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Ergonomic Challenges for Astronauts during Space Travel and the Need for Space Medicine

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Abstract

Engaging in and enduring space travel renders the human body exposed to a wide variety of acute and chronic stimuli which may necessitate pharmacological intervention. Such ergonomic challenges have led to coping and mitigation strategies and from the pioneering days of space travel in the 1950s to the current day, medications have been available on demand and proven successful in the treatment of conditions such as motion sickness, diarrhea and depression. Longer term space travel within and beyond the Solar system will require both a more detailed understanding of human tolerance to living in ergonomically challenging environment in space and new methods to manage and maintain the effectiveness of medicines to provide adequate and complete healthcare for astronauts.

Keywords: Ergonomics; Astronauts; Space travel; Space medicine; Human physiology

Introduction

Imagine it is 2117. The technology to enable space travel approaching 1/10th the speed of light has been developed and it is both physically and commercially feasible to send a human population, capable of procreating in space on a 150 year journey. The target destination is an 'Earth 2' newly categorized exoplanet, which lies in the habitable zone of Proxima Centauri and whose atmosphere comprises all of the molecules required to either harbour or sustain life. The planet is rocky, has a magnetic field and an axial tilt which may provide seasonal variations in climatic conditions.

Now in 2017, as we comprehend taking our first steps towards space travel within the solar system which are designed to lead to lunar or planetary colonization within the next 10-20 years, what will we need to know and to develop which will allow such a crew to be safely maintained for these first steps and which may ultimately provide a foundation to permit travel to and permanent colonization of a new world?

In this review article, I will provide an overview of both the physical and mental ergonomic challenges that space travel poses to astronauts together with a review of published work on the history of medication use on space missions. Drawing on scientific publications across many disciplines, I will also illustrate how the space environment has provided direct benefit to drug discovery and development and finally speculate on the challenges and opportunities posed to humankind which when solved, may permit space travel to support colonization of bodies within the solar system and one day, maybe to other Solar systems.

Physiological and psychological challenge to humans in space

The work place in space is, by necessity restricted and confined and the ergonomics imposed challenges the human body both physically and mentally. Understanding the need for space medicine dates back over 50 years [1]. In healthy human beings, all our physiological processes are tightly regulated with multiple homeostatic pathways which keep multiple normal functions under scrutiny, making adaptive responses where necessary. In space, chronic exposure to microgravity, enhanced levels of radiation, a perturbed circadian rhythm and psychological issues which arise from living in a confined environment with other people challenge that balance. Acclimation to spaceflight must accommodate rapid changes in biochemical processes and although the consequences of adaptation may resolve shortly after return to earth, bone demineralization for example and impaired vision may be a permanent consequence of long-duration space flight where the recovery period may be longer or much longer than the mission itself [2]. Not surprisingly perhaps, the anatomical, physiological and psychological differences between female and males appear to manifest in symptomatic changes in a variety of effector functions [3]. Published in 2014, The "Impact of Sex and Gender on Adaptation to Space" [4] is a series of six papers, addressing differences in cardiovascular, musculoskeletal, immune and neurosensory systems, reproductive and behavioural health. Accompanied by an executive summary and commentary, it remains the most current and comprehensive report on sex and gender differences related to human physiology and psychology in spaceflight and on Earth. There have been a number of excellent reviews [5-11] in many areas of human physiology and in the next section, I will provide a brief and up to date review some of consequences of space travel on human physiology and draw where possible on non-clinical studies in cell culture *in vitro* and in animal models which may help to build a picture of our current knowledge and the gaps that remain in our understanding.

Vision

It has been known for many years that astronauts who undergo prolonged space flight may be affected by visual disturbances [12-15]. These changes in vision may persist for years post flight and be more prevalent in male astronauts [3]. NASA has and continues to fund [16] a number of studies within a Visual Impairment and Intracranial Pressure program which aim to understand how the shifts in body fluid perturb intracranial and intraocular pressure which occur during

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spaceflight and how this may be modeled on Earth in head-down tilt clinical studies [17]. The results of these and other studies may be used to develop potential therapeutic regimes which rebalance the pressure gradient, likely with modified exercise programs. Interestingly, early studies may have identified that astronauts potentially at risk of developing ocular impairment suggest that in microgravity, polymorphisms in enzymes of the 1-carbon pathway may be, at least in part responsible for changes in vision [18]. For long-term space travel, it is of tantamount importance to understand both the effects of microgravity on vision, together with the astronaut's ability to adapt to these new conditions and ultimately to revert to relatively unimpaired vision on return to planetary gravity levels.

