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Journey to Mars: A Biomedical Challenge. Perspective on future human space flight

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Abstract

Manned space flight has been the greatest human and technological adventure of the past half-century. Putting people into places and situations unprecedented in history is stirred the imagination while the human experience was expanding and redefining. Yet, space exploration compels humans to confront a hostile environment of cosmic radiations, radical changes in the gravity and magnetic fields, as well as social isolation. Therefore, any space traveller is submitted to relevant health-related threats. In the twenty-first century, human space flight is poised to continue, but it will enjoy the ongoing developments in science and technology. It will become more networked, more global, and more oriented toward primary goals. A novel international human space flight policy could help achieve these objectives by clarifying the rationale, the ethics of acceptable risk, the role of remote presence, and the need for balance between funding and ambition to justify the risk of human lives. In order to address such a challenge, a preliminary careful survey of the available scientific data is mandatory to set forth adequate countermeasures. Envisaged solutions should provide a sound and technically feasible approach for counteracting microgravity and cosmic rays effects, which represent the main health risk for space crews. This objective must necessarily be sustained by national/international space agencies, which would coordinate their common efforts into a defined international spaceflight program.

Keywords: gravity; life in extreme environments; Mars; spaceflight; cosmic rays; international space cooperation

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1. Human Space Flights at a Crossroad

The future of human space exploration is today at a crossroad. Thirty-three years have elapsed since man last set foot on the Moon, and in that time, human space exploration has been confined to low-earth orbits. Enormous strides have been made in other venues of space exploration during that time, but human activity in space has faced numerous challenges and setbacks in recent decades. Today, some countries (and non-state actors) show resurgent interest in human space activities, spurring hope that a new reality may emerge. Namely, the human flight to Mars option recently gained momentum when the Mars One Project was proposed by the Dutch entrepreneur Bas Lansdorp (Mars One 2014). This program is seemingly a simple one: selecting a team of four volunteers to establish a permanent colony on Mars with the launch date in 2024. The project has been broadly criticized (Sidney 2014) as it underestimates numerous technological issues. Furthermore, an insufficient understanding of the human dynamics of a one-way trip to Mars is a more relevant issue. Some authors have identified it as a danger to the crew that is not only potentially harmful for

physical health (Putman 2015), but also raises mental health concerns, which were already highlighted by the Russian Mars 500 experiment (Mars 500).

National Space Agencies are indeed facing critical decisions on the future of human spaceflight. Will we leave the proximity of low-Earth orbits, where astronauts have circled since 1972, and explore the solar system, charting a path for the eventual expansion of human civilization into deep space? If so, how can we ensure that our exploration delivers actual benefits to Earth? Moreover, can we explore with an acceptable level of assurance of human safety? And can the nations guarantee the necessary resources to embark on such a mission? Whatever space program is ultimately selected, it must be matched with the resources needed for its execution. How can we provide such necessary resources? Currently, there are more options available than in 1961, when President Kennedy challenged the NASA and the nation to "land a man on the Moon by the end of the decade".

2. Why Fly People into Space?

Space flight has represented a Promethean dream, since the beginning of human history. The Greek myth narrates the tale of Icarus, the young son of architect Daedalus who attempted to travel beyond clouds to the sun, and its unfortunate conclusion. Lucian of Samosata, around the 2nd century BC, described voyages to the sun and moon while spoofing Greek romances. Cyrano de Bergerac revived the theme in a tale of the first space rocket in his Voyage dans la lune and L'histoire des etats et empires du soleil (1652). About two century later, Edgar Allen Poe sent a man to the moon in a hot air balloon in his hoax, The Unparalleled Adventures of One Hans Pfaall (1835). More recently, Jules Verne, in his novel From the Earth to the Moon (1865), sent the first "astronauts" to the sky through cannon, just less than a century before the first real cosmonaut, the Russian Yuri Gagarin, made his true space journey. The Mercury missions demonstrated that humans could consistently and repeatedly survive low orbit space flights.

These missions also demonstrated that human being are an invaluable component of mission success (Nicogossian 1994). Indeed, all accomplishments of complex, specific tasks, both scientific and technological, that far exceed the current capabilities of robots, require human intervention. Those days past, what was once the essence of the future – human ventures into space and to other worlds – is now only a relic of history.

Nonetheless, the question "why fly people into space?" is not a trivial one. It is likely enough that the answers keep changing across generations. Early on, cold war competition provided a "sufficient" rationale. Later, the goal became to develop routine access to space with the promise of commercial benefits. Recently, as clearly stated in the Augustine Report (2010), only the loftier aims of exploration seem to justify the risks and costs of sending humans into the hostile space environment. The report claims: "too often in the past we've said what destination do we want to go to rather than why do we want to go there. It's a question that in our view we have probably not answered correctly in the past".

