations; cell interaction; mutation induction; neoplastic⁴⁶ transformation (indicating the first step of tumour induction); tissue damage; and effects on progeny⁴⁷ (genetic and teratogenic⁴⁸).

DNA lesions cannot only lead to inactivation and mutation, but they may also change the expression of genetic information, which may influence the biological programme of the affected cell in a drastic way, e.g. cancer induction.

A. Acute health effects

The acute effects of ionizing radiation on humans at dose levels above 100 rem (1 Sv) of low-LET radiation are reasonably well understood. The acute effects of high-LET radiation

⁴⁶ Neoplasm: a malignant mass of tissue that arises without obvious cause from cells of preexistent tissue, and possesses no physiologic function.

⁴⁷ Descendants, children, offspring of animals or plants

⁴⁸ Teratogenesis is a prenatal toxicity characterized by structural or functional defects in the developing embryo or foetus. (ranging from growth retardation to death)

are not as well known with respect to dose, but qualitatively are the same as low-LET radiation.

Exposing humans to doses of total-body radiation greater than 50 rem (0.5 Sv) produces certain characteristic symptoms collectively known as radiation sickness. The onset, duration and severity of the symptoms depend on the dose of radiation. Symptoms may include headache, dizziness, malaise, abnormal sensations of taste or smell, nausea, vomiting, diarrhoea, decreased blood pressure, decreased white blood cells and blood platelets, increased irritability and insomnia. In humans, three organ systems are most important in the acute radiation syndrome. The *central nervous system* is most affected by exposures in thousands of rem (tens of Sv); the *gastrointestinal system*, between 550 and 2000 rem (5.5 to 2.0 Sv); and the *haematopoietic system*, by 550 rem (5.5 Sv) or less.

Acute radiation effects from an absorbed dose of less than 50 rem (0.5 Sv) are mild, and occur only during the first day after exposure. Blood cell counts may drop slightly, but survival of the individual is almost certain at this radiation dose level. As the dose range rises to 100 to 200 rem (1 to 2 Sv), the prodromal effects increase in severity. At 200 rem (2Sv), the incidence of vomiting increases to 70%; fatigue and weakness is evident in approximately 30 to 60% of persons. Significant destruction of bone marrow stem cells may lead to a 25 to 35% drop in blood cell production. As a result, mild bleeding, fever and infection may occur during the fourth and fifth weeks after exposure. At doses of 200 to 350 rem (2 to 3.5 Sv), prodromal symptoms begin earlier and affect a greater number of exposed persons. Moderate diarrhoea⁴⁹ at 4 to 8 hours may be experienced by 10% of the population. Most victims tire easily and experience mild to moderate weakness intermittently over a 6-week period. Under normal conditions, the vomiting and diarrhoea are not enough to cause serious fluid loss or electrolyte⁵⁰ imbalance. Injury to the haematopoietic⁵¹ system is indicated by moderate bleeding, fever infection and ulceration⁵² at 3 to 5 weeks after exposure in more than 50% of those exposed. During the fourth and fifth weeks, diarrhoea may complicate the condition.

Nearly everyone dosed at 350 to 550 rem (3.5 to 5.5 Sv) experiences severe symptoms. Severe and prolonged vomiting can affect electrolyte balance. Most persons show moderate to severe fatigue and weakness for many weeks. If untreated, 50 to 90% of those exposed will die from extensive injury to the haematopoietic system, as manifested by overwhelming infections and bleeding during the third to sixth weeks. Nausea⁵³, vomiting, and anorexia⁵⁴ may recur, and approximately half will experience diarrhoea, electrolyte imbalance and headache. Terminal conditions may be complicated by dizziness, and symptoms of infection.

⁴⁹ Diarrhoea: abnormally frequent intestinal evacuations with more or less fluid stools

⁵⁰ Electrolyte: (ionic) minerals dissolved in blood and other body fluids

⁵¹ Haematopoiesis: the formation of blood or of blood cells in the living body

⁵² Ulcer: a lesion on the mucous membrane of the stomach.

⁵³ Nausea: a stomach distress with distaste for food and an urge to vomit

⁵⁴ Anorexia: loss of appetite

EXPECTED SHORT-TERM EFFECTS IN HUMANS FROM ACUTE WHOLE-BODY RADIATION	
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Dose (rem)	Probable Physiologic Effects
10-50	No obvious effects, except minor blood changes
50-100	5 to 10% experience nausea and vomiting for about 1 day; fatigue, but no serious disability; transient reduction of immune cells; no death anticipated
100-200	25 to 50% experience nausea and vomiting for about 1 day, followed by other symptoms of radiation sickness; 50% reduction of immune cells; no death anticipated
200-350	Most experience nausea and vomiting on the first day, followed by other symptoms of radiation sickness, e.g., loss of appetite, diarrhoea, minor haemorrhage ⁵⁵ ; up to 75% reduction in all circulating blood elements; death of 5 to 50% of those exposed
350-550	Nearly all experience nausea and vomiting on the first day, following by other symptoms of radiation sickness, e.g., fever, bleeding, diarrhoea, emaciation ⁵⁶ ; death of 50 to 90% within 6 weeks; survivors convalesce for about 6 months
550-750	All experience nausea and vomiting within 4 hours, followed by severe symptoms of radiation sickness; death of up to 100%
750-1000	Severe nausea and vomiting may continue into the third day; survival time reduced to less than 2.5 weeks
1000-2000	Nausea and vomiting within 1 to 2 hours; all die within 2 weeks
4500	Incapacitation within hours, all die within 1 week

Almost all humans absorbing radiation doses of 550 to 750 rem (5.5 to 7.5 Sv) will experience severe nausea and vomiting on the first day, accompanied by dizziness and disorientation. Bone marrow stem cells and granulocytes are almost completely eliminated, leaving untreated persons susceptible to overwhelming infections, including those from their own injured gastrointestinal⁵⁷ tract. The combination of haematopoietic and gastrointestinal damage reduces the survival of all untreated persons to 2 to 3 weeks. Moderate to severe bleeding, headaches, hypotension⁵⁸, dehydration, electrolyte imbalance and fainting are common.

Doses of 750 to 1000 rem (7.5 to 10 Sv) reduce the survival time for untreated persons to about 2.5 weeks.

Doses of 1000 to 2000 rem (10 to 20 Sv) cause severe nausea and vomiting within 30 minutes of exposure, and the symptoms continue intermittently until death in the second week. A single acute 4500 rem whole-body exposure can cause death as early as 32 hours after exposure, and all die within one week.

⁵⁵ Haemorrhage: discharge of blood from the blood vessels

⁵⁶ Emaciation: to become very thin

⁵⁷ Gastrointestinal: stomach and intestine

⁵⁸ Hypotension: abnormally low blood pressure

B. Late health effects

Humans who receive radiation doses that are not acutely lethal usually seem to recover from the initial radiation syndromes a month or two after exposure; however, their incidence of certain *tumours*, *mutations* and *cataract*⁵⁹ is higher than that in control populations. *Carcinogenic*⁶⁰ effects are of the most concern in assessing radiation risk. The *genetic effects* of radiation are manifested by increased frequency of mutation; however, genetic effects have not been clearly demonstrated in the descendants of atomic-bomb survivors. The threshold for cataract seems to be several hundred rem of acute exposure to low-LET radiation; lower doses do not produce clinically significant damage.

Radiation carcinogenesis

Extensive clinical observations have shown that radiation, in sufficient quantities, can cause neoplasms in virtually all organs. The types of tumour that forms depend on the area irradiated, the dose and quality of the radiation and the genetic background, age and sex of the recipient. *Skin* and *bone tumours* appear most frequently after local irradiation; other solid tumours and *leukaemia*⁶¹ generally result from whole-body irradiation. Moreover, irradiation can speed the expression of pre-existing neoplasms, as well as increase the absolute incidence of types of cancer.

Insufficient data precludes estimating the effects of dose rate on cancer induction in humans. Animal studies have indicated that lowering the dose rate decreases tumour incidence. Splitting a dose seems to allow repair of lesions in skin and lung. Mice irradiated with gamma rays at low dose rates showed marked reduction in leukaemia and other tumours relative to higher dose rates. In addition, an age-dependent decrease in radiation-tumour susceptibility can be observed.

Radiation-induced cell transformation is a dynamic process. The process begins when radiation energy is deposited in the cell; then, free radicals are formed, DNA is altered and chromosomes are damaged, all in less than one second. This can then lead to loss of growth control (neoplasia).

Radiation mutagenesis

Direct evidence of radiation-induced mutation in humans is lacking. Studies of the descendants of atomic-bomb survivors have revealed no detectable effects on the frequency of prenatal or neonatal death or on the frequency of malformations. The number of exposed parents, however, was small, and the dosage was low; several generations may be needed to reveal recessive⁶² gene damage.

⁵⁹ Cataract: a clouding of the lens of the eye.

⁶⁰ Carcinogen: a substance or agent producing or inciting cancer

⁶¹ Leukaemia: neoplastic disease characterized by an abnormal increase in the number of white blood cells in the tissues and often in the blood.

⁶² Recessive: expressed only when the determining gene is in the homozygous condition.

Ionizing radiation can be expected to increase the mutation rate in humans. Data from mouse experiments have been used to estimate the doubling dose (the dose needed to double the spontaneous mutation rate) for humans at between 10 and 100 cGy (15 to 30 cGy for acute exposure, and about 100 cGy for chronic). However, animal studies have shown that specific doses of radiation cannot be associated with specific mutation rates. Gene loci differ markedly in their mutability. Mitotic stage, cell type, sex, species and dose rate all influence the rate of mutation. Some data are available, however, from studies of specific mutations in cell-culture systems.

