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Medical Aspects of Long-Term Settlements on Other Planets

"Earth is the cradle of humanity,
but one cannot remain in the cradle forever."

Konstantin Tsiolkovsky

THE CHALLENGE FOR SPACE MEDICINE

The dream of manned space travel has proved to be very attractive for centuries for scientists and the general population as well. "Man must rise above Earth to the top of the atmosphere and beyond, for only then will he fully understand the world in which he lives" – stated Socrates (469–399 B.C.). The first person to write about living and travelling in space was Johannes Kepler in the early 1600s. In 1865 the French writer Jules Verne wrote in his novel *From the Earth to the Moon* about the attempt to build an enormous "space gun" and launch three people in a projectile with the goal of Moon landing. In the 1860s, Edward Hale wrote about the "Brick Moon" which had many of the characteristics of a space station; it was a man-made structure that orbited Earth and provided housing and life support for its crew while serving as a navigation aid for people on Earth. The Russian theoretician Konstantin Tsiolkovsky (1857–1935) inspired by the fiction of Jules Verne theorised many aspects of space travel and rocket propulsion: he envisioned a certain design for a space station that would serve

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DOI: https://doi.org/10.36250/01209_02

as a miniature Earth, with the growth of vegetation in the interior and that could use sunlight as an energy source. In 1928 Herman Noordung gave the first details of the engineering, design and construction of a space station (*wohnrad* or *living wheel*). He identified the possible harmful effects of weightlessness and recognised the significant role of rotation (evolving centrifugal force) required to create artificial gravity for the crewmembers. Ley wrote about life in a space station in 1952 (well before it actually happened), also imagining "a wheel-shaped space station revolving around the Earth much as the moon does". The necessity of a new discipline concentrating on human factors of spaceflight emerged after World War II as technical development (ballistic missiles and rocket technique) stepped over the von Kármán line considered the aerodynamic cutoff limit (Ley–Bonestell 1950; Antonsen 2019; Nicogossian et al. 2016: 5).

For life science and space medicine specialists, the first spaceflight (limited one-turn-around 108 minute long "excursion" by Yuri Gagarin into LEO – Low Earth Orbit) on 12 April 1961 became the first solid evidence that spaceflight is survivable and humans can maintain their working ability with basic physiological functions. But even now and for the foreseeable future space travels continuously challenge our competency to maintain and extend even more our living capability and habitation onboard space stations, spaceships and on the surface of other moons and planets. Considering the habitability potential of celestial objects we should take into account chemical, physical, geological and geographic attributes that can shape the environmental settings on the surface: a combination of approximately 20 basic factors can predict the habitability of that planet or moon. We should prioritise the presence of water, overall atmospheric pressure (excluding poisoning gases), proper temperature range (avoiding extreme diurnal fluctuation), the availability of nutrients (C, H, N, O, P, S sources and essential metals, essential micronutrients) due to volcanic activity or production, an energy source, and protection from solar ultraviolet and galactic cosmic radiation, reduced gravity. All these parameters can interfere with deployed human life support systems and can deteriorate human adaptability to harsh environmental settings to withstand them in a sustained form (McKay–Stoker 1989: 189–214).

50 years after Apollo 17 set foot on the Moon for the last time, space exploration could get a new impetus: as a first step to returning to the Moon, the Artemis program is focusing on the development of a “Lunar Gateway” orbiting unit and a stationary lunar surface base (“Lunar Outpost” as a Base Camp Concept). But it is only a small step heading to and preparing for the much longer and more dangerous travel to Mars. Today’s advanced technology has enabled astronauts to live on ISS (International Space Station) since 2001 continuously (usually in six-month rounds), performing a wide range of biomedical experiments and research projects to better understand the effects of space environmental stressors on the human body. Outer space is really a hostile and harsh environment for any form of life, acute (explosive) exposure to it without any technical protection (encapsulation in a spaceship or hermetised spacesuit) can cause immediate incapacitation and even death within a few seconds. For prolonged spaceflights into deep space (despite hermetised and climatised modules and compartments onboard spaceships or space stations) other highly relevant stressors like extreme radiation levels and microgravity-induced pathophysiological processes can lead to diminished working ability and loss of functional activity. The imminent consequences on the human body can include circulatory changes (deconditioning cardiovascular reflexes, space anaemia – reduced red blood cell volume), space motions sickness, gradually worsening muscle atrophy (loss of lean body mass and strength), bone demineralisation (like age-dependent osteoporosis), eye problems with headache in SANS (space associated neuro-ocular syndrome) and we should consider the adverse long-term effects of confinement and isolation from psychological aspects as well (Ong et al. 2023: 895–900). Isolated settings combined with extremely threatening environmental challenges can easily lead to profound psychological changes (depression, mood instability) in a remote ground-based situation (e.g. Antarctic research station as a space analogue) and emotional downgrading (negative patterns) can interfere with proper verbal and written communication among team members. By content analysis of diaries and reports, we can characterise social dynamics as an essential parameter for teamwork efficiency (Ehmann et al. 2018: 112–115).