Respiratory system

Despite the fact that an early murine model study [19] identified that anti-orthostatic positioning, which is changing the direction of gravity relative to the body vertical axis, may increase water content in the lungs and reduce the properties of pulmonary surfactant, there appears to be little or no effect on lung function in humans in space [20]. Two areas are, however, worthy of further discussion. The first area aims to simulate the repeated changes in ambient oxygen that astronauts are exposed to when conducting one or multiple extravehicular activities [EVA] which will also exposure the body to enhanced levels of radiation. Studies in human lung epithelial cells grown in culture [21] and in mice exposed to elevated levels of oxygen and irradiation [22], showed an increase in markers of fibrosis and cell apoptosis which may suggest that astronauts undergoing such activities could be at increased risk of oxidative lung damage. The potential of cell co-culture systems where different cell types are grown together may provide a model for better understanding of the development of cancer in transformed lung cells which could be extended to challenge studies in altered gravity and/or oxidative stress [23]. The second area relates to the maintenance of healthy lung function and the possibility that space dust [24] may cause inflammation and that the fraction of exhaled nitric oxide [F_ENO], may be a proxy biomarker for determination of airway function. F_ENO is a widely used and cost effective biomarker for measuring lung activity in patients with asthma on Earth and this approach, when applied to astronauts on the ISS will benefit from a substantial scientific literature in inflammatory lung disease.

Sleep

In space, 'day' and 'night' are arbitrary assignments. On Earth, humans have evolved a circadian rhythm based upon a 24 hour light-dark cycle and a gravitational force of 1 x g. Sleep quantity and quality are both negatively affected during spaceflight and the use of medication to promote sleep is prevalent, especially as astronauts are required to execute part of the mission where there is misalignment to the circadian rhythm, brought about by vehicle launch, orbit and docking times [6,25-27]. Impairment of cognitive ability may be a concern and at worst constitute risk at the task or entire mission level with potentially life-threatening consequences. Currently, the mitigation used by astronauts is circadian alignment with time exposure to both light and darkness, with appropriate adaptation of work schedules [28].

Brain function

This area has been very recently reviewed [11] and despite over half a century of manned space flight and the widespread use of head down bed rest as an analogue for the simulation of cephalic fluid shift experienced in space [29], there is little information on the effect of spaceflight and microgravity on the human brain. A number of studies in mice [30-32] suggest attenuation of neurotrophic factors associated with neurotransmission, it remains unclear how these changes may affect alteration in behavior and how such changes may translate into humans. It is essential to develop a deeper understanding on the potential for attenuation of brain function given the striking effect of spaceflight on structural plasticity and changes in grey matter volume [33], some of which may be attributable to fluid shifts. Moreover, exercise in isolation has proven an effective countermeasure for both cognitive and mental impairments [34].

Musculoskeletal

The effects of gravity on bone and soft tissue loss associated with space flight have been very recently reviewed as part of an advisory group supporting Towards Human Exploration of Space: a European Strategy (THESEUS) [5,10]. The central issue is whether the countermeasures such as regular high-intensity resistance training and the use of anti-resorptive drugs taken by patients with osteoporosis on Earth [8,35,36] ameliorate bone and muscle loss to a level acceptable to sustain longer term space travel and in the first place return to Earth. To date, these measures, together with good nutrition seem to be effective, however, in spacecraft which like the ISS are not in low Earth orbit, spatial consideration needs to be given to accommodation of exercise regimes for multiple numbers of astronauts which may pose new challenges to spacecraft design.

Cardiovascular

Blood pressure is perturbed as a consequence of astronaut positional change and microgravity [5,37]. Cardiac electrical rhythm disturbances have been documented since the Apollo 15 missions as have non-fatal arrhythmias and atrial fibrillation in astronauts returning to Earth [38]. Research from the Canadian Space Agency suggests that despite exercise regimes in-flight, cardiovascular deconditioning and arterial stiffness is a common manifestation in astronauts returning to Earth [39]. Moreover as the pressure gradients associated with the arterial, venous and microcirculation are no longer present, fluid shift towards the thorax and head is associated with venous blood pooling in cephalic, splanchnic and pelvic regions [40]. As most drugs rely on the blood for distribution to the target tissues or organ, changes in blood parameters such a blood volume are likely to influence the pharmacodynamic activity of the medication and this may lead to loss of efficacy and accumulation of drug within a compartment [41]. At present, there is no clear mitigation and further research will be needed on future missions to monitor cardiovascular parameters and to instigate the necessary monitoring and risk management procedures to mitigate the potential for life-threatening risks.