Establishing exposure limits

Radiation exposure limits, in space or on Earth, are based on risk assessments, that is, estimates of the probable number of occurrences of a specific health effect caused by an exposure. Risks from exposure to radiation were to be consistent with other risks of space flight, and weighted against the potential gains. Radiation exposure is considered to be an occupational⁶³ hazard of space flight, but it is emphasized that crew members should not be subjected to an excess risk of late effects after they have completed their flight careers. Thus, planned exposures should be as low as reasonably achievable.

NASA radiation-career-limit:

For males: 200 rem + 7.5 x (age-30)

For females: 200 rem + 7.5 x (age-38)

Maximal career-limit: 400 rem (males) and 300 rem (females). This equals to 3% of increase in future cancer risk. The annual radiation exposure limit is 50 rem and 25 rem for a 30-day limit [Barratt, NASA 1996].

This limits do not apply to exploratory missions, e.g., a trip to Mars.

Uncertainties in estimating risk from radiation exposure

The uncertainty in estimating the radiation environment in space depends on the source of that radiation. Exposure to low-altitude trapped-belt particles can be estimated to within 10 to 15%. As models of GCR solar modulations improve, exposures to this type of radiation can be estimated to within 10%, although it should be noted that the intensity of GCR can vary by a factor of 10 over a solar cycle. Radiation exposures are impossible to predict at this time.

Mean Radiation Exposure to Crew Members during Apollo Flights			
Mission	Flight Duration (days)	Mission (mGy)	Dose
Apollo-7	10.83	1.60	
Apollo-8	6.12	1.60	
Apollo-9	10.04	2.00	
Apollo-10	8.00	4.80	
Apollo-11	8.08	1.80	
Apollo-12	10.19	5.80	
Apollo-13	5.95	2.40	

⁶³ Occupational: work related

Apollo-14	9.00	11.40
Apollo-15	12.29	3.00
Apollo-16	10.08	5.10
Apollo-17	12.58	5.50

The differences in exposure values for the various space missions shown here are due to mission characteristics as altitude, duration and quality of radiation shielding technology.

Mean Radiation Exposure to Crewmembers during Space Shuttle Flights					
Mission	Flight duration (hours)	Inclination / orbital altitude		Mission dose (mGy)	
STS-2	54.2	38° / 254 km		0.11	
STS-31	121.3	28.5° / 617 km		8.3	
Comparing Different Radiation Environments					
Average dose on Earth [rem/y]1	Intercontinental Flight [rem]1	LEO [rem/y]1	Van Allen crossing [rem]2	Mars Transfer [rem/y]3	Mars Base [rem/y]3
0.17	0.004	30 (without solar flare)	<0.5	50	<25

1. Tascone 1994 2. ISU 1991 3. ACTA 1993

Protecting crews from radiation during remote missions

The degree of protecting crew members from radiation on missions beyond Earth’s magnetic field, such as those to the moon or Mars, depends to a large extent on the duration of those missions, as well as the radiation environment in which those crews will live. Mission duration, in combination with evolving exposure limits, will drive the selection of radioprotective methods, which will probably represent some combination of shielding, onboard monitors and perhaps chemical radioprotectants and therapeutic measures. Although exposure limits for exploratory missions have yet to be established, all but the career limits will probably be governed by the concern for determining effects and are not likely to differ from those for low Earth orbit flights.

Shielding considerations

Transport vehicles and space habitats must be shielded in order to minimize the radiation exposure of the crew. For the shortest of these missions, probably 45-day trips to and from the moon, GCR will probably not be a limiting factor; shielding thickness instead will be determined by the need to protect crews from acute doses of protons during solar particle events (SPE). Shielding options include the entire spacecraft, or portions thereof, as well as partial-body shielding for its inhabitants, particularly bone marrow areas. Any material that attenuates photons or charged-particle radiation will provide some protection. For example, 8 g/cm² of aluminium shielding can reduce the dose-equivalent to the blood-forming organs (bone marrow) of humans on the lunar surface to less than 25 rem (0.25 Sv). The mass penalties associated with shielding of these magnitudes are considerable.

Other preventive measures

Galactic cosmic rays (GCR) are much more penetrating than solar flares because of their high energy and thus cannot be shielded completely. Energetic heavy ions can also produce secondary particles through their interactions with shielding materials, and these particles can cause biologic effects equal to or greater than those caused by the primary particles. For these reasons, other protective methods are being explored to mitigate the health hazards of galactic cosmic rays during interplanetary flights.

Chemical Radioprotectives:

Shortly after World War II, certain chemical compounds were found to reduce the lethal effects of low-LET radiation. Since then, many different chemicals and biologic materials have been synthesized and evaluated for their potential use in radiation protection. The substances which have been synthesized up to now have substantial side effects and were just tested on animals. The ideal radioprotectant for spaceflight use should be stable, effective when administered orally, provide protection over an extended period and have no side effects. Current evidence suggests that significant radioprotection may be possible through a combination of proper nutrition, vitamin supplementation, immuno-modulators⁶⁴ and other chemical agents.

Therapeutic treatments

Bone marrow transplantation is known to improve survival in experimental animals and in humans after lethal doses of total body irradiation. Bone marrow transplantation may benefit crews who receive accidental total-body irradiation in doses that preclude spontaneous marrow recovery. This technique has many limitations, however, including graft rejection, and thus should probably be considered only for those victims who have received a dose of more than 800 rem.

Doses of radiation exceeding 150 to 200 cGy produce bone-marrow hypoplasia⁶⁵ with a reduction of blood cells and a depression of the immune-system, which predisposes victims to infections and bleeding. Treatment with antibiotics is needed to prevent fatal infections.

Summary

The space environment includes types of radiation not encountered on Earth, such as that arising from trapped-belt radiation, galactic cosmic rays, and solar particle events. Charged particles present in space radiation can have very high energy, in the range of GeV per nucleon, and can penetrate through thick shielding and produce harmful biologic effects in astronauts. *Acute* as well as *delayed effects* of space radiation could limit the duration of certain missions.

⁶⁴ Immunomodulator: a substance that affects the functioning of the immune system

⁶⁵ Hypoplasia: a condition of arrested development in which an organ or part remains below the normal size or in an immature state

Radiation exposure of crews involved in ISS, Mir, Shuttle, Apollo and Skylab flights have been relatively low. Present radiation-exposure limits are strictly for low Earth orbit flights. Exposure limits for interplanetary missions have yet to be established and adopted. Clearly, as missions become longer and more remote, astronauts can receive considerable radiation from galactic cosmic rays in addition to possibly lethal doses from solar particle events.

Further research on biologic effects of heavy ions, shielding materials, radioprotectants, heavy-ion physics and particle detectors is needed to find optimal countermeasures that will protect crews from space radiation. Results from this research will also provide valuable information on nuclear physics, give insight on basic mechanisms of carcinogenesis, mutation and development, and generate technologies for medical applications.

III. Medical Hazards in Space Operations

The space environment includes conditions that are, in themselves, far more hazardous and inhospitable for humans than weightlessness. Prominent among these are *temperature extremes*, exposure to *toxic substances*, *infections*, *physical deconditioning*, and the *lack of the atmosphere* and *atmospheric pressure*.

Spaceflight and Risk Assessment:	
External hazards:	Radiation, meteorites Extravehicular activities: thermal, pressure, gases
Internal hazards:	Floating particles Instruments: dissection tools, freezer, furnace, Surfaces: microbiological contaminants, Physical deconditioning
Life support:	Air: pressure, temperature, H ₂ O, CO ₂ , N ₂ , pollutants: CO, CH ₄ Water: drinking, hygiene Sleep, food, noise, vibration

Some medical events, such as space motion sickness, are common but there are many other possible spaceflight-medical-events. The Russian experience suggests that the risk of medical events increases with the length of mission. Russian mission aborts have occurred at 49 days for intractable headaches, at 64 days for chronic prostatitis and at 174 days for cardiac dysrhythmia. A medical evacuation was planned due to a case of right lower quadrant abdominal pain in 1982. Fortunately, the cosmonaut successfully passed a kidney stone and the evacuation plans were cancelled. These incidents provide evidence that major medical events occur in space [Nicogossian, 1993]. Probabilities for a medical event in flight (Russian Cosmonauts): 1.4/year (total medical-event rate per person/year).

NASA uses medical data from analogous populations to calculate the estimation rate of medical risks associated with a remote hazardous environment. Each population is similar in some way to the astronaut population in terms of age, sex distribution, baseline health status and occupational exposures. Some of these populations are submarine crews, military aviators, deep-sea divers and winter-over Antarctic expeditioners.

Probability Ranking for Occurrence of Disease Categories during Space Flight		
<i>Disease Category</i>	Probability Ranking	Mission Effect
Skin disease	1 (high)	9 (low)
Mental disorders	2	5
Injury / Poisoning	3	2
Ear, Nose and Throat diseases	4	6
Muscle and Bone diseases	5	7
Sensory effects	6	8
Urinary tract diseases	7	4
Stomach and Bowel diseases	8	3
Cardiovascular diseases	9 (low)	1 (high)

[Billica et al., 1996]

This survey shows that, in general, medical events perceived to have the highest probabilities of occurrence (e.g. skin disease, injury / poisoning, ear-nose-throat diseases) were perceived to have low effects on mission success. In contrast, medical events perceived as having the highest effect on crew member health or mission success are least likely to occur (e.g., Cardiovascular diseases, stomach and bowel diseases).