Partially restored gravitational force on the surface of targeted moons and planets (the average gravitational acceleration on Mars is 3.72 ms−2, about 38% of that of Earth) can provoke again malfunctioning in readaptation, orthostatic intolerance (fainting tendency) and leaving the shield of spaceships can expose the astronauts to an even higher dose of cosmic radiation, especially during SPEs (Solar Particle Events). So maintaining the working ability and overall health of astronauts is a huge challenge for space medicine from the very beginning, demanding a complex medical support system, including telemedicine and surgical, resuscitative capabilities, with proper preventive countermeasures in certain pathophysiological processes like musculoskeletal atrophy, carcinogenesis, space radiation-induced atherogenesis. These entities might be showstoppers and can raise ethical concerns about the real cost and benefit of astronauts' health and well-being status (a "one-way ticket" to Mars is not a real option).

It is often criticised that human missions are too expensive compared to unmanned automatic platforms designed for Earth observation or Solar System exploration. But we shall be out there personally in order to utilise our competencies in an inherently inexact science: we should take into consideration individual physiological variability and execute repeated measurements to improve the survivability of humans. As Wilbur Wright, pioneer of the heavier-than-air flight stated: "If you are looking for perfect safety you will do well to sit on a fence and watch the birds; but if you really wish to learn you must mount a machine and become acquainted with its tricks by actual trial."

The same is applied to spaceflight: if you do plan to live in space and explore other moons and planets you are forced to prepare for unfamiliar and harsh environmental settings and forced to cope with them in a prospective way. With proper steps like medical surveillance (biomedical monitoring) methods and even therapeutical countermeasures, we can improve the quality of life in space. Furthermore, it may be possible that by using the same proper and effective countermeasures applied in space we can improve the health of people on Earth suffering from similar age-dependent clinical problems (like osteoporosis and muscle atrophy). In other words: patients with illness live in a normal Earth environment but evolve abnormal physiology. On the contrary, astronauts are scrutinously selected applicants with normal physiology who live in an abnormal (evolutionary not experienced and not adapted) environment: their adaptive processes can be evaluated and proactively utilised in general sick population on Earth as well (Williams et al. 2009: 1317–1323).

THE HISTORY OF SPACE MEDICINE

Space medicine as a new science was born after WWII, closely related to rocket research (planning and building), focusing on the physiological consequences of altered gravitational forces (accelerative overloads and microgravity as well) in animal experiments. In 1948, U.S. flight surgeon Harry G. Armstrong together with biologist Hubertus Strughold and astrophysicist Heinz Haber initiated the formation of a new aerospace discipline within the frame of preventive medicine and in 1951, a new Space Medicine Association formed within the Aerospace Medical Association in close cooperation with experts in astronautics, human factors, habitability engineering and biomedical research (Nicogossian et al. 2016: 5).

Dr Hubertus Strughold, a German medical doctor (former researcher in flight physiology in the Luftwaffe during WWII) became "the Father of Space Medicine" studying the physical and psychological effects of manned spaceflight. After WWII he became the director of the Physiological Institute at Heidelberg University. In 1947 he was invited to the United States as part of Operation Paperclip and working for the U.S. Air Force and NASA he was involved in animal (monkey) experiments and human medical investigations as well. NASA even used Primates and chimpanzee Ham flew onboard Mercury-Redstone in 1961 for a suborbital flight (Campbell et al. 2007).

Russian Vladimir Jazdovsky was the first space medicine specialist: working for the Aeromedical Research Institute of the Soviet Air Force he was invited by Sergei Korolev, chief constructor of space rockets to participate in preliminary animal tests in space programs (Russian scientists preferred dogs since Pavlov's famous experiments). The very first living creature Laika was launched into orbit onboard Sputnik 2 in 1957. It was planned to live for 6 days before running out of oxygen, but due to thermal instability, heat stress finally killed the animal within 6 hours (George 2018).

Commencing the era of manned spaceflight, the role of Flight Surgeons (aviation medicine later dedicated space medicine specialists) became even more complex and significant: they provide improved selection methods and medical surveillance for astronauts. Considering the increased mission length, space flight surgeons set up new equipment for biomedical monitoring of physiological parameters and improved tools for aerobic exercise to prevent cardiovascular deconditioning, bone and muscle atrophy. One of the most renowned NASA physicians was Charles “Chuck” Berry, who worked from the very beginning in the U.S. space program “Man in Space Soonest”. Later, he took full responsibility for Medical Operations during the Apollo program in NASA’s Manned Spacecraft Center – Johnson Space Center (Butler: 1999). He performed extreme stress tests at the selection phase of NASA classes and sent 42 astronauts into space in over 30 missions – including Apollo 11. During the historic mission of Apollo 11, he was the responsible Medical Officer while Neil Armstrong walked on the Moon. He also worked as an aviation medical examiner for the Federal Aviation Administration and was an aerospace medicine consultant for many years. He was considered a pioneer in aerospace medicine throughout his 68 year long career, and his son Michael Berry as a Federal Air Surgeon at the Federal Aviation Authority continues his mission dedicated to flight safety and new innovations in space travel (Ragin Williams 2020).