Pyscho-social

The effect of long periods of isolation in cramped living conditions and with crew members with which individuals may not be familiar is not unique to space travel. Prototype isolated contained environments [ICEs], such as the isolation experienced by submariners and explorers in, for example, polar expeditions may be a useful model to monitor and predict individual and group behavior. However, unlike the case in these ICEs, no help is at hand to call off the mission, provide a finite end date and return an astronaut to normality. A number of psycho-social problems may present which include boredom, clinical depression, acute and chronic anxiety and reduced ability to interact with other team members which may lead to aggressive behaviour and conflict [42].

Neuronal and neurovestibular

Perturbations of and risks of defects in central nervous system [CNS] function may be achieved by microgravity, magnetic fields

and exposure to ionizing radiation [43,44]. Effects of radiation on the CNS have been studied using non-clinical model systems from particle accelerators simulating space radiation and can be gleaned by systematically reviewing CNS effects on cancer patients who have received radiotherapy and subjects who have been exposed to radiation through nuclear warfare. Alterations in cognitive abilities, reduction of motor functions and behavioural changes are risks which must be accommodated within any risk management plan as they may occur on an acute or chronic basis [43]. Motion sickness and depressed mood may be treated pharmacologically with anti-emetics and anti-depressants. Clearly and unlike the situation on Earth with anti-depressant administration, the long term psychological effects of prolonged anti-depressant medication are completely unknown. Recently a study in a head-down tilt model as an analog of spaceflight using functional connectivity magnetic resonance imaging support brain neuronal network alterations which associated with changes in sensorimotor and spatial working memory performance [45]. This may suggest that alterations in neuroplasticity maybe a consequence of adaptation to simulated microgravity and further substantiate monitoring of sensorimotor performance as a part of the risk management plan.

Gastro-intestinal

Space travel, particularly the effects of microgravity and greater exposure to ionizing radiation can influence the gastro-intestinal system in several ways. The majority of medications taken in space, as on Earth will be via the oral route and so absorption through the GI tract is essential and any changes on the absorption rate may lead to alterations in drug exposure over time which may influence drug efficacy. First, alternations in gastric emptying, and intestinal transit rate may result in altered absorption medications [9,46]. Secondly, the ability of our GI tract to perform efficient and effective digestion is dependent upon bacterial colonisation known as microbiota, which constitutes the microbiome [47]. Conditions of stress experienced in space travel which include cosmic radiation [48,49] and microgravity [50], may induce microbial dysbiosis and changes in bacterial physiology [51,52]. Finally, as on Earth, maintenance of good nutrition, balanced appropriately to align with daily routine in space is essential to maintain GI physiology and effective function [53,54]. Thus the affects of space travel, on overall GI function both directly effecting physical processes and indirectly effect GI health as a consequence of microbiota physiology.

Immune function and potential for infection

Spaceflight has been documented to have deleterious effects on the immune system in animal models and in astronauts in actual or simulated spaceflight or stress conditions. Several studies have indicated a change in leukocyte distribution, reduction in T cell function, production of antibody heavy chains and increased pro-inflammatory cytokine profiles during flight [2,55-59]. It is perhaps a flag for caution that most of these changes in the repertoire of immunological mediators were observed in short duration low earth orbital flights.

For longer space missions, such as to Mars, sustained immune mediator changes may potentially cause clinically symptomatic adverse events. Given the clear link between maintenance of effective immune-surveillance and a number of cancers, this could be a serious concern for long and very long-term missions, where there may be a potential for an increased cancer risk as a consequence of perturbed immune response. Intriguingly a study in mice has reported that hypergravity, such as that experienced at take-off and landing modifies the T cell receptor β repertoire in newborns [60]. Though a distant goal at present, it is a formal possibility that in a population capable of procreation, human foetal development may acquire an altered immune capacity which may, or may not be capable of mounting a response when challenged. The attenuation of cytokines involved in mounting an immune response to infection [61,62] may be problematic given the confined nature of spaceflight and the potential for microbial particles and dust to become aerosolised, which will warrant rigorous control and mitigation processes [57]. Our ability to measure the effects of spaceflight on gene expression in the blood [63] and to determine an index of immune health status using transcriptomics from DNA derived from cells in the blood may be one way of developing an algorithm to check on the patency of the immune response [64].