Despite the fact that the rationale for sending humans into space has been challenged over the last years (van Allen 2004), we still rely on the "human touch" to perform many space-related tasks. In fact, there is currently a broad consensus that primary objectives of human spaceflight are those that can only be accomplished through the physical presence of human beings (extra-vehicular activities, experimental studies in space relying on human resources, biomedical research), that carry benefits in excess of costs, and may justify significant risks to human life (Mindell 2008). Finally, from a strategic point of view, the ultimate goal of human exploration is to chart a path for human expansion into the solar system.

By contrast, secondary objectives are those which may carry some benefits derived from the human presence in space, but do not suffice alone to justify related costs and risks. The latter includes science and educational advancements, economic developments, creation of new jobs, technology progress, and national security.

Undoubtedly, scientific data collected since the first half of the past century indicate that, if humans are to travel in space for long distances and duration, the ethical imperative is to understand the biomedical implications of prolonged exposure to space and planetary environments. (West 2000).

In fact, the medical challenges associated with maintaining safety, health, and optimum performance of astronauts and cosmonauts dispatched in long-duration missions are indeed considerable, and must be overcome in order to allow missions beyond low Earth orbit. The new missions should extend the time-distance constant of human space exploration.

3. Hostile Environment and Health-Related Threats

It was keenly stated that, on Earth, patients suffering illnesses could be described as people who live in a normal Earth environment but have an abnormal physiology. In contrast, astronauts are persons with normal physiology who live in an abnormal environment" (Williams 2009). Indeed, Space is perhaps the most hostile environment that the human life can encounter. It is characterized by extreme variations in temperature, absence of atmospheric pressure, solar and galactic cosmic radiation, and zero gravity. The astronauts challenged with long duration spaceflights must confront a host of unique physiological issues, many of which require either partial or complete solutions, so as to allow a sustainable human exploration beyond the protective environment of Earth (Van Loon 2007).

Under a simplified framework, space exploration subjects astronauts to three main challenges and related threats: 1) changes in physical forces (modified gravity and electromagnetic fields), impacting every and each level of organization of the human body (from cells to organs); 2) exposure to cosmic rays; 3) psychosocial threats induced by long-term confinement. The overall risks induced by such factors are hard to be grasped in depth. Nonetheless, according to the available data and by adopting a 'precautionary' attitude, current NASA/ESA rules state that no degree of 'acceptable' risk may be guaranteed for missions lasting longer than six months.

Medical data, gathered since the 1970s, regarding astronauts flying low earth orbits for extended periods of time (Perry 1983), show several adverse effects of weightlessness: loss of bone density, decreased muscle strength and endurance, postural instability, and reductions in aerobic capacity. Over time, these deconditioning effects can impair astronauts' performance or increase their risk for injury. In such an environment, astronauts put no weight on the back muscles or leg muscles used to get to erect position. These muscles then start to weaken and eventually get thinner. If there is an emergency at landing, the loss of muscle fibers, and consequently the loss of strength can be a serious problem (Baldwin 1996; Sandonà 2012). Sometimes, astronauts can lose up to 25% of their muscle mass on long-term flights. When they get back to the ground, they feel considerably weakened, and will be out of action for a while. In most cases, muscle mass and strength is fully recovered after 1–2 months back on Earth (Shackelford 2008).

Astronauts may suffer a significant bone demineralization (Whedon 2006), mimicking osteoporosis lesions, as documented by bed-rest models (Rittweger 2009). Radiographic studies documented a significant loss of calcium from weight-bearing portions of the skeleton; some regional losses were greater than two standard deviations above normal. This mobilization and loss of calcium suggests a significant risk of renal stone formation on long-duration missions (Whitson 1999). Osteoporosis and bone remodeling, induced by microgravity, are of major concern, since, as White and Averner, 2001, claim, "bone loss is likely to be progressive, at least to the point that fracture poses an immediate risk during space flight, such as proposed 3.5 years exploration mission to Mars". Undoubtedly, studies on microgravity-related osteoporosis have led to fruitful insights into bone and osteoblast physiology understanding. However, no convincing countermeasure has been so far developed. Instead, working out programs/regular schedules in space have not been proven effective nor have pharmacological treatments, nor did vitamin supplementation counteract bone loss (Smith 1999). Most astronauts on long-duration missions will fully recover their bone density within three years after the flight. However, some astronauts may never regain pre-flight levels, and the recovered bone may have different structure and mineralization (Clement 2003; Lang 2006).