Russian Boris Borisovich Yegorov was the very first physician participating in the first multimanned spaceflight onboard Voskhod (“Sunrise”) 1, on 12–13 October 1964, with cosmonauts Vladimir M. Komarov (later died in Soyuz 1 crash) and Konstantin P. Feoktistov (engineer). The results of medical research projects executed by the Voskhod 1 flight contributed to a better understanding of human adaptation processes and to the effective and successful preparation for long spaceflights performed in the 1990s for the MIR Russian space station. Doctor–cosmonaut Valery Vladimirovich Polyakov still holds the record for the longest single spaceflight in history. He joined the Institute of Biomedical Problems in Moscow and flew his first mission into space in 1988–1989 as the doctor–cosmonaut onboard Soyuz TM-6. During his 241-day flight aboard the MIR space station, he conducted numerous medical experiments. He flew again on Soyuz TM-18 to the MIR space station in 1994 setting the (still persisting) record of 438 days for the longest continuous stay in space, extensively studying the alteration of human sleep and circadian rhythm during spaceflight (Siddiqi 2023; Gundel et al. 1997).

The Hungarian Space Program aiming at sending the first astronaut into orbit in 1980 within the Intercosmos program (scientific organisation of the Warsaw Pact countries for space exploration) was a real success: Captain Bertalan Farkas, a fully trained military fighter pilot was selected in the Aeromedical Research Institute of the Hungarian Defence Forces, Kecskemét city in 1977–1978. From the 95 combat-ready fighter pilots the 7 best applicants were selected by Hungarian aeromedical experts. The team was led by Colonel Dr John Hideg, deputy chair Lieutenant Colonel Dr Péter Remes. From them the Russian expert team prioritised further; the astronaut training program was performed in the Gagarin Space Centre, and selected Bertalan Farkas and Béla Magyari. The latter became reserves for the flight onboard Soyuz 36. The mission was launched to the Salyut 6 space station on 26 May 1980 and he returned on Soyuz 35 on 3 June. Being the 7th nation and sending the 95th astronaut into orbit (51st from the Russian launching pad in the Baikonur Cosmodrome), Hungary has earned a prominent place in space exploration. With a wide range of biomedical experiments, including the "Pille" dosimeter and "Balaton" psychocalculator, Hungarian scientists have significantly contributed to the development of space sciences (Remes 2020: 281–340). In 2024 we are preparing for the training and launch of the second Hungarian astronaut in the HUNOR (Hungarian to Orbit) program, in close cooperation with ESA, NASA and Axiom Space Inc., a U.S. private company.

At the very beginning (practically until the Space Shuttles' era), the designated roles of astronauts onboard of spaceships and space stations were overlapping, providing multiple roles (and demanding huge responsibilities) for real military pilots as commanders, spaceship/shuttle pilots and mission specialists. Later on, the continuously increasing demand for more specialised experts has led to the subgroup of "mission specialised medical experts" with dedicated and tailored practical skills to perform research projects safely, but being aware of the dangers of spaceflight. Brave Flight Surgeons (colleagues from U.S. Navy Laurel Clark and David Brown) aboard the Columbia Space Shuttle on the STS-107 mission perished during the failed re-entry phase (disintegration) on 1 February 2003.

After the end of the Cold War other international space agencies like ESA (the European Space Agency) have started their developing involvement in cooperation, for example, at the European Astronaut Centre (EAC Cologne). ESA's Space Medicine Team comprises medical doctors, biomedical engineers, exercise physiologists, psychologists, IT specialists, education coordinators, administrators and project managers. ESA is also selecting from member countries its own astronaut classes, providing their full training and intercultural team building and contributing to the staffing of the ISS crew.

Emphasis is on the special knowledge and skills of each space crewmember: focusing on continuous medical support of the ISS, medical experts possessing special medical knowledge and competencies, performing active survival and ground-based aeromedical trainings. They can actively participate in future space missions as well, and can provide permanent medical support even onboard space stations and spacecraft travelling to the Moon or other satellites (possibly Titan orbiting around Saturn) and planets (Mars). It is the responsibility of the Medical Officer(s) to provide medical surveillance and possible intervention in case of medical emergencies and maintain spaceflight safety throughout the mission. The stake is high: medical human factors influencing overall crew performance are crucial for safe deployment and return.

Physiological hazards associated with space travel

Space as a harsh and hostile environment can pose unique sudden or sustained hazards to humans: considering the long process of biological evolution we are quite strictly adapted to the physical parameters of the atmosphere (overall pressure and partial pressure of oxygen) and gravitational force, building up and stabilising the internal environment for human tissues ("milieu intérieur" as defined by French physiologist Claude Bernard). We are not adapted to weightlessness, high intensity of cosmic radiation (provoking high rate of genetic mutations) and their threatening consequences on human organs – loss of muscle mass (atrophy), loss of calcium from bones, radiation-induced processes (like cataracts and long-term carcinogenesis). Depending on the time of space travel the psychological adverse effects of confinement might evolve as well, leading to instability in the small team of astronauts. The main objectives of space life sciences is to extend knowledge in human physiology, to maintain astronauts' health in order to withstand hostile physical and chemical parameters and to establish new medical technologies for adaptation. In the post-flight period, the support and improvement of medical recovery in a complex rehabilitation program is also essential (Clément 2011: 1–12, 36).

ACUTE EXPOSURE TO THE VACUUM OF SPACE

A person in space without any protective garment (spacesuit) or shielded and hermetised compartment (spaceship or space station living module) can be exposed to fatal physical stressors of vacuum: loss of ambient pressure and temperature drop can rapidly demolish internal environmental stability at tissue level. Depicting the "spacewalk outside in space" without life equipment assembly (spacesuit and helmet) like Bowman floated in Stanley Kubrick's movie "2001: A Space Odyssey" is surely fiction (with artistic liberty) and would be lethal for any human being.