Impaired healing

As discussed above, spaceflight induces loss of both bone and muscle mass. Moreover, these tissues and other which constitute other organs such as the heart exhibit an impaired healing capacity in a reduced-gravity environment [reviewed in 65]. Studies in animal models in spaceflight have shown impaired healing of fractures [66,67], delayed repair process in muscle crush injuries [68], an abnormal healing process in an incisional wound study performed on the space shuttle [65] and reduced human growth hormone production in tissue engineered muscle also flown on the space shuttle [69]. As on Earth, efficient wound healing demands and effective vascular supply of growth factors and cytokines and it is a possibility impaired tissue repair is as a consequence of reduced gravity on blood vessels [70].

Drug metabolism

Multiple drug metabolising enzymes, some with gene polymorphisms which can influence their activity and are dependent upon ethnic background and drug transporters play a vital role in drug absorption, distribution, metabolism and excretion [ADME], [71]. Spaceflight and simulated microgravity alters the activity of a number of enzymes in animal models [9,72,73] which may suggest that metabolism in humans could be altered and that monitoring of ADME processes is performed on space missions. The effects of spaceflight or simulated microgravity are summarised in Table 1, for each target class. As illustrated, there appears to be alterations of a wide number of targets across species.

These changes could lead to alterations in drug metabolism which could increase or decrease drug exposure during spaceflight, allowing in some cases for drug accumulation. Moreover, the very small number of humans travelling in space may necessitate a detailed understanding of an astronauts genetics and offer both the opportunity for better treatment and the potential to predict response to countermeasures [71,72,74], which may benefit some aspects of personalised healthcare development on Earth [75].

Counter-measures to the effects of spaceflight

As our knowledge increases on the effects of spaceflight on human beings, so does our understanding of risk. This allows mission planners to propose and agree mitigation risks, some of which will include the development and refinement of countermeasures. There are many reviews which summarise the potential and actual countermeasures which are in put in place and a representative set is cited for further interest [2,7,10,34,50,53,57,71,72,74,76-81]. In Table 2, countermeasures in operation today are described for each of the physiological and psychological effects of spaceflight described in the preceding sections. Future countermeasures, where research is actively

Species	Organ/medium	Target	Effect	Reference
Rat	Sublingual gland, stomach, colon, small intestine	Neutral and acid glycoproteins	Reduced protein levels	
Rat	Large intestine	Leucine aminopetidase, acid phosphatase, adenosine triphosphatase, glucose-6-phosphatase	Increased protein levels	[73]
Human	Blood serum, urine	Amylase	Increased protein levels	[72]
Rat	Liver	Hydroxy-methyl glutaryl-CoA reductase	Elevation in enzyme activity	[97]
Mouse	Liver	CYP2C29, CYP2E1, CYP1A2	Elevation of protein levels	[98]
E. coli	Reconstituted membrane	Porins	Opening of ion channel im hypergravity, closure in microgravity	[95]
N/A	In vitro vesicular transport assay	ATP-binding cassette transporter	Increased protein levels	[102]
Mouse	Liver	PPARa-mediated lipotoxic pathways	Increased accumulation of lipid droplets	[96]

Table 1: Effect of spaceflight on metabolic enzymes.

Physiological adaptation	Current countermeasures	Review reference	Future countermeasures	Reference
Visual disturbances and motion sickness	Vision - no known countermeasure. Pharmacological intervention.	[15] [2]	No immediate countermeasure	N/A
Neurovestibular	Pharmacological intervention	[2]	Optimisation of treatment regimes	N/A
Sleep quality	Alignment with time exposure to both light and darkness and adaptation of work schedules	[28]	Continued optimisation and monitoring of regimes, acquistion of more data for long (>1 y) residency in space	N/A
Brain function	Adaptive generalization, contextual adaptation	[11,80]	Continued study of behaviour for long (>1 y) residency in space, optimisation of unassisted egress	[79-81]
Cardiovascular function	Resistance training, monitoring and pharmacological intervention	[5]	Understanding what level of function is required	[62]
Psycho-social function	Crew selection, adequate metal stimulation and contact with Earth, pharmacological intervention	[2]	Monitoring complex human behaviour in space missions and other ICEs environments. Optimisation of exercise regimes,	[94,123]
Gastro-intestinal function	Diet maintenance, pharmacological intervention	[28,126]	Microbiome profiling before mission, monitoring during mission	[129]
Respiratory function	Limit number of EVAs and optimise hyperoxia-inducing regime	[20,21]	Construct 3D human lung models and characterise lung biomarkers under different conditions.	[23]
Immune function and infection	Vaccination, screening, pre-mission isolation, diet maintenance	[77]	Immunological, microbiome and genomic profiling before mission, monitoring during mission	[64,71,74]
Hard tissue loss	Regular resistance training, resistive vibration, nutrition, pharmacological intervention	[7,8,10,117]	Optimisation of exercise (e.g. vertical treadmills, nutrition and pharmacological regimes. Development of tools to predict muscle and bone loss	[76,78,79]
Healing capacity	Risk-based monitoring to reduce injury, pharmacological intervention	[7,77]	Limited data available on healing rates in humans in space. Translation of animal model to human healing rates in microgravity requires further exploration	N/A