Microgravity induces several other effects (Bizzarri 2015), including impaired cardiac function (Grigoriev 2011), orthostatic hypotension (Reyes 1999), enhanced susceptibility to ventricular arrhythmias (Fritsch-Yelle 1998), circadian rhythm disruption (Gündel 1997), endocrine changes (Stein 1999), immune-related problems involving higher rates of infections and immunodeficiency (Taylor 1993). Adaptive physiological changes to microgravity in space can alter the pathophysiology of diseases, the clinical manifestation of illness and injury, as well as the pharmacokinetics and the pharmacodynamics of drugs (Putcha 1991; Czarnik 1999).

Astronauts exposed to weightlessness often lose their orientation, experience motion sickness, and impaired sensorimotor coordination (McIntyre 2001; Zago 2005; Senot 2012). When they are back to Earth or any other planetary body with a significant gravitational field, they have to readjust to gravity and may have problems in maintaining the erect posture, focusing their gaze, walking and making turns. The predominant symptoms of "space motion sickness" include facial pallor, cold sweating, stomach awareness, nausea and, in some cases, vomiting (Heer 2006).

Importantly, those body-motility-related disturbances, subsequent to exposure to different gravity degrees, only get worse the longer the exposure to low gravity. These changes will affect operational activities including approach and landing, docking, remote manipulation, and emergencies that may happen while landing. These effects can be a major roadblock to mission success.

When engaged in long missions, astronauts are isolated and confined into small spaces. Depression, cabin fever, and other psychological problems may impact the crew's safety and mission success (Ephimia 2001). Moreover, astronauts may not be able to return quickly to Earth or receive medical supplies, equipment or personnel if a medical emergency occurs. For long periods, astronauts may have to rely on their limited available resources and on the medical advice from the ground. Neuropsychological correlates of space flight are generally studied in a laboratory, in unique natural (like Antarctica) or artificial (like that provided by the Mars500 experiment, or ESA-MARS500) environments. The ultimate goal is to avoid unexpected and potential harmful consequences (like those represented in the novel Solaris and the homonymous movie) through appropriate countermeasures.

Any space traveler, while away from the protective shield provided by both the Earth atmosphere and the magnetic field that shields our planet, is subject to a continuing (low) dose of Galactic Cosmic Rays (GCR), trapped ionizing radiation and transient radiation from solar particle events (solar flares) (Benton 2001).

Astronauts in outer space are exposed to two forms of radiation: the first one is due to a chronic low-dose exposure to galactic cosmic rays (GCRs), the other one is due to a short-term exposures to the solar energetic particles (SEPs), sporadically accelerated by the Sun solar flares and coronal mass ejections. GCRs tend to be highly energetic, highly penetrating particles that are not stopped by the modest depths of shielding on a typical spacecraft. The flux of GCRs consists of 99% of particles shared between protons (85%) and He ions (14%) which can reach up to 1000 MeV. The remainder of the flux is due to heavier ions called HZE particles (where "H" stands for high atomic number "Z", and high energy "E"). These charged particles differ from terrestrial types of radiation because the density of ionizing events deposited along the particles' trajectory leaves a track of damage through cells and tissues that prove difficult to resolve through cellular repair processes (Israel 2012). The biologic impact of such charged particles is also exacerbated by the secondary ionizations that extend from the primary particle track as delta rays, thereby extending considerably the range of resultant cellular damage throughout the various tissues of the body. SEPs are typically protons with kinetic energies up to a few hundred mega–electron volts, which can produce very large fluxes helium and heavier ions. The low energy part of typical SEPs can be effectively shielded also from the material of the current space ships.