Upon sudden decompression in a vacuum, rapid onset of hypoxia and gas (mainly nitrogen) bubble forming processes can commence immediately. Due to the lung distensive barotrauma (explosive expansion of trapped air in the respiratory tract) lung tissue rupture is imminent. Above the Armstrong line (19,200 metre altitude) as overall ambient pressure drops below 47 mmHg (less than the partial pressure of H_2O in body fluid compartments at 37 °C body temperature) the body fluids can boil: water vapour can also form bubbles in tissue compartments, giving way to ebullism (altitude subcutaneous emphysema, i.e. bubbles under the skin surface, with swelling and bruising) (Cooper–Hanson 2022). At worst, it can cause gaseous embolism, and gas bubbles in the bloodstream with blockage (like thrombi). Real hypobaric decompression sickness (starting above 18,000 feet altitude and unavoidable at decompression to vacuum) can provoke nitrogen bubble formation in all tissues (especially those that are considered "slow" from a circulatory aspect, like fat and bone marrow), explosively expanding by the entry of all other diffusion capable molecules following their diffusion gradients (Foster–Butler 2009: 678–690).

The most threatening and limiting factor is the full lack of oxygen, i.e. hypoxia. In vacuum, the normally large diffusion gradient from alveoli to pulmonary capillaries is reversed, and oxygen is sucked *out* of the bloodstream when the overdistended lungs are exposed to vacuum. Deoxygenated blood circulation (even without a real stop of perfusion caused by bubble blockage) can effectively stop normal brain functions in the imminent process of clinical death, commencing an unconscious state within 6 seconds (Kanas–Manzey 2008: 15–30).

Temperature drop alone is fatal in a slightly slower manner because heat transfer cannot occur as rapidly by thermal radiation separately: conduction and convection cannot physically work without matter, so heat transfer is limited in space. Due to the temperature of the "cosmic microwave background" (leftover from the Big Bang), the real temperature can drop to 2.7 Kelvin (–455 °F, –270.3 °C), and pending on the direct radiant heat from the Sun, the process of fatal freezing (if it could occur separately) would take a few minutes more (Lea 2022).

Long-term effects of space travel

After reaching weightlessness within half an hour after launch (stabilising the LEO – Low Earth Orbit – just around 400 km altitude high) both immediate and gradual, but long-lasting physiological changes can commence attributed to microgravity. The apparent lack of gravity (weightlessness) can provoke pathological consequences interfering with the normal responses and reflexes of the different systems of the human body. The loss of responsiveness especially in the cardiovascular, nervous and musculoskeletal systems can lead to deconditioning (loss of physical condition and mental alertness), but affected gastrointestinal, immune systems can also reduce working capability (loss of appetite, dehydration, anaemia).

The normal hydrostatic gradient at 1 G from head to toe linearly increases in standing position, but in microgravity, a dramatic redistribution of fluids from the legs to the upper body (torso and head) can commence within only a few moments of weightlessness, which is completed within days. Due to the cephalad shift, fluid volume in the legs decreases by 10%, accompanied by a 17% reduction in plasma volume due to the initially increased filtration through the kidneys. This fluid redistribution phenomenon is called "puffy head and birdy legs" and refers to significant facial swelling and significantly (by 10–30%) decreased leg circumference. Astronauts subjectively often complain of buzzing headache, nasal congestion and anosmia (loss of smell), diminished taste (and appetite) and eye abnormalities (blurred vision, diminished visual acuity) after extended stays in space, which are likely symptoms of SANS (space associated neuro-ocular syndrome) with increased intracranial pressure (Setlow 2003: 1013–1016).

The gradual decrease in erythropoietin secretion can commence, leading to a 10% decrease in total blood volume and decreased red blood cell quantity ("space anaemia"). Lower cardiac output and decreased stroke volume can commence due to lower demands on the cardiovascular system to counteract gravity. Upon return to Earth's gravity, due to a significant orthostatic intolerance, 25% of astronauts suffer a collaptiform episode (being unable to stand for 10 minutes without experiencing heart palpitations or fainting) (Williams et al. 2009: 1317–1323).

The functional inactivity of "antigravitational muscles" results in muscle atrophy, up to 50% muscle mass loss and a decrease in muscle strength. The muscular atrophy seen in astronauts is very similar to deconditioned bedrest patients, and upon return to Earth, some astronauts experience difficulty simply maintaining an upright posture with muscle soreness and tightness. Major postflight impairments require a proper rehabilitation programme after return to 1 G gravity on Earth: full recovery of muscle mass and strength can exceed 2 months (Payne et al. 2007: 583–591; Springel 2013).

Loss of physical stimuli from gravity in space on load-bearing bones in the lower torso and extremities can lead to demineralisation of the skeleton and decreased bone density, osteoporosis or osteopenia. Bone demineralisation is really an insidious and dangerously invisible threat: gradual loss of bone density (1–2% per month) accompanied by a 60%–70% increase in calcium loss by urine and stool, increasing the risk for bone fracture and kidney stones as well. Reduced parathyroid hormone and vitamin D production can also increase imbalance in bone structure maintenance processes (osteoclast decomposing versus osteoblast restorative building activity). After re-entry, the almost complete restoration of bone density can be 2–3 times longer than the space mission itself with an elevated risk for fractures (Williams et al. 2009: 1317–1323; Springel 2013).