Table 2: Current and potential future countermeasures for physical and psychological effects induced by spaceflight.

in progress are also indicated. From the summary presented in the table, it is abundantly clear that many studies have been performed with model systems on Earth and in space. These include non-clinical *in vitro* and *in vivo* studies and clinical studies with human subjects in simulated conditions experiences in space flight together with astronauts who have experienced the deleterious effects of leaving the Earth for short [weeks], medium [months] or long term [>1 year]. The gradually increasing data base of humans exposed to pharmacological interventions in space will provide us with much needed data which will enable a 'Space Index' of benefit:risk to be evaluated for each particular drug. This may or may not be very similar to that on Earth and given the very large safety databases for many medicines developed to date, it should be straight forward to modify dosing regimens for where drugs are administered singly or in co-administration with other drugs.

Use of Medication in Space Travel

For the next part, I will concentrate on the specifics that relate to the history, present and likely future pharmacological treatment of some of the conditions treated, together with actual and potential limitations. There have been a number of excellent publications either as reviews [1,82-89] or as original research, including publications which illustrate the effect of gravity on drug targets, processes which affect drug behavior in physiological systems [72,73,86,89-104] and this section will summarise the major findings. When planning astronaut healthcare for a space mission, there are a number of basic considerations which are, in part dependent upon the duration of the mission;

- Which medications are to be included?
- Which conditions are they to be used?
- What is the route of administration [e.g. topical, oral, injected, rectal, inhaled]
- Under what environmental conditions are medications stored?
- What is the shelf life of the active pharmaceutical ingredient [API]?
- What is the benefit: risk ratio of using the drug?

Use of Medication in Space-The Early Years

In the early years of space flight, missions were of the period of days and a very restricted number of medicines were carried, some of which are shown in Table 3 [84,105,106] and illustrated in Figures 1-5.

Evaluation of medications used in-flight in 79 space shuttle missions showed that the majority of medications provided for and taken were for motion sickness, sleep disturbance and as analgesics or anti-congestants [100]. All drugs administered were associated with adverse events which were manageable and most reports of drug ineffectiveness were reported after the first day of administration. Although there was a paucity of available information on drug effectiveness, these early findings stimulated investigation into understanding pharmacokinetic-pharmacodynamic relationships and whether the space environment per se may effect drug properties such as stability [83,88-90,94,101-104,106-108]. To date, there have been two published studies which have investigated the effect of space flight on the pharmacokinetics of the analgesic acetaminophen [paracetamol] [91,109] and a further study investigating the same parameters of the stimulant dextro-amphetamine and the anti-emetic scopolamine [92]. In the first study of short flight duration [25], the absorption rate was seen to increase after 2 days and decrease after 4 days of flight, whereas in the second study [109] of longer duration, space flight decreased the absorption rate of acetaminophen when taken in tablet form, but increased the absorption rate when taken in a capsule formulation. In the study which co-administered scopolamine with dextro-amphetamine, there was a high level of inter-individual variability in the level of drug absorbed when compared with a similar drug administration regime dosed pre-flight on the ground [92]. Although small studies, where sample size may be insufficient and replication of results is not possible which may lead to greater variability, they illustrate a point, which is that variability in absorption rate over time, together with drug presentation may lead to variability in efficacy.

Drug	Mode of action	Drug	Mode of action
Epinephrine	Stimulant	Tiagn	Anti-emetic
Cyclazine	Anti-emetic (motion sickness)	Demerol	Anti-analgesic
Meperidine	Anti-analgesic	Secobarbital	Sedative
Acetoaminophen	Anti-analgesic	Oxymetaxzoline	Decongestant
Dextra-amphetamoine	Stimulant	Quinidine	Anti-arrthymic
Diphenoxylate	Anti-defaecant	Dipyramidole	Anti-coagulant
Bisphosphantes	Anti-resorptive (bone)	Aledronate	Anti-resorptive

Table 3: Name and mode of action of drugs commonly used in early space missions.