Zeitlin et al. (2013) have reported SEP and CGR measurements performed by Mars Science Laboratory MSL from December 2001 to March 2012. While the SEP total equivalent dose for the period of measurements was of the order of 24.7 mSv, the CGR equivalent dose was of the order of 1,84 mSv/day. Taking into account the MSL's cruise to Mars of 253 days, the equivalent dose was of the order of 466 mSv. Based on the conventional risk assessment approach, adopted by various Agencies, the exposure limit for the astronauts' career is of the order of 1 Sv for a one way Mars mission, with a standard cruise averaging 180 days. Doubling the time, one obtains a GCR in the range of 662 mSv, discounting an error margin of 16% together with an additional variable contribution of SEP. It means that if astronauts reach their exposure limit during the cruise, the risk to develop cancer becomes unacceptable. In addition, Schwadron et al. (2014) using observations from the Cosmic Ray Telescope for the Effects of Radiation (CRaTER) on the Lunar Reconnaissance Orbiter (LRO) have examined the implications of highly unusual solar conditions for human space exploration. They showed that, while these conditions are not a showstopper for long duration missions (e.g., to the Moon, an asteroid, or Mars), galactic cosmic ray radiation remains a significant and worsening factor that limits mission durations. Recently, Parihar et al. (2015) using mice subjected to space-relevant flux of charged particles, showed significant cortical and hippocampal-based performance decrements six weeks after acute exposure. Animals manifesting cognitive deficits exhibited marked and persistent radiation-induced reductions in dendritic complexity and spine density along medial prefrontal cortical neurons known to mediate neurotransmission specifically related to the behavioral tasks. Overall, these data highlight how challenging are the risks posed by cosmic rays for human health.

Radiation hazard is indeed known to exert radiobiological consequences at all levels of the organism. Four major challenges can be recognized: 1) carcinogenesis, 2) central nervous system damage, 3) tissue degeneration, and 4) acute radiation disease (Sihver 2008).

Despite increased knowledge gathered during the last decades, the radiation risk remains a difficult topic of study, because radiation effects depend on non-linear dynamics (Averbeck 2010; Durante 2010) and the natural space radiation environment has a stochastic character (Petrov 2011). Moreover, in addition to well-known mechanisms (protein and DNA damage, ROS induction), radiation-related biological effects in space involve other, less-understood mechanisms, including altered communication between damaged and undamaged cells (Azzam 2001). Indeed, space radiations produce distinct biological damage compared with radiation on Earth, leading to significant uncertainties in the projection of cancer and other health risks, and preventing an accurate assessment of the real effectiveness of possible countermeasures (Durante 2008). In fact, ground-based accelerators typically generate radiation of a fixed nature and energy, whereas cosmic rays display extensive energy spectrum and heterogeneous composition. Besides, cosmic rays and microgravity may induce synergistic, combined effects that cannot be simulated by our current technological tools. Therefore, the NASA Strategy Report recommended, "a comprehensive research program to determine the risks from different types and energies of HZE particles and from high-energy protons for a number of biological end points" (Tobias 1975).

Spacecraft walls have helped to protect astronauts orbiting aboard the ISS and making short travels from Earth to Moon, but for longer flights, the conventional shields cannot block radiation below the required level without making space vehicles too heavy. In fact, shielding is very difficult in space: the very high energy of the cosmic rays and the severe mass constraints in spaceflight represent a serious hindrance to effective shielding. While shielding remains the only feasible countermeasure, it cannot constitute a comprehensive solution to the GCR problem, even though it can significantly contribute to risk reduction (Parker 2006). Massive shields are impractical on spaceships, although small ''storm shelters'' can be designed to counter intense SPE. Other strategies include choice of an appropriate time of flight, i.e., mission planning and ability to predict solar particle events; administration of drugs or dietary supplements to reduce the radiation effects; enhancement of cell repair; and crew selection based on genetic screening. New promising solutions are underway, specifically those based on active magnetic shielding (Towsend 2001). The experience gained during the development of the alpha magnetic spectrometer (AMS) super-conducting magnet was useful to develop ideas and techniques to be applied to radiation shields for exploration missions (Battiston 2008). However, significant money and time need be invested in the next decades to develop an effective shielding strategy.

While considerable knowledge exists regarding the physiological changes associated with the adaptation of humans to short-duration missions in space, less information is available in reference with physiological changes related to long-duration missions, extending from one month to several months in orbit (Williams 2003). In an attempt to gain insight about the biological impact of prolonged manned space flights, scientists at best are forced to extrapolate data obtained from the International Space Station. Other information is obtained from short-duration flight missions, although none of the latter can fully reproduce the characteristics of a real interplanetary flight. Given the above, the researcher is forced to rely mostly on simulated microgravity-based experiments as well as on computer modelling, even though these methods are largely unsatisfactory being still in their infancy. Besides, space physiology is considerably more constrained than most other fields of medical study. We just mention high costs, a limited sample of subjects, inadequate experimental models, limited opportunity for reproducing the experimental conditions, high incidence of unexpected intervening threats, among the factors affording limited reliability to predictive accuracy. So far, the shared experience highlights how necessary are efforts directed to substantially enhance biomedical research and promote significant developments in human spaceflight studies, particularly because today's space programs are considering again longer-term human expeditions beyond near-Earth space, to destinations such as Mars.