Injuries and *toxic exposures* can be expected to be the most common medical events occurring to an otherwise healthy population in a hazardous environment. Events in the skin-category consisted of minor events, such as *skin irritation* due to fibreglass, *skin infection*, *contact dermatitis* and *rash*. These skin diseases have high probability of occurrence, but low health and mission effects.

Mental disorders are also likely to occur; however, the US and Russian in-flight data do not reflect a notable incidence of mental disorders. Psychological factors were recognized as of great importance early in the Soviet space programme, and intensive psychological testing was used during the selection and training of cosmonauts. Psychological incompatibility between crew members may exist, but is not publicly discussed or published in the scientific literature.

Air-borne toxic hazards

The closed environments of spacecraft have always presented unique challenges to toxicologists; however, as planned missions become longer and more distant, those challenges will grow exponentially. No environmental resource is more immediately essential than air suitable for breathing. A major threat to safe cabin air is contamination by chemicals that either accumulate slowly or are released suddenly by accident. Counterstrategies include meticulous control of materials off-gassing and flammability, and careful review of all onboard chemicals.

Propellants, because of their reactivity, are toxic in small quantities. During the descent of the Apollo capsule after the successful Apollo-Soyuz mission in 1975, toxic quantities of propellant entered the crew compartment through a pressure-equalization valve and resulted in hospitalization of the crew after landing. Several less severe toxicological incidents have taken place during Space Shuttle missions. The most serious one was the release of formaldehyde and ammonia into the mid-deck air by an overheated refrigerator motor during STS-40, causing irritation, nausea and headaches in crew.

A wide variety of chemicals are stored in large quantities on the Shuttle, outside the habitable area. The toxic propellants nitrogen tetroxide, hydrazine, methyl hydrazine, and dimethylhydrazine and Freon 21, a toxic heat exchanger, pose the greatest toxicological concern. Unreacted fuel from the rocket thrusters could enter the cabin through the open hatch after landing or after an EVA if crystals formed by its rapid evaporation in the space vacuum were to become enmeshed in the space suit fabric. Any crystallized propellant could then vaporize in the pressurized airlock and enter the cabin with the crew member.

Potential sources of chemical contamination from inside the spacecraft

A wide variety of contaminant gases and particles are released continuously into the spacecraft interior during all manned missions from crew metabolism (carbon dioxide, carbon monoxide, ammonia and others) and from off-gassing of non-metallic materials (aliphatic hydrocarbons, alcohols, aldehydes, chlorinated hydrocarbons and siloxanes). Escape of payload chemicals or thermodegradation (fire) of materials can also produce unexpected toxic contaminants in the spacecraft living environment. The thermodegradation of polymeric materials during spaceflight is a safety concern, because many of these materials release highly toxic pyrolysis products; however, the likelihood of a large self-perpetuating flame arising from spacecraft materials is quite small because of strict flammability standards for all materials that are exposed to the spacecraft atmosphere.

Microbiology

Long before the first humans boarded the International Space Station (ISS), something else was living there; something unseen, but potentially dangerous, something with an uncanny ability to survive and reproduce in even the most hostile environments, something capable of attacking the Station's crew and even the Space Station itself.

Of course we are not talking about some man-eating alien from a science fiction movie. These lurking, mischievous life forms aboard the Space Station are simply microbes: viruses, bacteria and fungi.

Microbes were the first inhabitants of the Space Station. The Space Station's micro-organisms are hitchhikers; they were carried there on ISS hardware and by the assembly crews themselves. When the Station went up, microbes went with it. Microbes will be the last ones in the Station, too. Microbes are a fact of life anywhere humans go. The majority are harmless, and several types are actually beneficial to humans. Nevertheless, certain microbes can pose a health threat to the Station's crew and can even attack the materials and hardware of the Station itself. Scientists and engineers must find ways to keep such micro-organisms on the Space Station under control.

Although humans are continually exposed to a wide variety of micro-organisms, only a small number of those microbes are capable of interacting with the host such that infection and disease develop. In fact, disease is a rare consequence of infection. Usually, the presence of micro-organisms on or within the host does not result in clinical disease; however, some bacteria, fungi, viruses, and parasites clearly are capable of causing disease, and reasonable precautions must be taken to prevent infectious diseases from these principal pathogens during a space mission. Past experience clearly demonstrates that reducing crew members' exposure to potential pathogens before flight reduces the incidence of infectious disease during those flights.

Space flight effects on the human immune system

Accumulating evidence suggests that the human immune response may be attenuated during space flight. Most of the results collected to date point to a *decrease in the cell-mediated immune response* during flight.

The increased number of neutrophils, accompanied by decreases in lymphocyte and eosinophil numbers, suggests that microgravity or the multiple stresses associated with launch, entry and landing contribute to these immune system alterations. Increases in epinephrine⁶⁶ and glucocorticoids⁶⁷ have been suggested as possible causes for the immune alterations.

Space flight effects on microbial function

Experiments show that bacteria such as *Escherichia coli* and *Staphylococcus aureus* showed increased resistance to selected antibiotics. These findings are relevant to the in-flight dosage necessary to treat some infections. Electron microscopy of *Staphylococcus aureus* cells after space flight revealed increases in cell wall thickness. Changes in cellular morphology, physiology (e.g., capsule formation, toxin production) and population dynamics may significantly alter the pathogenicity of micro-organisms in the space environment.

Sources of microbial contaminants

The primary source of micro-organisms in spacecraft and future space habitats are the crew members. A healthy individual maintains about 10^{12} bacteria on the skin, 10^{10} in the mouth, and 10^{14} in the alimentary canal. This leads to the release of tremendous numbers of bacteria into the environment. In fact, bacteria in people's intestines help to digest food, providing some otherwise unattainable nutrients, such as vitamin K. A person's resident microbes also actually protect them from infection by competing with dangerous microbes looking for a place to grow. Another common human source of microbes is the respiratory tract. Sneezing, coughing, and even talking produce aerosols laden with micro-organisms and produce an effective means of spreading diseases. On Earth, the large droplets produced by cough and sneeze settle to the floor quickly. Gravity serves an important function in contamination control. In microgravity, all of these droplets remain airborne regardless of size until they collide with a surface.

⁶⁶ Epinephrine: sympathomimetic hormone that is the principal blood-pressure raising hormone secreted by the adrenal medulla and is used medicinally esp. as a heart stimulant, a vasoconstrictor in controlling haemorrhages of the skin -- also called *adrenaline*

⁶⁷ Glucocorticoids: any of a group of corticoids (as hydrocortisone) that are involved esp. in carbohydrate, protein and fat metabolism, that are anti-inflammatory and immunosuppressive

While it is natural for a person to live with a host of resident microbes, seven people -- each with their own set of microbes -- living in a small, air-tight can for months or years is certainly not. When the crew goes up to the station, they each have their own microbial flora, and when they return back, for the most part they have exchanged that flora with each other. Most of these exchanged microbes are fought off by the crew's immune systems and their own resident microbes, but the potential for infection is there.

The first step in protecting the health of the crew is testing each crew mate for infection before launch. Only healthy crew members are allowed to fly into space, and they are quarantined before launch to prevent them from contracting harmful germs at the last moment. Implementation of contamination-control measures, in combination with the Health Stabilization Program, can minimize the occurrence of in-flight infectious disease and other negative effects of microbes on the habitability of spacecraft and space habitats.

Ground personnel readying the spacecraft or the various payloads may also be significant contributors to the microbial contamination problem.

Once on the Space Station, the [air](#), [water](#) and surfaces with which the crew members interact must be kept clean. Water will be disinfected by a machine called a "catalytic oxidator," which heats the water to as much as 130 degrees Celsius. The organic molecules in microbes are oxidized by this process, which kills nearly all of them. Just to be sure, the water is then treated with iodine.

For the health of the crew, as well as the Station's hardware, microbes must also be kept from growing on surfaces and in corners and gaps. A big threat to the Station from the microbes is degradation of the materials. The microbes eat pretty much anything. As they grow on surfaces, fungi produce an acid which will eventually corrode the material. They start using most materials as a source of food. As exemplified by the Russian space station Mir, microbes can not only survive in the metallic world of a space station, they can thrive. Growth of microbes on the Station's hardware is controlled in several ways. First, all materials used in the Space Station are tested for resistance to fungi, such as mould. Paint with a fungus-killing chemical is also used. Controlling the humidity of the air in the Station is also an effective way of discouraging microbe growth. Housekeeping duties will include regularly wiping down surfaces with a cloth containing an antiseptic solution. All of these measures to minimize microbes in the air and water and on surfaces should allow the Station and its crew to conduct their mission in good health.

Infectious disease in the US space programme

Since the inception of the US human space programme, the prevention of infectious diseases among the crew members before, during and after flights has been given a high priority. The early Apollo missions saw the highest incidence of infectious disease before and during missions. During this period, over 50% of the Apollo crew members reported illnesses during the three weeks before launch, the most common of which were respiratory infections, gastroenteritis, urinary tract infections and skin infections. The Flight Crew Health Stabilization Programme implemented after Apollo 13, and since expanded to include comprehensive pre-flight examinations and isolation of flight crews, has decreased the incidence of infectious diseases.

As humans prepare for the longer duration spaceflights, necessary to enter the era of manned planetary exploration, it is critical to develop a better understanding of the changes that may be induced in the host-microbe relationship in the unique environment of spaceflight. Development of countermeasures to undesirable microbial interactions with the spacecraft and crew members is an important part of current research efforts. The study of microbial impacts on humans and spacecraft will continue to be a vital part of manned space exploration.