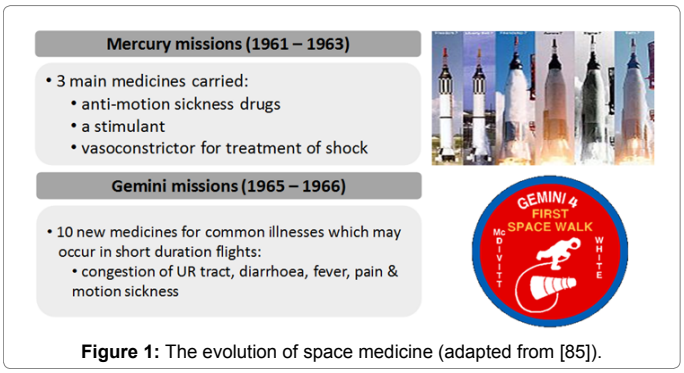

Figure 1: The evolution of space medicine (adapted from [85]).

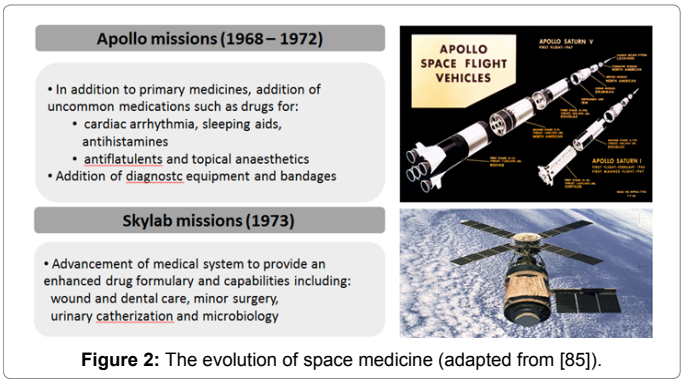

Figure 2: The evolution of space medicine (adapted from [85]).

Use of Medication in Space – Drug Inventories on the International Space Station

The evolution of the number of medications available for use throughout the history of space travel has been summarized elsewhere [84,85,105]. In 2016, a request via the Freedom of Information Act describes an extensive set of medications and a comprehensive list of medical procedures which are to be followed in an emergency [106] and these are shown in Figure 5. The medications, their doses, intended uses and side effect profiles are described in (Tables 1-3) and 8 in this publication [106] and the reader is recommended to visit this

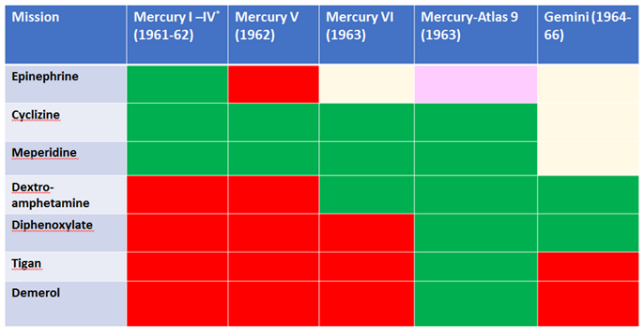

Figure 3: The evolution of space medicine (adapted from [84,85]).

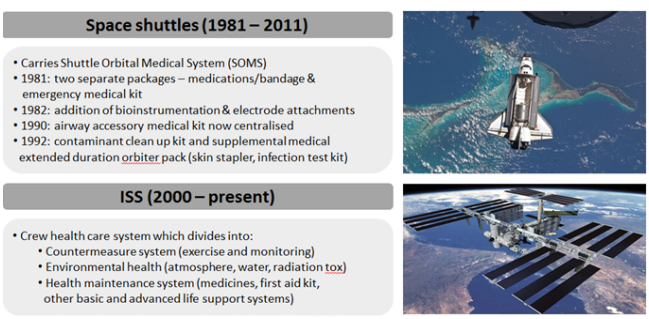

Figure 4: The evolution of space medicine (adapted from [85]).

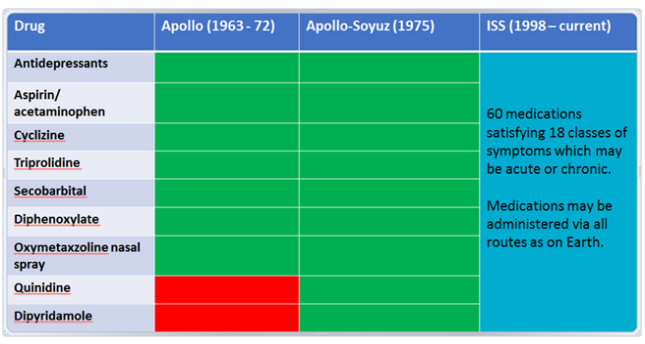

Figure 5: The evolution of space medicine (adapted from [84,85,106]).