4. Mission to Mars

The Apollo-era shortcomings have become fully evident only in recent years. More rigorous techniques of quantitative risk assessment (developed in response to the preliminary analytical procedures of the Apollo program), showed in hindsight that this program was "safe enough" to fly. Calculations indicated that crew survival chances were higher than 98%, and mission success chances were in the 75% range for the early missions. However, when the same techniques were applied to the then-popular Mars astronaut mission profiles, they generated horrifying results. The mission success chances were less than 10%, and crew survival chances

were less than 50% (Rapp 2007). Early estimates of the cancer mortality risk linked to space radiation ranged from 400% to 1500% (NASA 1998). More reliable assessment showed uncertainties at the 95% confidence level of 4-fold times the point projection (Cucinotta 2006). In addition, space flight was ascertained to expose astronauts to other significant health risks. From 1981 through 1998, 1,777 single medical events occurred in the outer space: heart rhythm disturbances, anemia, kidney stone, space motion sickness and many others, including 141 events due to injury and 18 fatalities, during the Soyuz 1, Soyuz 11, Challenger and Columbia missions (Billica 2000). It is surprising that such a crucial problem is only rarely (or marginally) addressed when it comes to future mission planning, generally focusing only on analyzing technical and socio-economic implications of space explorations (Sherwood 2011). Additionally, what we do not know about human physiological limitations hinders our ability to plan a human exploration campaign of Mars. In any event, the most limiting factor that makes human space exploration unsuitable is strictly related to safety and biomedical considerations. Therefore, the principal barriers to human exploration, particularly of Mars, are given by uncertainties in the medical science. These latter include, in particular, the physiological and psychological burdens placed on the crews and assessing an acceptable level of risk that can be assumed. Space exploration is indeed a risky adventure and cannot be reduced to a challenging technological endeavor, even if the crew would consist only (but unlikely so) of two astronauts (Salotti 2011). The recent Augustine report recognized the important role humans can play in exploration. However, it went on to say that "in hindsight . . . it was . . . inappropriate in the case of the Challenger to risk the lives of seven astronauts and nearly one-fourth of NASA's launch assets to place in orbit a communications satellite" (Augustine Report 2010). A rational approach would be to use robots until we can define objectives for which humans are essential. We could also conduct experiments to determine the contribution to field exploration that is gained by having humans in situ.

Yet, no compelling case has been made that human exploration is strictly necessary to accomplish the goals currently assigned to the hypothesized forthcoming space explorations.

It is widely accepted that a long-term human expedition to Mars would require approximately 2.4 years for completion, characterized by a 6-month flight to the red planet, an approximately 500 day surface stay and a 6-month journey back to Earth (Bonin 2005). Almost all the physiological issues, previously reported, would manifest over the course of such a mission. Starting from radiation exposure beyond the protection of Earth's magnetic field, up to the cardiovascular and muscular-skeletal deconditioning, to neuro-vestibular and orthostatic intolerance upon Mars descent and landing. Over 2.4 years, the cumulative and interactive effects of such physiological problems could potentially be devastating, even though they remained silent, for the astronauts, and thus, the mission itself. Furthermore, severe singular incidents could occur throughout the duration of the space flight. Martian gravity is approximately 40% that of Earth's, and the physiological degradation experienced by astronauts in zero-g can be expected to slow somewhat during surface exploration.

Data are still unavailable about the existence of a threshold value of microgravity in inducing measurable biological effects, and no studies have been carried out in order to ascertain the reversibility of microgravity-related effects after prolonged exposure. It is a matter of speculation whether even a 'limited' reduction in g levels might trigger significant health threats. Eventually, the same issues experienced by astronauts on the outbound leg of the trip can be expected to show also during the inbound voyage. All in all, there does not seem to be any doubt that the Mars missions would translate into significant physiological and psychological challenges for crewmembers.

Such worrying scenario could hardly be reconciled with some popular misconception too easily diffused in the media by authoritative scholars ("A man can stay in space for more than six months – even 1,000 days! – without experiencing irreversible health risks", "We can send humans to Mars in ten years" with "the primary objective of having them to remain there") (Zubrin 2005). Statements of such kind should be placed in the context of a scientific and rational debate. Moreover, it is quite alarming that some reports willfully fail to deal with safety challenges posed by human space flights, outlining that they are "not discussed in extensive detail because any concepts falling short in human safety have simply been eliminated from consideration" (SUMMARY REPORT of the Review of U.S. Human Space Flight Plans Committee 2008).

