Chapter VII: Sporadic High LET Radiation

"Radiobiology of Space Radiation"

Jeffrey Jones, M.D.[1], Carlos Montesinos, Ph.D.[2], Fathi Karouia, Ph.D.[3, 8], Dmitri Popov, M.D.[4], Doug Boreham, Ph.D.[5], Octav Cristea, M.D.[6], Joel S. Greenberger, M.D.[7]

1. **Center for Space Medicine and Department of Urology, Baylor College of Medicine, Houston, TX**
2. **Brain Health Education and Research Institute, Potomac, MD**
3. **Department of Pharmaceutical Chemistry, University of California, San Francisco, CA**
4. **Advanced Medical Technologies & Systems, Richmond Hill, Ontario, Canada**
5. **Northern Ontario School of Medicine, Radiation Health / Medical Sciences Division, Sudbury, Ontario, Canada**
6. **Division of Urology, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada**
7. **Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA**
8. **NASA Ames Research Center, Biosciences Division, Moffett Field, CA**

Introduction

What is the scope of this chapter?

A comprehensive discussion of radiobiology cannot exclude the importance of cosmic or space radiation. As discussed in Chapter I by Dr. Valerian Kagan on origins of life on Earth in the midst of ionizing irradiation, the iron core of the Earth and its rotation on its axis creates an electromagnetic field, which directs charged particle radiation to the planet's poles. There has also been greater elucidation, in recent decades, of the ozone layer's protective role in shielding the planet from harmful ultraviolet irradiation. These mechanisms protect life on the planet surface. Were it not for the radio-protective electromagnetic belt around the Earth and the dense atmosphere encasing it, life as we know it on the planet's surface would not exist; alternatively, it may have taken a different evolutionary course, with different radio-resistant life forms arising over the past several billion years.

Thus far, relatively little attention has been directed to solar proton (or particle) events (SPEs), which follow the appearance of sun-spots or solar storms. Even less has been said about galactic cosmic radiation (GCR), which is comprised of charged atomic nuclei ranging in mass from protons to the isotopes of iron, carbon, silicon, and other heavy elements, known as HZE particles. These are thought to be the products of supernova events (explosion of stars in distant solar systems and galaxies) and, possibly, active galactic nuclei.

This chapter will focus on the relative importance of SPEs and GCR as they relate to space travel in the modern era, with a principal focus on a potential mission to Mars, during which astronauts will be exposed to radiation outside of the protective environment of the Earth's electromagnetic field. This chapter includes a review of the important data collected from the International Space Station, Space Shuttle, Apollo Program and earlier U.S. and Russian space missions, as well as other data characterizing the radiation exposure of personnel who have spent significant time away from the Earth's surface, including airline pilots. It will also include a discussion of the possible strategies that can be employed to protect space crews from radiation and its biological effects.

This chapter will rely on reference to other sections in the textbook. Readers should first review chapters on high LET (linear energy transfer) radiation, which includes particle radiation relevant to the radiobiology of space radiation; principally, protons and Fe^{56} charged ion particles. Readers should also review Chapter V on the topic of basic radiobiology, which includes discussions of high LET radiation, the effects of oxygen in radiation induced biological damage, clonogenic radiation survival curves, and the very important concept of relative biological effect (RBE). RBE between SPEs, GCR, and conventional therapeutic x-rays remains a significant subject of controversy among senior scientists in radiobiology, thus complicating attempts to extrapolate data derived from exposure to photon-based radiation (x-rays, gamma rays) to the space flight environment.

Understanding Space Radiation

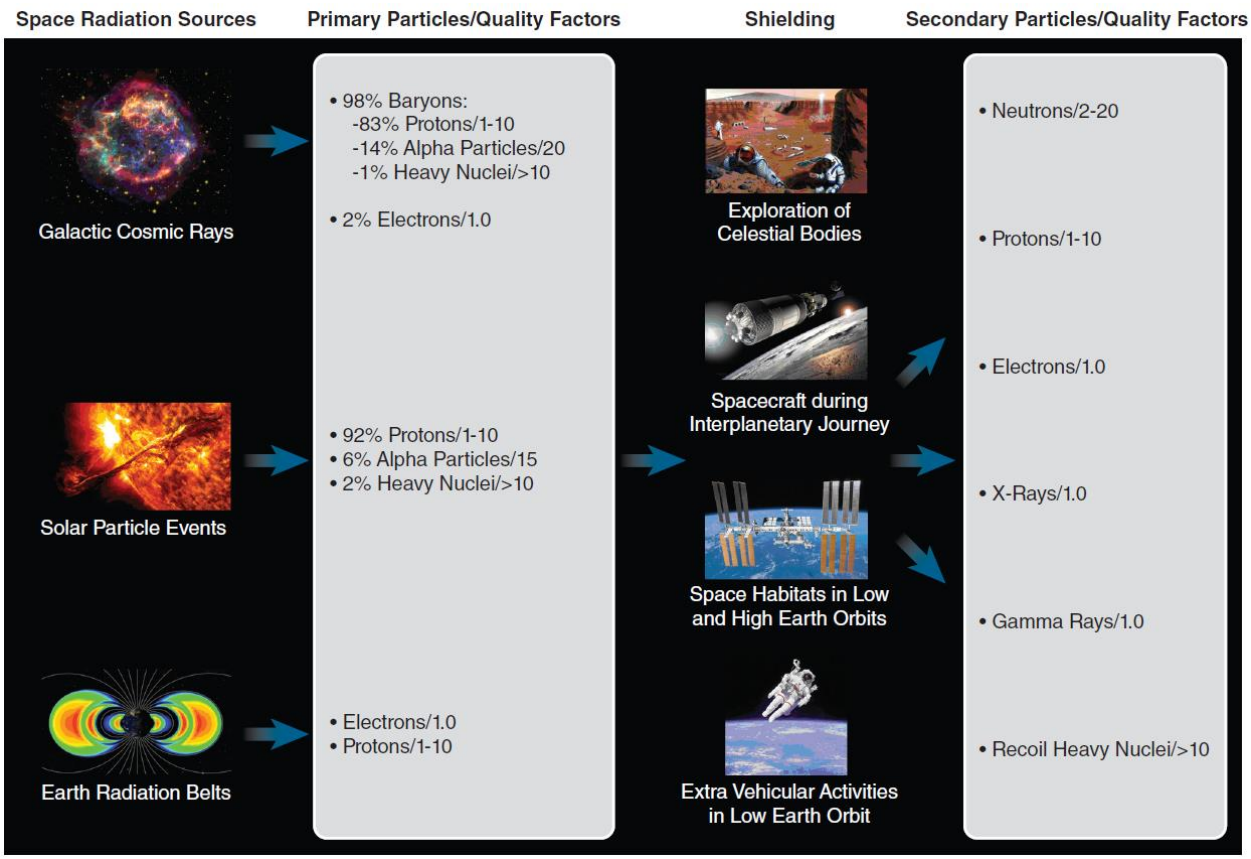
What is Space Radiation?