Health Stabilization Programme

The Health Stabilization Programme was designed to minimize crew exposure to potential infectious disease before missions. The Space Shuttle Program requires to limit the number of contacts with flight crews before each mission. Those who must contact crew members are identified, medically screened and badged. Crews live in restricted crew quarters beginning about seven days before launch, after which contacts are restricted. Family members of the crew are also medically screened and monitored as part of this programme. To date, only one flight, STS-36, has been delayed because of crew member illness during the pre-flight period, however, minor illnesses still occur occasionally during that time.

Medical monitoring

Space missions are monitored continuously by flight-support teams at the mission control centre using audio-links, video imagery and down-linked telemetry data. The medical team receives health-related information via spacecraft telemetry, supplemented by a daily private medical conference between the crew and their flight surgeon. During critical in-flight operations, e.g., extravehicular activities (EVA), biomedical testing or hazardous payload procedures, biomedical data can be monitored directly like electrocardiography.

IV. Living in Space

The first vehicle for powered flight was invented in the late nineteenth century. In 1989, the unmanned Voyager spacecraft completed a rendezvous with the planet Neptune, surveyed the solar system, and is now travelling through interstellar space. The evolution of spaceflight has been rapid and progressive: seven planets – and many of their satellites - have been studied; Apollo astronauts have worked on the lunar surface; and both the scientific community and the general public enthusiastically await a return to the moon and human missions to Mars.

The need to sustain life and productive human function in spaceflight has presented many unique challenges to medicine and life-support technology. Concurrent advances in spacecraft design and mission sophistication have spurred numerous technological breakthroughs in the biomedical sciences. The symbiotic relationship between astronautics and medical sciences will continue to develop space exploration and benefit terrestrial medicine.

The era of human spaceflight began on 12 April 1961 with the launch of Yuri A. Gagarin aboard Vostok-1. The two-year preparation for the historic mission included two suborbital and six orbital unmanned test flights, some of which carried dogs.

Spacecraft life support system

The need to control the conditions of the spacecraft environment and to surmount the logistical problems associated with eating, drinking, personal hygiene and waste management in microgravity are crucial aspects of living and working in space.

The atmospheric environment of Earth, with its particular combinations of gas pressure, composition and temperature, does not exist in space. At sea level, atmospheric pressure on Earth is one atmosphere (14.7 psi, or 101.4 kPa), and its composition is 78.08% nitrogen, 20.95% oxygen, 0.93% argon and 0.04% carbon dioxide, by volume. Average atmospheric temperatures over most of Earth's surface range from 22° to 27°C. For humans to survive in space, living quarters must be provided in which the atmosphere is controlled for proper pressure, gas concentrations and temperature.

Gas pressure and decompression sickness

From a physiological perspective, the most significant concerns associated with changes in atmospheric pressure are *barotrauma*, *explosive decompression syndrome* and *altitude decompression sickness*.

Barotrauma occurs when free gas, temporarily trapped in tissues or body cavities, is subjected to changes in external pressure. The resultant pressure differences across the walls of the cavities can produce pain and tissue injuries. Barotrauma is most likely to occur when swollen mucous membranes⁶⁸ have obstructed passages that normally permit rapid equilibration of pressure in the ears and cranial sinuses⁶⁹. Barotrauma can be avoided by controlling predisposing factors and limiting the rate of which pressure can be changed. In the Space Shuttle, for example, cabin pressure is reduced from the normal 1.014 bar to 0.703 bar only before EVA, and later adjusted in the airlock to the level of the pressure suit (0.296 bar). The maximum rate at which pressure is changed during nominal decompression and recompression procedures is 0.007 bar/sec; during emergency recompressions, the rate of increase is limited to 0.07 bar/sec.

Explosive decompression occurs when external pressure drops so rapidly that a transient overpressure develops in the lungs and other air-filled cavities. The lungs may rupture at a pressure differential as low as 80 torr⁷⁰ (0.11 bar). If lung tissue were to tear under these conditions, blood vessels would be severed and the positive pressure in the lung would force gas into the bloodstream, producing potentially fatal air embolism⁷¹.

In space, given a relatively small cabin volume, and assuming that the lung volume of the crew members is constant, an event that would create a large orifice in the spacecraft cabin such as loss of a window or hatch could result in a fatal air embolism.

Decompression sickness takes place when the sum of the partial pressure of gasses dissolved in the tissues exceeds the ambient pressure of those gases. The gas phase formed in tissues can distort them, provoke nervous discharges experienced as pain and effect

⁶⁸ Mucous membrane: a membrane rich in mucous glands; specifically, one that lines body passages and cavities which communicate directly or indirectly with the exterior

⁶⁹ Sinus: cavity in the substance of a bone of the skull that communicates with the nostrils; contains air

⁷⁰ 1 torr = 1 mmHg

⁷¹ Embolism: the sudden obstruction of a blood vessel by an embolus (an abnormal particle, an air bubble, circulating in the blood)

haematological⁷² changes. Under some conditions, the free gas phase formed in tissues (such as fat or muscle) can be transported by the blood stream to the lungs, where it can evoke “chokes⁷³” and cardiovascular collapse. If gas bubbles in the blood are not filtered by the pulmonary capillaries⁷⁴, they can travel via the arteries to the central nervous system, where they can produce neurological symptoms (sudden diminution or loss of consciousness, sensation and voluntary motion caused by obstruction of an artery of the brain).

Decompression normally is not a problem when the initial partial pressure of the diluted gas (generally nitrogen) in the atmosphere does not exceed the final decompression pressure by more than 1.2 to 1. If these limits are exceeded, the pressure of dissolved inert gases in the tissues must be lowered before decompression (“wash-out”) to avoid all risk of decompression sickness. For “wash-out”, Oxygen is used because its high rate of tissue utilization ensures that it does not contribute to the formation or growth of bubbles in the tissue. Breathing 100% oxygen before decompression thus constitutes an effective means of protecting against decompression sickness.

The cabin pressure on ISS and Shuttle vehicles is maintained at 1.014 bar. Although decompression sickness is no longer a concern during lift-off, crew members perform EVAs in suits pressurized to 0.296 bar and therefore must take protective measures. The present procedures involve breathing 100% oxygen for 1 hour and then decreasing the Shuttle cabin pressure from 1.014 bar to 0.703 bar at least 24 hours before EVA. The crew members then don the pressure suits, which are maintained at 0.703 bar, and breathe 100% oxygen for another 40 minutes. Finally, the suited crew members undergo decompression in the Shuttle air lock to a suit pressure to 0.296 bar (100% oxygen).

Carbon Dioxide

On Earth, carbon dioxide (CO₂) is normally present outdoors at a concentration of approximately 0.04%. A product of respiration, CO₂ concentration increases in indoor environments that are crowded or poorly ventilated. Accumulation of this gas presents a problem in the closed-loop environmental-control systems of the spacecraft cabin and pressure suit. CO₂ is removed from the Shuttle atmosphere by chemical reaction with lithium hydroxide. ISS uses a reversible gas absorption system for CO₂ removal.

The physiologic effects of CO₂ partial pressure in the atmosphere depend on the concentration and the duration of exposure. Acute responses to increased CO₂ are increased heart rate, respiration rate and minute heart volume. Chronic exposure to CO₂ can disturb the acid-base balance of the body.

Factors affecting human performance

Personal hygiene

For general crew well-being, facilities provided for personal hygiene on long on-orbit stays will approximate those on Earth. These will include facilities for hand and face washing,

⁷² Haematological: relating to blood or to haematology

⁷³ Something that obstructs passage

⁷⁴ Pulmonary capillary: the smallest blood vessels in the lung

bathing, hair washing, grooming, shaving and oral hygiene. Experience from Skylab and Mir show that a shower requires excessive time to assemble and operate and was judged ineffectual for that reason. The greatest challenges to developing workable systems for space flight are the effects of microgravity on water management.

Reorientation

From an Earth-gravity perspective, the Shuttle flies upside-down, with the cargo bay doors, tail and cockpit pointed towards Earth. This seemingly peculiar orbital flight pattern illustrates the novelty of operating outside the influence of gravity. “Up” and “down” are meaningless terms in space; one’s position is relative to other objects only.

During the first few days in flight, Space Shuttle crews attempt to maintain a normal “Earth-upright” orientation within the Shuttle – even though the Shuttle is upside-down relative to Earth. This orientation, learned over a lifetime of standing on the floor or ground, allows crew members to maintain their previous Earth perceptions of the layout of the Shuttle interior. After several days in space, crews tend to move almost unconsciously into positions that facilitate accomplishment of the tasks at hand. No longer orienting to the old gravity references as they perform their tasks, crew members discover a new-found freedom of body-positioning.

Changes in circadian rhythms / sleep-wake-work cycles

Desynchronization, or disruption of the body’s normal circadian rhythms, has long been known to produce physical symptoms such as insomnia⁷⁵, anorexia, malaise⁷⁶ and nervous stress. In space missions, desynchronization has been associated with disrupted sleep or work schedules.

The importance of synchronizing crew schedules with ground control was first recognized by Soviet scientists, who established a sleep- wake-work cycle keyed to normal Moscow time.