The sensorial network (visual, vestibular and sensorimotor proprioceptive systems) can provide spatial orientation on Earth that contributes to a normal sense of balance and can maintain upright postural tone and harmonised motor coordination. Even during a flight on the Kepler path onboard aircraft spatial disorientation (loss of situational awareness) can commence just in seconds in simulated short-term weightlessness. The majority of astronauts (in the Apollo program about one-third of the space crew, from the Russian side e.g. Valentina Tereshkova during a solo flight onboard Vostok 6) suffered from nausea and physical discomfort. A full spectrum of space motion sickness or incapacitating disorientation can commence for the first few days in space, and these symptoms usually stop or weaken by the fourth or fifth day. During the flight of Apollo 8 in 1968 (the first human space mission to leave Earth and orbit the Moon) commander Frank Borman had nausea and vomiting as a first manifestation of space adaptation syndrome (Fong 2019). After returning to Earth, the same process as "debarkation" can confuse the sensory organs for a while, causing a "wobbling" phenomenon as a transient imbalance period (quite similar to the recovery phase after long-term bedrest) (Springel 2013; Mulavara et al. 2018).

Normal sleep cycles might be affected as well: orbiting within 90 minutes around Earth (resulting in 16 sunrise and sunset daily) the dream phases of astronauts are distorted, and circadian dysrhythmia can commence due to the altered light-dark cycle (Miller [s. a.]). High-energy cosmic radiation can cause bright flashes in the visual fields, disturbing deep sleep periods of space crew (Narici et al. 2004: 1352–1357).

Another main source of long-term harmful effects is cosmic radiation. The Earth's atmosphere can dampen space radiation: ultraviolet (UV) radiation from the Sun is largely absorbed by the Earth's atmosphere (ozone layer between 12–42 km with maximum concentration just around 30 km altitude level). The ionosphere can reduce the primary cosmic radiation into less harmful secondary ionising radiation with considerably less energy and diminishing the ionising effect, falling to 1/70 portion compared to the dose measured at 21 km altitude level (Gradwell 2006: 7).

Leaving the atmosphere (even the van Allen magnetic protective belt) a human would suffer sunburn from UV radiation within seconds and can receive a high dose of primary cosmic radiation. Cosmic electromagnetic radiation (depending on the wavelength) can be reduced with a specially designed fabric layer in a spacesuit (EMU – Extravehicular Mobility Unit worn for 6–8 hours outside of the space station) but high-energy nuclei particles in solar and galactic radiation can penetrate shielding and astronauts' bodies (Setlow 2003: 1013–1016; Springel 2013; Barratt et al. 2019: 520).

Radiation (by means of stochastic/probability based and deterministic/dose dependent effects) can cause radiation sickness, genetic abnormalities (mutations in DNA), can damage brain cells (leading to neurodegenerative diseases), increase the risk of early onset cataracts and can provoke carcinogenesis, can boost atherosclerosis ("ageing of arteries"). Radiation induced immune system suppression and microbiome distortion in the bowels can provoke infections, radiation sickness can occur with a higher cumulative incidence above a certain threshold intensity. Chromosome break yields were doubled in the Apollo space crew compared to

Gemini astronauts, giving way to harmful mutations. For Apollo 14, the highest skin dose was 14 mSv, and for MIR crewmembers 30 mSv/event during a magnetic storm in 1989. Based on a full review of cancer incidence and mortality in the U.S. space crew population, the increased case number for melanoma and reduction in colon cancer rate was explained by UV radiation related to lifestyle (not to space specific exposure) and enhanced screening methods (Williams et al. 2009: 1317–1323; Barratt et al. 2019; Reynolds et al. 2021).

Even long-term, low-energy levels of radiation can provoke DNA damage possibly leading to carcinogenesis or fetal malformations without real threshold. Based on the Radiation Assessment Detector measurements of NASA's Curiosity rover during its transit to Mars, the astronauts would be exposed to a minimum of 660 ± 120 millisieverts during a full mission. NASA's career exposure limit set for astronauts is around 1,000 millisieverts (as analogues to nuclear industrial plant workers, maximising the dose in 100 mSv for any 5 consecutive working years, aiming to keep ALARA as low as reasonably achievable). Powerful ionising radiation particles can target living tissues within the body throughout the mission, so presently the unpredictable radiation burden might be even showstopper from an ethical aspect (Townsend 2005: 44–50; Kerr 2013: 1031; Chylack et al. 2009: 10–20; Zeitlin et al. 2013: 1080–1084; Springel 2013; Onorato et al. 2020; Nicogossian et al. 2016: 25, 206–207).

Challenges for future deep space missions and colonisation

> "Who are we? We find that we live on an insignificant planet of a humdrum star lost in a galaxy tucked away in some forgotten corner of a universe in which there are far more galaxies than people."
>
> Carl Sagan

In 1950 Ley envisioned that "life will be cramped and complicated for space dwellers [...] it will be a self-contained community in which all man's needs, from air-conditioning to artificial gravity, have been supplied" (Ley–Bonestell 1950).