Since a small number of astronauts have operated for as long as a year in space, it has been argued that no major physiological problems would prohibit long-term human exploration (Committee on Human Exploration 1997).

This assumption is unwarranted. An accurate assessment of current research in space biology and medicine shows that a viable solution of the major problems posed by prolonged exposure to space flight was any more evident in 1993 than it had been in 1961, the year of the first human spaceflight. To make matters worse, space biology and medicine are in the very earliest stage of development as rigorous scientific disciplines.

These fields should be investigated to afford a reasonable degree of scientific soundness prior to attempting to send humans on extended missions to Mars. "Space biology and medicine are in such a primitive state of development that knowledgeable researchers cannot state with any degree of assurance that human crews will be able to operate their spacecraft or function usefully on Mars after their voyage. Even if nuclear- or solar-thermal (or nuclear- or solar-electric) propulsion systems are realized, traveling time will still be nearly six months each way.

Even this is well beyond U.S. experience, and the former-Soviet Union's program offers very limited solid biomedical data for missions of this duration." (Augustine Report 2010).

The danger posed by biomedical uncertainties is related to another important element, not often publicly recognized: the role of individual braveness. Humans who venture into space must and do accept a high degree of personal risk. However, as the Challenger accident made clear, the public is not eager to accept losses that can be anticipated and avoided. A sustained program of human exploration must adopt the prudent strategy of reducing to an acceptable minimum both the immediate and long-term risks astronauts will face. Thus, the potential hazards of exposure to radiation and weightlessness must be addressed within the context of a comprehensive program of health and safety. To do otherwise would impose unacceptable risks on the entire human exploration enterprise.

5. The next step

Advances in Space Biomedicine are necessary to ensure better astronaut performance and recovery after return on Earth. Moreover, the biomedical support to space missions had significant impacts on the delivery of terrestrial health care for years after the program concluded (Bizzarri 2008). Namely, the improvements in the ability to monitor astronauts in space during Mercury and Gemini projects, as well as research programs performed on the Skylab Space Station (Johnston 1977), fostered the early development of monitored patient environments and hospital intensive care units with similar technologies (Turner 1997).

Nonetheless, in almost five decades of manned spaceflight, our understanding of physiological change during long duration missions remains limited. The implications of coupling both long duration and long distance space exploration remain largely unknown at present. Yet, our experience of both low-Earth orbit and brief lunar expeditions allows us to make reasonable assumptions about the primary stressors that human explorers would encounter, as space missions grow lengthier. The physiological impact of human spaceflight is both significant and varied. Some issues – such as radiation exposure and immunologic depression – represent serious concerns while a mission is ongoing, while others – such as cardiovascular deconditioning and orthostatic intolerance – only manifest themselves upon return to Earth.

A successful space mission would not only ensure crew health during the journey, but would also minimize the impact of spaceflight-induced deconditioning after returning to Earth. Counteracting both in-flight and post-flight physiological issues is vital for the purpose of developing an aggressive, sustainable program of human space exploration beyond Earth.

Several key questions have been left aside from the scientific mainstream. Is the microgravity-related effect on living organisms irreversible? Can an adaptation of some sort be envisaged for long-duration space flights? Is there a threshold value for microgravity effects? Can its biological effects be efficiently counteracted by some kind of drugs, exercises or artificial gravity devices? (Kotovskaya 2011) Can we obtain a satisfactory protection from radiation exposition trough appropriate shielding? The unfathomed nature of gravity-biology interactions is still awaiting a reliable explanation. It is hard to understand how the absence of the effects of such a weak force like gravity can produce these "catastrophic" events at both molecular and physiological levels (Kondepudi 1981). Most recent studies have shown that several biological structures (cell shape, bone architecture) and cell functions (cell cycle control, apoptosis, differentiation) are noticeably affected by microgravity. Moreover, several molecular pathways have been extensively studied and recognized in the last decade (Hammond 2000; Masiello 2014). Yet we are far from having an overall exhaustive comprehension of the processes involved. This means that, first, a general theory about the relationships between gravity and life is urgently needed (Bizzarri 2014; 2017). From a clinical point of view, we have to know if gravity-induced

alterations are irreversible beyond a temporal threshold value. Although several attempts have been made to extrapolate both predicted and experienced risks to longer-duration flights, yet the actual biological impact of endeavors such as interplanetary flight currently remains thoroughly unknown. The answer we will provide to such a question may potentially determine our future in space.