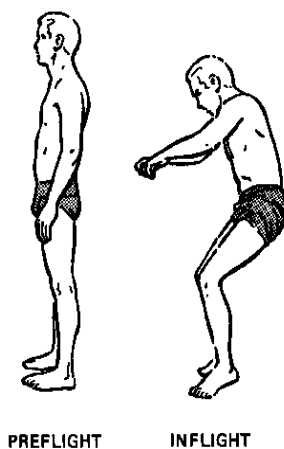
The quality of sleep during spaceflight was measured objectively during Skylab using electroencephalograms, electro-oculograms and measures of head motions during sleep. These experiments revealed no major adverse changes in sleep as a result of prolonged spaceflight, although sleeping medication was required occasionally. Shuttle crew members reported experiencing the greatest sleep disturbances during the first and last days of missions, with the most disturbing factors listed as space motion sickness, noise and excitement.

⁷⁵ Insomnia: abnormal inability to obtain adequate sleep

⁷⁶ Malaise: an indefinite feeling of debility or lack of health often indicative of or accompanying the onset of an illness

Habitability⁷⁷

Figure 10:
Postural changes
in flight.



Spacecraft habitability issues encompass not only sustained human life, but also ensuring the highest possible quality of life in that setting. Issues include environmental safety, sanitation, nutrition, and subtle factors such as *environmental richness, temperature, humidity and crew compatibility*.

Ergonomics in Space: Anthropometrics⁷⁸ and biomechanics⁷⁹ are focal points for ergonomics that seek to quantify human capabilities and physical limitations of spacecraft configurations. Changes in resting posture to that resembling a “foetal” position (Figure 10) can adversely effect

the ability to reach and position the arm and hand accurately. Because crew members tend to “overshoot” a target to be grasped before they adapt to the space environment, space system designers should ensure that switches are easy to manipulate and do not require unnecessary delicate turning.

Nutrition

Spacecraft food systems seek to provide the following characteristics: minimal in-flight preparation time, minimal waste, microbial safety under ambient-temperature storage conditions and good taste, as well as nutritional soundness. Foods are provided in individual portions for the convenience of the crews and are packed for ease of use in microgravity.

Foods on the International Space Station consist mainly of commercially available items and include thermo-stabilized, rehydratable, intermediate-moisture and natural-form items. Pre-assembled menus are stored in dry form whenever possible and are rehydrated during flight with water produced by the Shuttle fuel cells in order to minimize launch weight. Rehydratable foods are packed in moulded, high-density polyethylene bases covered with a laminated film lid heat-sealed to the base, with a needle septum for adding water. Other packages include flexible aluminium pouches for beverages, cans for thermo-stabilized foods and plastic pouches for nuts and cookies. The Shuttle galley dispenses hot and cold water, and features a forced-air convection oven for warming foods. Before missions, crew members can select their meals from a large number of food items. Cosmonauts and astronauts receive in addition to the dehydrated foods, regular shipments of fresh apples, cucumbers, tomatoes, lemons, onions and garlic, delivered by the Progress supply ship, the Space Shuttle or Soyuz spacecraft carrying the crews.

Taste and Aroma: Both Russian and American space crews have reported changes in their responses to taste or aroma during space flight. Diminished sensitivity to odours might be expected to result from the often-reported passive nasal congestion; symptoms of space motion sickness early in flight also may affect gustation. Another factor hypothesized to affect

⁷⁷ Habitable: suitable for habitation

⁷⁸ Anthropometrics: the study of human body measurements esp. on a comparative basis

⁷⁹ Biomechanics: the mechanics of biological and esp. muscular activity (as in locomotion or exercise)

the sense of taste in weightlessness is reduced stimulation of taste buds as a result of changes in convective activity in microgravity.

Psychology

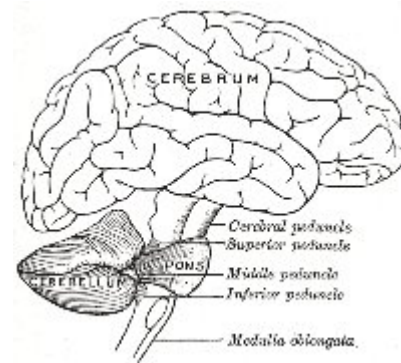
Most astronauts, at least once they get over any space sickness, report an initial exhilaration at their freedom from weight. They are all disciplined, highly trained people, too, who share a sense of being part of an elite team with important work ahead of them. So it is not surprising that psychological problems are unusual on short-duration space missions.

Sooner or later, though, despite the marvellous views and the sense of mission, astronauts do feel the pressure of confinement in what amounts to a few small rooms. One Russian cosmonaut wryly remarked, "All the conditions necessary for dispute are met if you shut two men in a cabin measuring 5 metres by 6 and leave them together for two months." But Russian psychologists - with almost 90,000 flying hours aboard the old Mir station to provide their data - have learned a good deal about the psychology of long-term spaceflight. Generally, they observed their cosmonauts go through three distinct phases. During the first, which usually lasted about two months, people were busy adapting, usually successfully, to their new environment. In the second phase, there were clear signs of fatigue and low motivation. And in the final phase, cosmonauts could become hypersensitive, nervous and irritable - a group of symptoms the Russians called "asthenia".

Other than a return to Earth, there seems to be no instant cure. But an easier workload, coupled with frequent opportunities for private communication with families back home, are important morale boosters. ISS operations managers have learned a great deal from the Russian experience, which is one reason why duty tours aboard the station will normally be limited to three months.

In the last several decades, several academic disciplines have been applied to spacecraft operations including psychology, habitability, human factors, sociology and performance. The newly emerging discipline of space psychology involves the application of psychological and behavioural principles to the support of crew health and well-being before, during and after spaceflights. The experience of the Russian Federation and the US in long duration spaceflight has revealed the need for psychological countermeasures to support human crews in space and facilitate their resistance to the stressors of spaceflight. Accordingly, countermeasures are being developed, validated and implemented, which aim to lessen the impact of these stressors on crews and subsequently increase mission safety and success while lowering risk. Psychological countermeasures involve astronaut selection, training and in-flight support. Such countermeasures are currently being employed in varying degrees, by Russian, European, Japanese, Canadian and US space programmes in an effort to overcome the stressors of spaceflight.

Figure 11:



V. Space biology

The goal of this section is to review the fundamental questions: how do cells “feel” gravity and how are their development and function changed in the space environment?

Gravity provides a directional stimulus that may play an important role in basic life processes in the cell, from individual biochemical reactions to overall cell growth and development. Can organisms undergo normal development in microgravity, or is development so abnormal that a stable population cannot be maintained indefinitely? Virtually no information exists. Few organisms have been kept in space through one life cycle (from fertilization through to subsequent production of progeny). Only a relatively small number of organisms have been taken into space at all, the experiments have often given inconsistent results and lacked necessary controls.

The growth and development of plants are determined by several factors, i.e. enzymes⁸⁰, proteins and hormone-like substances. The transport and behaviour of these substances is also influenced by gravity. Will these cellular functions proceed normally when deprived of the gravitational stimulus? The gravity-sensing mechanisms, the roles of the various hormones and the physiological mechanisms by which they stimulate growth all remain to be elucidated.

Microgravity provides a unique opportunity for conducting plant and cell research, which will have two broad objectives: first, to help to elucidate the fundamental mechanisms regulating normal plant and cell growth and development on Earth; and second, to assess the feasibility of using plants and micro-organisms to provide a life-support system for humans during the deeper exploration of space.

Cell and gravity

An obvious effect of reduced gravitational force is that the physical pressures and loads in organisms and cells change. Consequently, there will be a change in membrane stress, and in the cytoskeleton⁸¹ of the cell. Another effect is that sedimentation of particles in fluids is diminished or even totally absent. Correspondingly, gas-filled volumes, vesicles, etc. will not move as effectively because of reduced buoyancy, or will simply remain in place under microgravity. When density gradients are present in a liquid or gas under normal 1 G conditions, stirring and mixing take place. Because of the movement, the gradients ultimately disappear. A thermal gradient induces convection and mixing in the same way. In microgravity, such effects simply do not occur. This absence of mixing may result in limitations of the transport of material into and out of the cell through the cell membrane⁸².

Several processes will therefore be affected in space as a consequence of the effects on transport processes in organisms, uptake processes by, for example, plants and roots and growth processes. These processes may change mechanisms governing fundamental cellular functions; however, these alterations may be exploited for bio-processing in microgravity.

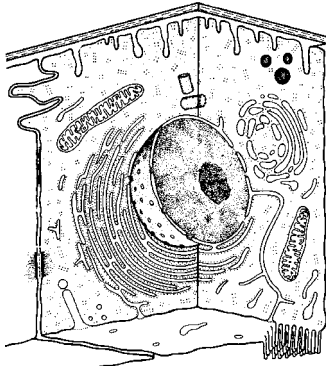
⁸⁰ Enzymes: proteins which are able to start and speed up chemical reactions in cells

⁸¹ Cytoskeleton: internal supporting-structure made of protein to keep the cell's shape

⁸² Cell membrane: wall around the cell

One of the tasks on future space missions will be the selection of biological systems suitable for bio-technology applications.

Figure 12: Animal Cell



In addition, the separation and isolation of biological specimens is of great importance to the life scientists. The absence of convection and sedimentation is crucial to many bio-processing techniques that need to be investigated in space. These range from the very fundamental production of protein crystals for basic life-science research, to the delicate fabrication and separation of important medical substances.

Results of space investigations on cellular function

*Bacteria*⁸³

Bacteria increase in number by simple cell division, and generation time for most bacteria is about 30 minutes. In bacteria, the genome is a single circular molecule of DNA which is replicated throughout most of the cell cycle. An increase in bacterial growth and genetic transfer has been observed during spaceflight. Also, bacteria grown in microgravity showed increased resistance to antibiotics.