Even now with long-term rounds of space crew on ISS, space adaptation involves some very complex changes in the human body, both short-term and sustained ones. These changes can cause health problems both in space and on return to Earth or in settlements on the surface of other planets/moons (Easter 2019).

Due to the new challenges of the return to the Moon with Artemis and the prospect of interplanetary missions with colonisation purposes require flexibility. Ground-based solutions should be adapted and altered to endure the space environment. Presently the most frequently observed clinical signs and symptoms related to space adaptation syndrome are back pain, headache, constipation, insomnia, nasal congestion, motion sickness and visual impairment (Antonsen et al. 2017).

Sustainable Lunar–Martian orbital flight ("staging capability" on orbiting the Lunar–Martian Gateway) and surface exploration (with Base Camp Conception, Surface Habitat and Habitable Mobility Platform) require adaptation to weightlessness and then (after a long deconditioning process) readaptation to a certain level of gravity of the Moon or Mars.

Polyakov, the Russian cosmonaut spent 438 days in space (but more astronauts spent more days in space on consecutive missions altogether: Russian Gennady Padalka more than 1,000 days, Peggy Whitson from NASA more than 665 days). For a longer deep space mission even the possible deterioration of cognitive performance should be calculated due to the high intensity of cosmic radiation. Microgravity itself through different changes in cerebral perfusion due to the cephalad shift can contribute to the deterioration of certain cognitive functions based on comparison with ground-based head-down tilt bedrest (Cherry et al. 2012; Barkaszi et al. 2022).

The other key point is the selection process of new astronaut candidates with proper somatic and mental features to endure the possible harsh environmental conditions during routine workdays and in emergency situations as well. From the very beginning, there was a great emphasis on "selecting in" proper physical abilities (muscle strength and stamina, aerobic exercise capacity) and psychological mental capabilities (cognitive functions like attention, multitasking problem solving and decision-making capacity). At the same time, it was important to "select out" unfavourable parameters (low physical and mental working capacity, dangerous psychological traits and attitudes like psychopathology), and improve the cohesion of the space crew as a team: proper communication techniques, complacency, cooperation (smoothing possible intercultural differences) can lead to enhanced overall performance during a mission by means of CRM (Crew Resource Management). Even more difficult is to augment the prognostic value of selection standards: the longer the space mission, the more unforeseeable changes can occur in somatic and mental health state as a complicated interference between individual genetic background and actual environmental challenges, leading to real clinical symptoms and entities. The same is applied to "space tourists" with less detailed mission oriented tasks, but with possibly enhanced risk for incapacitation and diminished working ability (Seedhouse 2008).

The most frequently occurring medical conditions can be categorised as common (already experienced) problems: Space Motion Sickness, headache, nasal–sinus congestion (both related to cephalad fluid shift), constipation (related to dehydration), back pain (related to the increased water content of disc and elongation of the spinal column), upper respiratory tract infection (related to dysbiosis and thermal discomfort), minor abrasion and musculoskeletal traumas (related to inadvertent movements during EVA – extravehicular activities), corneal irritation and insomnia (related to circadian dysrhythmia). Less common but already observed and anticipated conditions are renal stone formation, acute urinary retention, cardiac dysrhythmia, including benign extrasystoles, bigeminy, and a more serious complex form of Supraventricular Tachycardia (SVT) and non-sustained ventricular tachycardia (asymptomatic salve), inflammations like gastroenteritis, prostatitis, serous otitis media (tympanic membrane and middle ear inflammation), contact dermatitis (skin allergic inflammation). Especially after EVA decompression accidents DCS decompression sickness (joint pain), near drowning (after spacesuit failure) can commence, and aspiration of a foreign body might be a threat as well. One case of venous thrombosis was detected by ultrasound imaging incidentally in the left internal jugular vein (and no symptoms accompanied). Presently, there are no real medical training methods and toolkits addressing the treatment of cardiogenic shock, malignancies, acute glaucoma, compartment syndrome, serious head injury, hypovolaemic shock, lumbar spine fracture or major joint (shoulder–elbow) dislocation (HODKINSON et al. 2017: i143–i153; PIETRZYK et al. 2007: A9–13; AUÑÓN-CHANCELLOR et al. 2020: 89–90).

In the early phase of space exploration, the extended morphological and functional medical examinations provided the proper assessment of physical and mental health state and the prognostic evaluation of working ability. Diagnostic procedures included vitamax aerobic exercise capacity (physical performance on treadmill or bicycle up to age-adjusted maximum pulse rate) and special ground-based simulated exposition to aeromedical stressors like hypoxia (in a barochamber), simulated weightlessness (on tilting table head-down position up to 15–30°) or acceleration and overloads (in a centrifuge). Pressure breathing training is also critical in preparation for extreme hypobaric-hypoxic settings. These physiological exhaustive examinations could provide information about the endurance, stamina, responsiveness and functional reserve of the cardiovascular and musculoskeletal system, while psychometric and cognitive tests could give cues about the mental performance of astronauts. Regarding the huge development in clinical diagnostic tests including new visualisation technologies (Magnetic Resonance, Computer Tomography and Ultrasound imageries), now we are able to describe the anatomy and functions of even smaller organ tissue details, observing their possible adverse alteration during repetitive simulated or real space travel.