6. Throw the heart beyond the obstacle

A recent report (Kahn 2014), bucking the trend in popular scientific literature, openly acknowledged that long duration and exploration spaceflights (including extended stays on the ISS or exploration missions to an asteroid or Mars) would likely expose the crewmembers to levels of known risks beyond those allowed by currently-accepted health standards. They would also be exposed to a wide range of risks that are poorly characterized, uncertain, and perhaps unforeseeable. Openly recognizing those problems constitutes a step ahead. In order to address that issue, it is recommended to develop an ethics framework and to identify principles to guide decision-making about health standards for long duration and exploration class missions "when existing health standards cannot be fully met" or adequate standards cannot be developed based on existing evidence (Kahn 2014). Once the options of modifying existing standards or creating a separate set of standards is excluded, the committee concludes that the only ethically acceptable option that may allow increased risk exposure in the context of long duration and exploration spaceflights would consist of granting an exception to current health standards. Yet, this approach does not provide a satisfactory answer, as it does not deal with the achievable scientific objectives we should pursue. Indeed, the only way to reduce health hazard below the acceptable risk, is by improving our fundamental and applied knowledge on Space Biomedicine. Specifically, three main goals should be attained: a) provide a reliable shield protection from radiation exposure; b) develop a device for achieving artificial gravity conditions; c) perform special training to teach astronauts coping with modified gravity and extreme environmental contexts. These issues have been dramatically underestimated during the last two decades, as documented by the large cuts in both funding and programs devoted to space biomedicine investigations. Therefore, if long-duration spaceflight missions were to be undertaken, it would be mandatory to review in depth the scientific policy of national space agencies in order to meet the basic requirements outlined above. We must bear in mind that no risk in the long run, ever prevented humankind from trying to satisfy his unquenchable thirst for knowledge. Therefore, as witnessed by history, neither ethical boundary nor health risks will likely impede the man's race to an endless progress.

Indeed, facing these challenges, NASA as well as other national space agencies, fostered in the recent years of lot of studies aimed at identifying and evaluating the biological hazards linked to human space missions. Undoubtedly, NASA recognizes that "an adequately safe system is not necessarily one that completely precludes all conditions that can lead to undesirable consequences" (NASA System Safety Handbook 2011). Accordingly, adequately safe systems follow two primary safety principles: (1) they meet a minimum threshold level of safety, "as determined by analysis, operating experience, or a combination of both" and aim to improve over time, and (2) they are as "As Safe as Reasonably Practicable".

To systematically address such issues the Human Space flight Architecture Team was created in 2012 to inform NASA's Human Explorations and Operations Mission Directorate regarding possible mission architectures and campaigns beyond Low Earth Orbit (LEO). Following a Capability Driven Framework approach, no single destination has been specifically considered, but a road map of possible destinations that lead towards an ultimate goal of a human mission to Mars was developed (Culbert 2011). However, even if those achievements provide a lot of reliable assessment and useful evaluations, the issue related to safety of human crew during travel from Earth to Mars as well as during the stay on Mars surface, was not adequately addressed by the preliminary reports. Likewise, that topic is nearly absent in the Mars Science Goals, Objectives, Investigations, and Priorities document (2010). Facing the biological challenge represented by a long stay in a microgravitational environment, and by the prolonged exposure to cosmic rays, medical and technological countermeasures are recognized to be still inadequate, as already previously recognized (NRS 2002). Indeed, it is clearly stated that "NASA has allocated risk factors and reliability requirements for missions in low Earth orbit and for the International Space Station but has not done so for missions travelling beyond Earth orbit" (NRS 2002). It is therefore mandatory establishing the risk standards necessary to provide preliminary guidance to Mars mission planners and hardware designers.

Hitherto, NASA's Human Research Program has identified 32 space-related health risks that are being