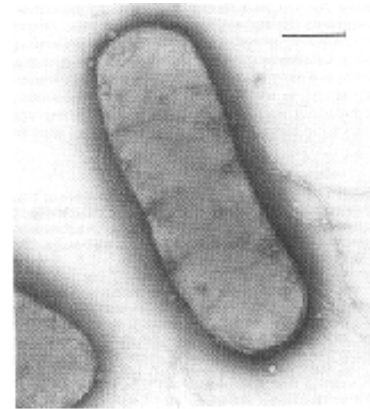


Figure 13: Bacteria cell

When gravity is altered, biological changes are observed even when cells are isolated from the whole organism and grown in culture. Physical scientists predicted this would not occur because gravity is an extremely weak force compared with the other fundamental physical forces acting on or within cells; however, Shuttle/Mir results suggest that spaceflight may alter the characteristics of cultured cells. Most cells flown in space have either been suspended in an aqueous medium or attached to an extra-cellular matrix bathed by an aqueous medium.

The bacterium *E-coli* has flown experimentally in culture seven times aboard the Space Shuttle (Klaus *et al.*, 1997). During spaceflight, *E-coli* exhibited a shortened lag phase, an increased duration of exponential growth and an approximate doubling of final cell population density compared to ground controls. These differences may be related to lack of convective fluid mixing and lack of sedimentation, processes that require gravity. During exponential growth in minimal gravity, the more uniform distribution of suspended cells may initially increase nutrient availability compared to the 1-G-sedimenting cells that concentrate on the container bottom away from available nutrients remaining in solution. If waste products build up around cells in the absence of gravity, then given sufficient time, they could potentially form an osmotic solute gradient or a pseudomembrane that decreases the availability of nutrients or directly inhibits cell metabolism. It is suggested that inhibitory levels of metabolic by-products, such as acetate, may be formed when glucose is in excess within the medium. Therefore, although perhaps somewhat counter-intuitive, a reduction in

⁸³ Bacteria: the simplest form of life on Earth, whose genetic material is not extra in a distinct nucleus; they proliferate by repeated cell division.

glucose availability may actually be beneficial to cell growth. Also, local toxic by-products could become concentrated on the bottom of the 1-G container with cells in increased proximity to each other. Such a process could limit cell growth. Thus, changes in *E-coli* and possibly other cells during spaceflight may be related to alterations in the microenvironment surrounding non-motile cells, e.g., the equilibrium of extra-cellular mass-transfer processes governing nutrient uptake and waste removal.

*Protozoa*⁸⁴



Figure 14:
Protozoon

Protozoa, e.g., *Paramecia*, are covered with cilia and are about the size of the full stop at the end of this sentence. These organisms feed mostly on bacteria by phagocytosis. Nutrients are transported across food vacuoles and circulate within the cell by cytoplasmic streaming, nutrients are transported across vacuole membranes into the cytoplasm and undigested wastes are eliminated by exocytosis as the vacuoles fuse with specialized regions of the cell surface. *Paramecia* reproduce asexually but also transfer genes between two individuals. Experiments aboard Salyut and Spacelab showed that paramecium grew three times faster than on the ground. Besides this increased growth, there was a 20% decrease in cell volume and loss of intracellular calcium and magnesium, and possible changes in membrane assembly. The increase in proliferation rate may be caused by cosmic radiation or it can be due to more available reserve energy (in microgravity *Paramecia* do not need to orient themselves against the gravity vector).

Mammalian cells

Unlike bacteria or paramecia, mammalian cells have shown a two- to three-fold decrease in growth rate in microgravity compared to ground controls. The reasons for this decreased growth are not yet known, but growth may be reduced as a result of metabolic changes (reduced glucose utilization or changes in the membranes).

In vitro cellular responses in live animals (mainly rats) flown in microgravity showed reduced protein synthesis (probably responsible for loss of muscle weight), reduced growth rates in blood cells, changes in growth hormone secretion and cytoskeleton synthesis. Calcium loss and reduced bone density is constantly reported in all animal specimens as a result of spaceflight.

Plants

Single cell plants respond to microgravity more like bacteria in that they demonstrate an increased growth rate. The responses of higher plants are more complex and sensitive to the conditions of spaceflight. Cells differ from the ground controls as follows: there is usually a rearrangement of cell organelles⁸⁵, a reduction in the amount of energy reserves, increases in cell vacuoles and mitochondria volume, and disturbance in the process of cell division. Some

⁸⁴ Protozoa: most simple living unicellular organism (e.g. paramecium; Organisms that consists of a single cell. It has a distinct nucleus and several organelles, and grows by repeated cell division)

⁸⁵ Organelle: small compartments (bodies) which have specialized functions inside a single cell

of the changes in microgravity may be due to change in calcium flux. Circadian rhythms⁸⁶ were not significantly affected.

Developmental biology

Developmental biology includes all aspects of the life span of an organism, from fertilization through aging. Topics for research include gamete⁸⁷ production, fertilization⁸⁸, embryogenesis⁸⁹, implantation⁹⁰ (in mammals), the formation of organs (organogenesis) and postnatal development (changes after birth).

Developmental biology research in space focuses on the influences of gravity and microgravity on reproduction, differentiation, growth, development, life span, aging and subsequent generations of animals. Before humans can attempt missions for long-duration space exploration, they must thoroughly understand the effects of microgravity on developmental processes. The absence of gravity during development can also be used to elucidate the effects of gravity during normal development on Earth.

Even if humans do not yet need to reproduce in space, they will need to raise multiple generations of plants and animals to feed themselves in a closed-system environment for long-duration missions. A major question that has yet to be answered in an animal subject is whether or not an organism can undergo a complete life cycle in microgravity. Current research has focused on whether normal development depends on gravity exposure during critical time periods during development, whether such exposure results in irreversible changes in morphology and function in adulthood and whether an organism can undergo a complete life cycle or several life cycles in microgravity.

It is known that at some point after fertilization, depending on the organism, cells become committed to developing along a certain pathway. This restriction in fate is called *determination*⁹¹. For instance, if the two cells in a cleaving sea urchin embryo are separated, each may give rise to a complete, normal, but one-half-sized larva. But if one of the cells from the sixteen-cell stage is separated and raised in isolation, it does not give rise to a normal but one-sixteenth-sized larva; it develops into a specific subset of larva tissues. During early cell divisions in most animals embryos, there are gradual restrictions in developmental potential; this is not the case in plants. Sooner or later in all animals, most cells in the embryo give rise only to a certain tissue or organ. They have lost their plural potential. The second process of development is *differentiation*⁹², a term that refers to the process whereby the differences that were “determined” manifest themselves. In other words, differentiation is the selective expression of genetic information to produce the characteristic form and functions of the complex, fully developed embryo. A third aspect of early development, the mechanisms whereby the determinations and differentiations occur at the right time to produce the normal organisms, is called the formation of pattern (not only do they realize their fates, but they do so in the correct place at the correct time).

⁸⁶ Circadian rhythms: biological activity occurring in approximately 24-hour periods or cycles

⁸⁷ Gamete: a mature male or female germ cell, usually possessing a haploid chromosome set and capable of initiating formation of a new diploid individual by fusion with a gamete of the opposite sex

⁸⁸ Fertilization: insemination

⁸⁹ Embryogenesis: the formation and development of the embryo

⁹⁰ Implantation: the process of attachment of the embryo to the maternal uterine wall

⁹¹ Determination: the fixation of the destiny of undifferentiated embryonic tissue

⁹² Differentiation: determines the species/function of a cell coming into being

It is difficult to visualize the entire developmental process at one time in one organism, because the formation of the various tissues and organs (organogenesis) not only spans several developmental stages, but also continues after birth and into the neonatal period.

Furthermore, the transition from the neonatal period to adulthood is marked by fundamental developmental events such as cell specialization, developmental transitions, cell-cell interactions and inductions, the development and integration of many physiological and biochemical functions and growth. Regenerative processes are fundamental developmental processes to postnatal tissue loss and injury. In many situations, developmental processes along with adaptive functions are responses to pronounced changes in the environment to which the individual is exposed.

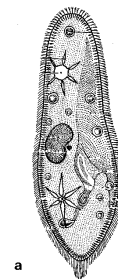
Stress and/or adaptive effects may lead to the failure of normal developmental and reproductive pathways regardless of microgravity effects. Similarly, stress and adaptive effects could lead to problems in the physiology encountered in the environment of space since they might relate to specific kinds of developmental effects. Different types of organisms have evolved different strategies to deal with gravity, or its absence, and some organisms are better suited to certain studies than others. Different organism types are presented in the following sub-sections.

Development of animals

Invertebrates

Invertebrate animals, those without backbones, have been used to investigate the basic processes of development since the beginning of modern biology. While the organs that form in these creatures can be quite different from those of vertebrates, they serve the same purpose of nutrition, respiration and reproduction, and are formed during early development by the same fundamental processes. The supposition of most scientists is that exposure to microgravity will have little effect on these processes. This is especially true for aquatic invertebrates, which often are not orientated with respect to gravitational fields, since they are submitted to physical forces in oceans, lakes and rivers. Terrestrial invertebrates are exposed to 1 G, and some of their developmental processes might be more susceptible to microgravity; however, judgment remains largely intuitive due to the lack of information.