Practical training sessions should include flight on the Kepler trajectory simulating weightlessness for 30–40 seconds (!), immersion training in pool (imitating EVA protocols in spacesuit), hypoxic training in barochamber, thermo-barochamber (heat exposition), isolation exercises to tolerate confinement, centrifuge runs, vibration platform training, vestibular training, parachute (and land-sea survival) training, general physical training, sports, education of first aid (first-line management of injuries–diseases), team building processes.

In the future we should forecast the possible deterioration during space travel by assessing genetic susceptibility for clinical problems (like space-induced accelerated atherosclerosis, perhaps carcinogenesis and cataract tendency), acknowledging that certain other problems (caries, impacted wisdom tooth, appendicitis, traumas) can commence just "out of the blue". Certain medical capabilities (including medication, operational toolkits) should be available onboard spaceships heading to deep space or other planets (e.g. a rare case of jugular vein thrombosis occurred and ISS medical decision required concerted efforts to overcome the numerous logistic and operational challenges). Heading to Mars, active astronaut surveillance by Medical Officers and experimental models in Earth-based space analogue settings will be essential to prevent or properly manage such unusual clinical entities (Auñón-Chancellor et al. 2020: 89–90). (And due to the limitation in technologies and knowledge onboard perhaps we should be aware of the possibility of a fatal outcome, loss of astronaut comrades.)

The final goal of space medicine is to keep astronauts healthy in space: maintaining their working ability during LEO or deep space missions, minimising the harmful effects of microgravity on different organ systems and reducing the risk of radiation-induced atherosclerotic and carcinogenetic processes. Proper medical toolkits for operational procedures, extended use of telemetry and AI might be helpful in responding adequately to threatening medical conditions.

The future of space exploration will be linked to the development and application of artificial intelligence (AI) technologies. The ever-increasing distances in space missions (and the time demand for radio communication) can cause significant logistical-technical problems and challenges in command and control systems. In medical issues Earth-based monitoring will no longer be real-time, requiring telemedicine capabilities, and perhaps a medical expert "Avatar" artificial intelligence will be present to react immediately to urgencies (not waiting for response from Earth-based experts during deep space missions). Robotic (robot-assisted) surgery might help to perform minimally invasive surgery with proper flexibility. Long-duration missions necessitate further technological breakthroughs in teleoperations and autonomous technology (Mayo Clinic [s. a.]).

On the road to Mars, we anticipate even more complicated and dangerous scenarios, with new physiological challenges for the human body and mind, requiring common efforts and forcing peaceful cooperation in space. There will be a huge emphasis on the competencies of spacewalking space crew as EVAs are being conducted in Earth orbit, on the Moon's surface and in deep space and dedicated to vital assembly and critical maintenance missions on the soil of Mars. Possible traumatic injuries due to outer construction works and compromised cardiovascular and postural stability and working inability caused by deconditioning and SANS (or VIIP syndrome, referring to visual impairment and intracranial pressure increase driven by cephalad fluid shift) could threaten the success of deep space missions (Nicogossian et al. 2016: 233).

Effective countermeasures are currently under investigation to explore how we could mitigate accompanying risks: medical device intervention (load-bearing regular exercise and low-level vibration provoked strain), nutritional supplementation (micronutrients and vitamins), artificial gravity (centrifugal rotating arms?), radiation shielding and possible antioxidant countermeasure and enhanced pre-flight risk assessment are the most important opportunities to combat the deconditioning process (Springel 2013; Schwirtz 2009).

1. Lower body negative pressure (LBNP) is a well-established, non-invasive device (Russian name is Chibis) that can maintain the negative pressure (20 mmHg as optimal level) by hermetised covering (encapsulation) of the lower torso and extremities and redistributing blood away from the cephalad region (upper torso and head), decreasing ICP (intracranial pressure) as the main factor in SANS induced headache. Mobile, flexible LBNP gravity suits might be an efficient and effective countermeasure for astronauts during future missions generating "ground reaction forces": blood is forced down to the wearer's legs, increasing the heart rate and cardiac output (Ashari–Hargens 2020).

2. Venoconstrictive thigh cuffs can force back blood and can elevate venous return and restore effective blood volume: it might be useful during the early phase in the gravity field, or generated artificial gravity can be maintained via centrifugation with proper arm length. Centaur is a corset-like garment worn

like a pair of shorts. It is worn during descent to keep blood from pooling in the legs on the return to gravity and prevent fainting (Robin et al. 2020).

3. Penguin-3 suits or bungee cords are jumpsuits embedded with sewn-in elastic straps which provide resistance loads for the wearer in response to the arm and body movement (making periodic pedalling leg movements for 5–10 minutes, 6–8 times per day). Providing exercise for the musculoskeletal system can reduce the inactivity-induced deleterious effects of microgravity. With a combination of aerobic and resistive (resistance) exercise lean muscle mass can be preserved. Further investigation of drug therapy (as skeletal muscle growth factors, human growth hormone, thyroid hormone, insulin-like growth factor) is necessary to introduce as preventive measures for proper maintenance of muscle mass and strength (Nicogossian et al. 2016: 353).

4. Pressurised goggles can locally modulate cerebro-ocular hemodynamics as a countermeasure for SANS. It might be useful in the prevention of retinal disc oedema by diminishing the pressure difference between normally higher intraocular pressure (IOP) and lower optic nerve sheath (myelin) pressure (Ong et al. 2023).