studied for possible prevention, treatment, and mitigation approaches. This strategy includes engineering, design, mission planning, basic and clinical research, surveillance and medical monitoring, preventive and treatment countermeasures, and health standards (NASA 2014). A similar survey has been made by ESA (ESA 2011) and other national space agencies, like Italian Space Agency (ASI 2011). Risks are currently extensively documented and, if possible, quantified. When risk is considered unacceptably high, alternative designs and missions scenarios are considered and the risk assessment continues iteratively. A further step in settling a unified strategy for planning a Human mission on Mars was accomplished by the release of the "Human Exploration of Mars Design Reference Architecture 5.0" document (NASA 2009). This report provides a vision of one potential approach to human Mars exploration that is based on best estimates of what we know and it would be deemed a common framework for future planning of systems concepts, technology development, and operational testing. Human health risks were evaluated in both the short-stay and the long-stay mission architectures for the human mission to Mars. The survey recognized that our current knowledge is inadequate to ensure astronaut health safety and, consequently, "the problem of developing effective countermeasures to reduced gravity is significant". Accordingly, " a thorough ground-based research program that is coupled with flight research on the international space station and the lunar surface must be conducted to provide an understanding of the physiological basis for human responses, develop appropriate treatments and countermeasures, and decide how best to support crew members". It is worth noting that the report outlines the need to counteract microgravity-induced effects on human physiology by employing "artificial gravity countermeasures within the spacecraft either by providing an on-board centrifuge or by spinning the spacecraft itself". However, the specific level of the artificial gravity and the minimum effective duration of the exposure that is necessary to prevent deconditioning are not yet known. Similarly, recognizing to what extent artificial gravity may induce relevant side effects (including disorientation, nausea, fatigue, and disturbances in mood and sleep patterns) is an absolute requirement. Therefore, significant research must be done to determine appropriate rotation rates and durations for any artificial gravity device. The report states that radiation risk still represents an unavoidable hazard. Advances are required in radiation protection and countermeasure development from galactic cosmic radiation, including the generation of the secondary radiation that is produced by the galactic cosmic radiation interaction with spacecraft materials. On the Mars surface, "the planet's bulk shields against half of the cosmic radiation that is received in space; but again, the generation of secondary radiation from the atmosphere and surface materials may prove to be problematic".

For copying with both expected and unexpected health hazards, health systems would be required to provide appropriate medical care, environmental monitoring and regulation, and optimization of human performance. The approach to health and performance systems is expected to evolve toward increasingly higher levels of self-sufficiency. Besides the development of more sophisticated telemedicine devices (mainly relying on a differentiate set of biosensors able in catching different medical parameters), on-site medical care would be needed to accommodate major and minor illnesses and injuries and perhaps surgical capability.

Yet, to meet these aspirations, a new space race must be promoted. We propose an international endeavor to coordinate the various Space Agencies' efforts as to create an operative committee, specifically focused in addressing the complex tasks associated with a long-lasting mission to Mars. Such a committee, first and foremost, should determine, according to widely accepted ethical principles, an acceptable threshold level of health risk. Second, the Committee should promote more systematic biomedical studies, aiming at developing reliable countermeasures. Namely, two main issues deserve an urgent program of in-depth investigation a) development of an artificial gravity device; b) an affordable and technically feasible tool for cosmic rays shielding. Undoubtedly, this program needs to be carefully time-framed into a detailed roadmap, so as to protect the project from the mists of pseudo-scientific divagation, and allow it to become realizable. To fulfill these objectives, it is imperative to decide whether the International Space Station (ISS) can play a strategic role in biological space research. Consequently, NASA and other Agencies must allocate funds for either the space station's continued operation or its destruction. In our opinion, if people are going to live and work in the outer space for prolonged periods, we should test technologies and evaluate human performance under those conditions; to this aim, the ISS remains the ideal laboratory. Moreover, keeping the station operating will preserve an important international partnership for future missions. Such a policy development – and the related decision-making process – would definitely be entangled with a number of relevant technological and political

issues, and so far no clear consensus has been reached among NASA and the other space partners, even if the ISS lifespan was recently extended up to 2020.

Hence, in light of previous experiences obtained since the negotiation of the Outer Space Treaty (1967), it would be necessary to consider a renewed and different attempt to establish an International Space Committee. This would be an urgent step forward to overcome the inadequacies we are currently facing when it comes to devise a sound space exploration strategy. Among other considerations, this statement posits that a broad and consistent autonomy should be allowed to Space Agencies by national governments to raise the needed international cooperation. In our opinion, such initiative would also carry significant consequences aimed at the establishment of far-reaching economic and peaceful programs of worldwide relevant impact for human wellness.

7. Conclusion

Manned space flight has been the great human and technological adventure of the past half-century. Space flight has stirred our imagination expanding and redefining the human experience. In the twenty-first century, human space flight will continue, but it will become more global, and more oriented toward primary objectives. A new international human space flight policy can help achieve these goals by clarifying the rationales, the ethics of acceptable risk, the role of remote presence, and the need for balance between funding and ambition to justify the risk of human lives.

By no doubt, eventually, we will hit the mark! However, for now, we must emphasize that a long and uncertain path lies ahead: "It is a long way to Tipperary". As Ariosto's masterpiece (Orlando Furioso 1516) goes, walking on the Moon was previously considered as pure madness. Will this be true for walking on Mars in the near future? We think not, provided a sounded scientific approach will be taken concerning the full cohort of potential biomedical issues, some of which we reviewed here.

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