Because of documented changes in bone calcium in mammals exposed to microgravity, studies on the formation of skeletal hard parts in invertebrates during later development are appropriate. The formation of exoskeletons (shells) and endoskeletons (internal spicules of echinoderm larvae) in invertebrates usually involves calcium carbonate. The precise details of just how the calcium forms crystals at the right time and at the right place are still a mystery. Many invertebrates also possess sensory organs that are used to sense the orientation of the organisms in the Earth's gravitational field, and these are analogous to vestibular functions of vertebrates. One might inquire whether gravity-sensing organs develop normally in microgravity.



*Figure 15:
Invertebrate*

Lower vertebrates

Several animal eggs, including those of birds, turtles and amphibians display an unequivocal response to microgravity in establishment of the embryonic axis. For example, while frog eggs within the ovary are randomly orientated with respect to gravity, fertilized eggs orient so that the darkly pigmented animal hemisphere is facing upward. This rotation allows for reorganization of the egg cytoplasm, which leads to the establishment of dorsal-ventral polarity. Fertilized frog eggs were flown on Biosatellite II; normal morphogenesis occurred, suggesting that gravity-driven cytoplasmic rearrangements are not essential

In chicken embryos, the positioning of the body axis is also known to be affected by gravity. During the passage of the fertilized egg down the oviduct⁹³, the egg axis is always formed with a definite orientation with respect to gravity. Removing the egg from the oviduct and placing it in a new orientation with respect to the Earth's gravitational field causes changes in the orientation of the primary body axis. Thus, it is of interest to ask if a plane of bilateral symmetry can be established in eggs passing down the oviduct in microgravity, and whether normal development can progress under these circumstances. Both European and US space agencies have flown experiments involving the induction of ovulation⁹⁴, fertilization and subsequent development through organogenesis⁹⁵ in living frogs and birds; results showed that these functions occurred normally in microgravity.

Mammals

The development of mammal embryos occurs within the body of the mother. Consequently, to understand the effects of the space environment on mammalian development, it is necessary to be concerned also with physiological responses of the female (mother) to microgravity. For example, redistribution and volume changes in the body fluids, and changes in the concentrations of plasma electrolytes, notably calcium and potassium, could affect the composition of oviductal fluid, which could then have effects on the level of fertility as well as early embryogenesis.

Cosmos 1129 carried 5 female and 2 male rats for 19 days. The rats were intended to mate in space, resulting in pregnancies of 1 to 16 days duration before re-entry. Birth was to occur on the ground. Neither the flight animals nor synchronous controls exposed to the stimulated stress of re-entry successfully gave birth. Later experiments showed that reproductive failure was not solely due to stresses of launch and re-entry, but that microgravity could have an effect on implantation events.

Previous space missions have failed to reveal any effects of the space environment on cleavage⁹⁶ rates and early stages of development in non-mammal embryos. Neither does it

⁹³ Oviduct: a tube that serves exclusively for the passage of eggs from an ovary

⁹⁴ Ovulation: the discharge of a mature ovum from the ovary

⁹⁵ Organogenesis: development of bodily organ

⁹⁶ Cleavage: the series of synchronized mitotic cell divisions of the fertilized egg that result in the formation of the blastomeres and changes the single-celled zygote into a multicellular embryo

seem likely that microgravity would have direct effects on cleavage in mammal embryos. On the other hand, the drop in plasma potassium observed in crew members placed in microgravity for 3 to 4 weeks or longer is worrisome from the standpoint of reproductive failure since this ion can regulate the rate at which embryos develop into blastocysts⁹⁷.

The interval between the time of implantation and birth is divided into the period of *organogenesis* and the period of *foetal development*. Organogenesis is the structural establishment of the major organ systems in the body. This occurs in a well-ordered sequence of events. By the end of organogenesis the species is easily recognizable; however, these newly formed organs are functionally and biochemically immature. During the foetal and neonatal period, these structures undergo both functional maturation and continued structural development to accommodate the increasing functional requirement of the organ. Each organ or structure has specific times in the development when it is extremely sensitive to the effects of exogenous influences or defective gene expression⁹⁸. During the period of uterine development, mammalian embryos display no gravity orientation and organogenesis and foetal development might be expected to be relatively insensitive to microgravity; however, indirect effects of the physiological changes observed in microgravity (calcium loss, muscle atrophy, fluid shifts) on the development of certain organ systems could become a problem.

Postnatal development

There is scarce information as to whether or not microgravity alters postnatal developmental events. Many aspects of the bodily functions are immature at birth, and the postnatal maturation involves functions and activities such as recognition and stabilization of synaptic units, the differentiation and stabilization of molecules and receptors, the maturation of nerve and muscle, as well as the transmission of nerve impulses. For example, because of the normally continuous impulses between the muscles and the central nervous system, the development of postural muscles would be expected to be most noticeably affected in microgravity. The postnatal development of the skeletal system is affected by the mechanical environment in which it develops. Other structures and functional systems that need to be examined carefully are: the architecture of the connective tissues⁹⁹ to the body, the structure of blood and lymphatic vessels and the heart, the development of control of blood pressure, late-developing components of the CNS, the development of circadian rhythms, etc.

Is gravity necessary for life as we know it?

Life most likely will look and, perhaps, move quite differently after many generations in space. We have learned that life is “plastic” and changes with the environment; it adapts at least transiently to changes in gravity. The microenvironments of spaceflight require more study so that we will understand how to overcome them effectively. We certainly have a lot to learn about the complexity of biological responses to altered gravity. Data to date suggest that certain biological structures have evolved to sense and oppose biomechanical loads, and those structures occur at the cellular as well as at the organismal level. Certainly, the load-bearing

⁹⁷ Blastocyst: a distinctive stage of a mammalian embryo. It is a form of berry-like cluster of cells

⁹⁸ Gene expression: whatever the cell synthesizes is determined by its genetic code

⁹⁹ Connective tissues: connective tissue of spindle-shaped cells with interlacing processes that pervades, supports and binds together other tissues and forms ligaments, tendons, and aponeuroses

systems of vertebrates change following acute exposure to space; what will happen over multiple generations is speculative. The “functional hypothesis” theory suggests that what is not used is lost. If this theory holds over multiple generations in space, then gravity-dependent structures may ultimately disappear or assume a very different appearance in space. Many questions remain to be answered. Gravity most likely is essential for life as we know it.

Does gravity play a role in evolution?

Gravity affects the environment. It is required for convective mixing and other weight-driven processes such as draining of water through soil and assuring that what goes up comes down. One might predict that plants would grow taller without gravity, yet the boundary layers produced by a lack of gravity might facilitate increased levels of growth-inhibitory or ageing environmental factors around the plants, thereby causing them to dwarf. Ecologies stratifying by weight on Earth might tend to form as three-dimensional communities without gravity. Gravity also has a role to play in development of load-bearing structures. The scaling effect of gravity is well known: the percentage of body mass relegated to structural support is proportional to the size of a land animal (e.g. 20g mouse = ~5%, 70kg human = ~14% and 7000kg elephant = ~27%). This scaling effect in land animals would likely change in space and could result in a static scale comparable to marine mammals on Earth (~15% of mass as supporting tissues over a wide range of weights). Human legs are bothersome in space and not only get in the way but are also involved in the fluid shifts that occur early in flight. Whether legs would disappear over time without gravity or become more like grasping talons is unknown. Form follows function and as function changes, so will form. How much change and what form organisms and ecologies will assume over time in space is unknown. We only have short snapshots of organisms in the space environment.

A fascinating suggestion that gravity might play a role in evolution comes from snakes. On Earth, snakes have evolved in different environments. For example, tree snakes spend their days crawling up and down trees and exist in an environment where they must cope with gravity. Land snakes spend most of their life in a horizontal position. Sea snakes are neutrally buoyant and spend their life swimming within their habitats. Lillywhite and collaborators (1988) noticed that the heart of the tree snake was closest to the brain, suggesting that it would be more gravity tolerant than the other snakes as it did not have to carry blood over as great a distance from the heart to the brain. He centrifuged the animals and found that the sea snake had the least gravity tolerance (i.e., fainting), the tree snake had the most, and the land snake was intermediate. Changes in heart position, likely related to gravity, most certainly happened over evolutionary, rather than single-generation, time scales. Gravity may determine the location and size of internal organs such as the heart.

We will appreciate the influence of gravity on evolution of species only after prolonged periods in space. The role of gravity in evolution remains speculative, leaving room for much investigation, but one certainly can say that *gravity shapes life!*

Development of plants

Plants are an integral part of our daily life. They provide oxygen, food and shelter as well as a variety of other products we use on a daily basis. Most likely, what you had for breakfast came directly, or indirectly, from plants as did the paper you write on, the materials used to shelter and clothe you, the medicines used to heal you and even the oxygen you breath. Plants have adapted to the most severe climatic conditions on earth: desert,

underwater, salt water, extremes in light, altitude, cold and heat, often allowing humans and other animals to inhabit these regions.

Not surprisingly, as man moves into outer space, plants would need to follow, especially to provide the "closed system" necessary for long term space flight. But, could plants grow in the spaceflight environment? Space is an ecosystem plants have never encountered. The biggest question, of course, is gravity or lack thereof. Nutrients and light could be provided. Gravity was taken for granted on Earth, to such an extent that it was not even considered a variable in experimentation. But in 1961, Yuri Gagarin propped the door open for all time to space flight. He opened new possibilities for mankind and gravity became a variable!