site for more information. To summarise, medications are available as a]. antibiotics, b]. anti-diarroheal, c]. anti-histamine/allergy, d]. decongestant, e]. lubricant, f]. anti-analgesic, g]. sleep modifying, h]. stimulant, i]. anti-inflammatory, j]. stool softener, k]. cardiac, l]. altitude/motion sickness, j]. anti-fungal, k]. anti-seisure, l]. anti-viral, m]. behavioural health modifiers, n]. stimulant, o]. gastrointestinal and p]. urinary. The inventory comprises 60 medications and which satisfy the treatment of acute and chronic symptoms which either have, or may be experienced on the ISS.

Taken together, experience gained over the last 54 years of space travel has recognized the symptoms experienced by astronauts, the need for provision of medications for both short and long term space travel, the requirement to develop predictive non-clinical models of drug degradation and bioequivalence [110] and the need to accommodate a growing number of available medications which ultimately may be used on much longer missions, such as those to Mars. In the next section, I will briefly describe some of the challenges which relate to the storage of medications and maintenance of an active pharmaceutical ingredient [API] which are necessary to retain drug efficacy and which must be overcome if missions of many years are to be undertaken.

Use of Medication in Space – Considerations for Long Term Space Travel

As on Earth, all medicines comprise an API and the API will reduce over time as the medication degrades [111]. This is often referred to as the shelf-life and describes the period of time after which the drug loses its potential to bring benefit and although it may do no harm, neither may it be of use in symptomatic control. This may be less of an issue for the relief of acute symptoms but may be a clear limitation, possibly life-threatening for the treatment of chronic conditions such as cardiac or the potential to treat latent infection, reactivated over time.

One study has shown that after storage for 28 months on the ISS, the ability of 4 out 14 solid drugs failed to meet the United States Pharmacopiea [USP] dissolution requirements when compared to 2 controls on Earth [94]. 6 medications changed their physical characteristics compared to 2 on Earth which may affect their efficacy. However, in another study analysis of drug degradation and chemical potency as defined by the API, showed that 8 out of 9 medications met USP criteria for achieving an acceptable API and did not identify unexpected degradation products [103].

The stability of a vitamin B complex as two separate brands in a multi-mineral supplement in a tablet formulation has also been investigated after 4 months storage on the ISS [90]. This small study may suggest that one brand of vitamin B is slightly more prone to degradation than the second brand and this type of investigation may guide the mission physician in the selection of this supplement for future missions.

Drug stability is typically determined by Raman spectroscopy which has been employed to determine the constitution of four commonly used drugs and their degradation products used on the ISS [101]. This study, which was employed for spectral analyses of mixtures of acetaminophen, azithromycin, epinephrine and lidocaine returned results in approximately 10 mins and may be of use for evaluating the APIs of other drugs and perhaps may be employed *in situ* on longer space missions. It appears logical and to be the case that the effect of radiation in space may enhance the degradation of medications at a faster rate than on Earth [85] and a number of approaches are suggested to optimize the stability of medications exposed to the space environment. These include exploration of protective packaging and storage, studying the effect of cryogenic storage on potential radiation-induced degradation and the development of formulations which may contain excipients which protect the primary medication from damage. For the future, it is possible that a new generation of drugs will be deployed as nanomedicines where there has been intensive effort on Earth to achieve organ specific targeting [112]. Perhaps the future we will also witness drug discovery projects specific for medicines in space and in the last section I will describe some of the ways that spaceflight may assist in the discovery and development of new space therapeutics.

Assisting Drug Discovery and Development

The unique environment of microgravity or zero gravity has been shown to be a great assistance in enhancing crystallization quality of a number of proteins which are or may be drug targets [113-117]. In 2015, NASA published a preliminary report addressing the potential economic and commercial benefits of protein crystallization for drug discovery [38]. The report concluded that the potential to provide better quality crystal structures of potential drug targets and co-crystal structures of drugs with their targets may improve the overall speed and attrition rate of drug development. The final report to assess the true value of space borne crystallization studies is awaited.