5. Certain genetic backgrounds (critical alleles) in combination with reduced vitamin B2, B6 and B9 status can increase the risk of vision deterioration. Vitamin B supplementation as proper antioxidants (riboflavin, pyridoxine, methylcobalamin and folate) can reduce cytotoxic oedema – local oxidative stress at the optic nerve head from microgravity-induced venous stasis (Smith–Zwart 2018: 481–488).

6. Beyond proper technical radiation shielding some initiatives for pharmacological protection are under investigation: drugs can play the role of radioprotectors (which decrease or prevent tissue damage before exposure), radiomodulators (which increase baseline resistance to radiation exposure) and radiomitigators (which limit or prevent tissue damage after exposure). Real medications like statins widely used on Earth (against high blood lipids), nonsteroidal anti-inflammatory drugs and antihypertensive drugs (ACEIs and ARBs, calcium channel blockers, β adrenergic receptor blockers) are also under investigation to prevent accelerated atherosclerosis (possibly induced by cosmic

radiation). Special combination of antioxidants and other micronutrients (N-acetyl cysteine, pentoxifylline, ascorbic acid (vitamin C), α-lipoic acid (a type of vitamin B), coenzyme Q10, vitamin E succinate, sodium ascorbate and L-selenomethionine (SeM), perhaps Bowman-Birk Inhibitor Complex (BBIC, a protease inhibitor derived from soybeans) can diminish the radiation induced cardiovascular alterations as well (Meerman et al. 2021; McLaughlin et al. 2017: 665–676).

7. Aerobic exercise of 2.5 hrs/day is time consuming, but low intensity vibration strain and pharmacological countermeasures might have added value against osteoporosis: reduced bone formation, increased bone resorption, inhibition of mineralisation might be influenced by properly administered new bisphosphonates (blocking the breakdown of bones) and PTH (parathyroid hormone slowing down the excretion of calcium). Presently long-term measurements show that only 50% of the bone structure (density) would recover by 9 months post-flight. Possible use of "nutraceuticals" (micronutrients, antioxidants, vitamins as dietary supplements) or gene-derived therapies might be promising options in the future. Unfortunately, the exercise itself can further elevate core body temperature set for a higher level of weightlessness, as a further component of physical discomfort (Clément 2011: 219; Nicogossian et al. 2016: 353–356; Stahn et al. 2017).

CONCLUSIONS

Medical research aiming at sustainable human life in space should address not only spaceflight itself (with permanent microgravity resulting in overall atrophy, deconditioning, higher flux of cosmic radiation resulting in possibly accelerated atherosclerosis and carcinogenesis), but the "colonisation" phase as well, as utilising new settlements on the surface of the Moon, and on the surface of other planets and their moons. From an occupational aspect, possible professions like mining, construction or industrial processes require at least partial readaptation to gravitational force (although it might be reduced compared to Earth, disturbed by orthostatic intolerance and post-flight hypotension), breathable ambient air in self-supporting containment equipped with environmental control system, fully pressurised mobile compartments in order to provide "short sleeve" working environment. But it also means that stepping out from the protected zone we face the harsh environment settings again with extreme thermal conditions, winds, poisoning or polluting components (like regolith dust, as loose, unconsolidated superficial deposits in the soil of Mars and Moon, and perchlorates in Martian soil). Spacesuit-like personal protection assembly with higher mobility is a must to provide even limited working capability for a while. Adapting the Fine-Kinney occupational risk matrix as mathematical risk analysis to the long-term surface missions, not only the microgravity and radiation but "traditional" Earth-based occupational risk factors, like noise, vibration, dust exposure to the airways during mining procedures and industrial accidents can occur as well (Yilmaz–Ozcan 2019).

The next generation of pioneers should rely on their creativity very much to utilise all elements of their limited cargo with a small chance of an emergency return to Earth. A NASA report emphasises that "advanced frontier technologies (robotics, machine intelligence, nanotechnology, synthetic biology, 3D printing/additive manufacturing, and autonomy) combined with the vast natural resources should enable to greatly increase reliability and safety pre- and post-human arrival ISRU (In Situ Resource Utilization) and reduce cost for human colonization of Mars" (Moses–Bushnell 2016).

In 1928 Tsiolkovsky in his work *The Will of the Universe. The Unknown Intelligence* was convinced that humans would eventually colonise the Galaxy. His prophetic thought preceded the Space Age by decades, and some of his ideas have come true. Now the voyage of exploration continues with new demands. New ways of thinking and technical approaches – "curiosity and readiness for adventure" – are required from that idea, through design and test procedures to the validation and execution phases to overcome hurdles (Fong 2019: 205–207).

"Space: the final frontier. These are the voyages of the starship *Enterprise*. Its continuing mission: to explore strange new worlds; to seek out new life and new civilizations; to boldly go where no man has gone before!" (Star Trek) Science fiction is turning into reality: pioneers of mankind are really pushing the limits to the endless final frontier. As it was cited by NASA administrator Bill Nelson in his eulogy of Frank Borman astronaut, commander of the first flight to the Moon on Apollo 8 who passed away recently at the age of 95: "Exploration is really the essence of the human spirit" (Nelson 2023).

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