Since 1806, we have known that plant organs use gravity as a guide for growth to ensure proper positioning of leaves for efficient photosynthesis and gas exchange and of roots to allow for uptake of water and nutrients needed for proper growth. Plant/gravity experiments continued in the late 1800s. In 1880 Darwin wrote detailed descriptions of gravitropism in "The Power of Movement in Plants". Researchers at the time recognized that a structure at the tip of the roots, the root cap, was essential for root gravitropism. During the same period, Thomas Hunt Morgan (1880) explored the effects of rotation on seed germination, the first clinostat, or simulated microgravity, experiment; however, only in the last 30-40 years, with the advent of the space programme, has plant gravitropism been studied in earnest.

Plant growth has a definite orientation with respect to gravity. Roots grow in a downward direction, while stems grow upward. Several processes are involved: the perception of gravity, its transduction into a physiological signal within the sensing cell, the transmission of the signal from the sensing cell to the other regions of the cylindrical plant organ and the differential growth of the two sides of the organ that determines whether it will curve upward or downwards. The sensing of gravity is done by amyloplasts, starch-containing organelles contained in specialized cells, the statocytes. Since the density of amyloplasts is greater than that of the surrounding cytoplasm, they will settle to the bottom of the statocyte. The transduction mechanism between amyloplasts settling and signalling is not known. Signalling is most likely done by growth hormones. The concentrations of growth hormones are higher on the rapidly growing side than on the slowly growing side of plant shoots that are stimulated by gravity. The mechanisms of transduction, the role of the various hormones and the physiological mechanisms by which they stimulate growth remain to be elucidated. Both ground-based research and spaceflight research is needed to resolve these issues.

Generally speaking, tropisms are permanent, directed growth responses generated by plants in response to external stimuli including light, touch, water, temperature, chemicals and gravity. They involve asymmetric growth of the stem or root. The most familiar and best studied of these is phototropism in which the shoots of plants grow toward a light source. Gravitropism is specifically the gravity-directed growth process that directs both shoot and root growth from seed germination throughout the plant's lifecycle. Growth toward (positive gravitropism) or away from (negative gravitropism) the Earth's gravitational pull are examples of gravitropism. Simplistically, roots are usually considered positively gravitropic, and plant shoots considered negatively gravitropic, although the extent to which this occurs is quite variable. For example, lateral roots, the shoots of hanging plants, trailing or winding plants and weeping forms of trees, all have variable responses to the gravity vector.

Other areas of plant physiological and biochemical research that can be significantly advanced by studies under microgravity are: the mechanisms of plant responses to other environmental stimuli, (such as light and magnetic and electrical fields) which are masked on Earth by the overriding response of plants to gravity, and the effects of the absence of 24-hour cycles in environmental signals on circadian rhythms in plants.

Plant research in space

Like bacteria, plants were exposed to space flight very early in the space programme. Seeds of five species were first sent up on Sputnik 4 in 1960, and simple *Chlorella pyrenoidosa* cells were sent on Discover 17. Since then there has been a bias to send a variety of plants into space rather than picking one or two species and studying them in detail over the decades. In part, this is because different scientists have "specialty" systems that they work on, or they pick certain plants as best for particular tests. In part, it is because of practical concerns (e.g., a need for plants with short life spans to match short space flights) or a desire to see whether a variety of possible foodstuffs would do well. A few of the plant types sent so far have included algae, carrots, anise, pepper, wheat, pine, oat, mung beans, cress, lentils, corn, soybeans, lettuce, cucumbers, maize, sunflowers, peas, cotton, onion, nutmeg, barley, spindle trees, flax, orchids, gladiolas, daylilies and tobacco.

As in cell biology, and as in virtually all other areas of biological experimentation in space, plant biologists may feel that the opportunities for in-depth study of plants have been sparse. This is simply the nature of the current space programme, with much to do and a few flight opportunities that must be shared. Experiments that might take weeks on Earth, take years to plan and execute in space. Limitations of the space flight environment also have limited control experiments and often kept the number of specimens studied far from statistically ideal. Often, plant studies are paralleled by Earth-based horizontal clinostat studies, but results in actual microgravity are somewhat different.

Results from in-flight experiments show that abnormalities have been encountered frequently in various organs examined from plants grown in spacecraft. In many instances, the abnormalities seem to have arisen from adverse growing conditions, especially water stress; but in some experiments the effects have probably been attributable to the space environment. Detailed examination of the plant material grown in space reveals disturbances in cell division, nuclear¹⁰⁰ and chromosomal behaviour, metabolism¹⁰¹, reproductive development, orientation and viability¹⁰². These disturbances do not lead to major morphological or functional abnormalities in a plant grown from normal seed over a period of one to two weeks. With time, however, these cellular and sub-cellular disturbances will have increased effects on the functional integrity of the plant, and will undoubtedly lead to gross morphological and functional abnormalities in later developmental stages such as floral development, fertilization and seed formation, as well as in subsequent generations of plants grown from seeds that are themselves formed in the absence of gravity.

There is a need for more sophisticated and closely controlled microgravity experimentation, especially with experiments addressing specific physiological and

¹⁰⁰ Nucleus: site of the molecules carrying the genetic code inside a single cell

¹⁰¹ Metabolism: transformation and degradation of ingested materials within the cell for production of substances which are essential for its survival

¹⁰² Viability: capable of living

biomechanical events at the organ, cellular and sub-cellular levels. The use of plant-cell cultures may also produce spin-offs in space plant biotechnology.

Microgravity may influence certain time dependent biological processes in the single cell. There is some evidence from experiments aboard Spacelab that there is a marked reduction in the amplitude and clarity of the coordination rhythm in some plants after six days of weightlessness; however, the biological rhythm of simple algae cells in Biorack on Spacelab-D1 appeared to be totally undisturbed. One of the questions still to be answered is whether circadian rhythms in cells are ruled by an exogenous pacemaker, so called "*Zeitgeber*", i.e. some extra-cellular time signal. For instance, the cell cycle, i.e. the sequence of events between two cell divisions, ranges from 15 to 24 hours for an animal cell, and between two and four days for plant cells, with a characteristic duration for each type of cell. Since it is conceivable that certain dynamic cell functions, such as cytoplasmic streaming, are influenced by gravity, it is of primary importance to assess the effects of space on biological clocks.

Plant Radiation Effects

Plant cells are affected by radiation, just like any other cell. Chromosome damage and abnormalities are seen in a variety of plants in space. In general, seeds are less sensitive than developing embryos or growing plants; this may be because their cells are not actively dividing. Several studies have been done to try and determine which radiations are most damaging, or even whether the damage was solely due to radiation at all. Some studies showed that standard radioprotectant chemicals like cysteine, aminoethylthiourea and 5-methoxytryptamine did not stop the damage. This might indicate that low-LET, indirect radiations are not at primary fault; however, some of the flights on which damage was found were short enough that GCR dosages were low. Of course GCR remain a possibility, but the possibility that some of the chromosomal damage and abnormalities are due to some other environmental factor (like microgravity) also remains a possibility.

Bibliography

Barratt M.; personal communication, 1996

Billica RD, Simmons SC, Mathes KL, McKinley BA, Chuang CC, Wear ML, Hamm PB. Perception of the medical risk of spaceflight. *Aviat Spca Environ Med* 1996; 67:467-73.

Bjurstedt H (ed). *Biology and Medicine in Space*. ESA BR-01, Paris, 1979

Cogoli A, Tschopp A & Fuchs-Bislin P. Cell sensitivity to gravity, *Science* 225 pp. 228-230, 1984

Churchill SE (ed.), *Fundamentals of Space Life Sciences*. Krieger Press, in press 1996

Johnston R S & Dietlein L F (eds). *Biomedical Results of Skylab*. NASA SP-377, Washington DC 1977

Koch C.J., Painter R.B.; The effect of extreme hypoxia on the repair of DNA single strand breaks in mammalian cells. *Radiat.Res.*64:256-269, 1975.

Kozlovskaya I.; personal communication, 1996

Lewis M & Hughes-Fulford M. Cellular Response to Spaceflight. In: *Fundamentals of Space Life Sciences*. S.E. Churchill (ed) Krieger Press, Fla. 1997

Malmejac Y, Bewersdorff A, Da Riva I & Napaolitano L G. Challenges and Prospectives of Microgravity Research in Space, ESA BR-05, Paris, 1981

Mattoni R H, Ebersold W T, Eiserling F A, Keller E C & Roming W R. Induction of lysogenic bacteria in the space environment, In: *The Experiments of Biosatellite II* (Ed. J F Saunders), NASA SP-201, pp. 309-324, 1971

Moore D., Bie P., Oser H. *Biological and Medical Research in Space*, p.213; Springer Verlag; 1996

Nicogossian AE, Huntoon C, Pool S.(ed.) *Space physiology and medicine*, 3rd edition, Lea & Febiger, 1994

Ono T., Okada S.; Estimation in vivo of DNA strand breaks and their rejoining in the thymus and liver of mouse. *Int.J.Radiat.Biol.*25:291-301,1974

Oser H (ed). *Space Biology with Emphasis on Cell and Developmental Biology*. ESA SP-206, Noordwijk, 1983

Oser H & Battrick B (eds) *Life Science Research in Space*. ESA SP-1105, Paris, 1989

Petrov V.P., Kovalev E.E., Sakovich V.A.; Radiation: risk and protection in manned space flight. *Acta Astronautica* 8(8-10):1091-1098,1981

Planel H & Oser H (eds) A Survey of Space Biology and Space Medicine. ESA BR-17, Paris, 1984

Prigogine I & Stengers I. Order out of Chaos, Bantam Books, Toronto, London, New York & Sydney, 1984

Schopp A, Cogoli A, Lewis M L & Morrison D R. Bioprocessing in Space: Human cells attach to beads in microgravity, J. Biotechnol., 1, pp. 287-293,1984

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