As discussed earlier, bone loss is a well documented issue for astronauts and may be mitigated to some extent by regular exercise and compliance with administration of bis-phosphonates [118] which are used for the treatment of osteoporosis in patients on Earth [35]. The use of model systems such as meduka fish studies on the ISS [119] demonstrate a rapid alteration in gene expression in osteoblasts and osteoclasts which suggest involvement of genes associated with growth and differentiation which have been shown to drive the production of bone [120]. Recently, a new osteo-inductive protein called NELL-1 has been shown promotes bone growth in non-clinical animal models [121] where bone loss is artificially induced by ovariectomy, which is a standard methodology for the short term assessment of potential new agents with anabolic and anti-osteoclastic activity [122]. A new study will assess the potential of injected NELL-1 protein to ameliorate bone loss in a rodent study to be conducted on the ISS, where microgravity induces bone loss under the same conditions faced by astronauts. The 8 week study will utilise the Dragon spacecraft developed by SpaceX which berthed with the ISS on June 5th 2017 and will bring back live rodents from the ISS for analysis [123].

More futuristically still, NASA is funding efforts to discover new drugs in space [124]. The fungus *Aspergillus nidulans* can only generate secondary metabolites, which may have drug like qualities, when grown under conditions of stress. Microgravity may be an ideal environment to produce secreted proteins which may have, for example, anti-bacterial properties in their own right or represent the starting points for new terrestrial drug discovery projects.

Speculations on Future Astronaut Healthcare

The inventory of medical supplies onboard spacecraft, whether ISS or otherwise and any planetary landers or colonies, together with the medical capabilities of the crew selected for the mission [e.g. whether to include a flight surgeon or other medical personnel] will need to be carefully selected. A review of the medicines inventory on board the ISS has demonstrated that most if not all predicted medical issues may be accommodated and it is clearly recognised that medication shelf-life, as on Earth is a problem which requires attention, even if drug stability exhibits parity with stability of drugs on Earth.

Despite intensive interrogation of data from a relatively limited number of manned space craft voyages [and even less of greater than 6 months duration], extensive non-clinical studies in cellular, animal model systems and in analogs of spaceflight in which humans participate, provide one obvious conclusion. Human beings have not evolved to live in space and our bodies are unable to rapidly adapt to the extreme conditions faced by astronauts. Many of the deleterious effects of space travel described above may simply be as a consequence of having to live in microgravity and the solution would seemingly be equally obvious, namely the development of systems to simulate gravity, so called 'artificial gravity' [AG] [125,126]. The notion of giant spinning wheels portrayed in science fiction, at least today are perhaps impractical to construct and the potential positive attributes for astronaut health remain theoretical and unproven. However, smaller systems such as that envisaged at the design stage of the Nautilus-X spacecraft, which incorporated a centrifuge may, once again be revisited [127] and some elegant designs have been proposed in collaboration with NASA [128]. A complete review of concepts proposed to generate AG is beyond the scope of this article, however, it would seem that this preventative approach for astronaut healthcare may be a necessity if mankind is to travel to Mars and almost certainly further into the solar system and beyond. A combination of risk reduction manifested by the space environment together with judicious use of medicines appropriately stored and packaged for travel together with the rigorous pre-screen approaches in place today should permit long term missions of the order of several years.

Discussion

What will we have achieved by 2117? Let us make some assumptions. In the first instance, we will assume that the ergonomics of space travel has been optimized to be at least tolerable for voyages of up to 2 years duration. We will also assume that colonization of Mars is successful and that mankind has demonstrated that it can propagate and maintain a colony of humans on Mars in a restricted environment and with a risk to human health that is acceptable. Not without challenge, this would appear a reasonable assumption. Secondly, let us assume that the technology will have been developed to achieve space travel at between $1/20^{th}$ and $1/10^{th}$ the speed of light, an increase in velocity of between 500 to 1000 fold of travel today and that multi-generational voyages are about to become reality [129]. We will have instigated many of the countermeasures for maintenance of healthcare for astronauts as described as above and we will have fully developed the necessary life support systems which demands efficient uses of all of our available resources to sustain a multi-national population [130-132]. We will have capitalized on the potential of a commercial return on the development of medicines in space not solely for space travel but for mankind on Earth [75,133]. We will have used the battery of 'omics' technologies [63,64,71,72,74,134] to pre-screen and select astronauts whose health status and predisposition to disease is exquisitely understood [90,134] and for whom the best possible survival outcome is predicted.

Perhaps this is a fantasy today. However, all of the tools are in place to achieve this possibility and taken together with an inexorable drive to discover and develop new drugs on Earth which would, 100 years ago, appear unachievable predicts a very exciting future for space travel. As with the vast majority of major scientific advances achieved by mankind, progress is made by team work and the pooling and orchestration of multiple multi-disciplinary skills of scientists working across international boundaries. Both the public and the private sectors have equal roles to play in the development of procedures which maintain and further improve our vast ability of sustainable resources and providing a legacy for future generations of space faring astronauts.

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