From the time of the first orbiting satellites, manned missions, and the medical management of personnel during long duration spaceflight, data has been carefully collected and analyzed. It is noteworthy that, at the time of this chapter's writing, the first United States astronaut to orbit the earth, John Glenn, has only recently passed away. Since the time of the first U.S. manned missions by Alan Shepherd and John Glenn, the exposure of humans to the space radiation environment has increased from mere minutes at the dawn of the space age, to missions that have now lasted close to a year. Data has been collected in low earth orbit and inter-planetary space by use of several dosimetry-measuring devices. (Readers should refer to Chapter XXXII by Dr. Ke Sheng, Ph.D. to learn more about dosimeters and how measurements are made.) It has become clear that understanding the complexity of space radiation involves not only the need to measure several different types of radiation, but also the need to understand the very unusual and unpredictable nature of sporadic exposures.

Space irradiation is defined as the radiation experienced by a particular target volume, which may include: satellites, unmanned spacecraft, or biologic entities in space irradiation experiments, including bacteria, non-human primates, and, of course, humans within space vehicles or performing extra-vehicular activities (EVAs). These exposures occur during the complex space flight environment whose conditions are characterized by microgravity, alongside other factors that vary from those found on the surface of the earth. Two very important concepts have emerged from data obtained from measurements of radiation events in space:

1. The quality and quantity of space radiation is far from uniform, with many particle types playing a role. These include gamma rays, protons, alpha particles, and heavy nuclei, all of which can be encountered at a broad range of energy levels.
2. Exposure to certain radiation events is sporadic and unpredictable, with variable time between events. The dose rate of each event also varies based on the complex quality of radiation experienced. For example, gamma rays from a SPE precede proton events in the SPE; GCR events may be widely different with respect to the diversity, energy, and spectrum of the charged particles experienced.

Figure 1: The three principal sources of space radiation and their characteristics
(Source: Jones et al. 2018 [1])



Space Radiation Dosimeters and Dosimetry

How is Space Radiation Measured?

The most recent and important quantitation of space radiation has come from instruments aboard the Mars Curiosity rover. During this mission, an unmanned space vehicle left the Earth's atmosphere, traveled to Mars, established a circular Martian orbit, and landed a mobile mechanized rover on the surface. Throughout all of these activities, radiation exposure was measured. The reported total radiation exposure was 1 Gy. This dose, however, does not represent the expected dose during a manned mission. The measurements obtained during the trip to Mars, in orbit, and on the Martian surface were combined to calculate total radiation exposure. For a manned Mars mission, however, it is expected that the outbound trip to Mars would last 6 months, with a 6-month return and a total of 6 months spent on the surface for a total 1.5 Earth years. Estimates of total expected exposure therefore range from 1 – 2 Sieverts (roughly 1 – 2 Gy, correcting for estimated RBE of the various radiation types encountered). While these numbers, taken at face value, might not be considered excessive, the radiobiologic interpretation of these measurements brings into focus many areas of interest and concern.

The measuring device on the spacecraft traveling to Mars used physical radiation measuring techniques, including physical dosimeters, film dosimetry, ionization chambers, and other conventional measuring tools. The quality and type of radiation may not have been recorded, however, including the relative contributions of protons, and type and distribution of HZE particles. The sporadic nature, dose rate, and frequency of irradiation may also have been incompletely recorded. Measures of radiation exposure on the Martian surface present another potential conundrum. Having no iron core and therefore no electromagnetic shielding, the atmospheric protection from direct charged particle radiation on the surface of Mars would be far lower than that on Earth. Only the physical geography and geology of the planet (e.g. mountains, hills, and craters) would shield against SPEs and GCR. While it is known that the radiation dose and risks to astronauts during the trip to and from Mars could be determined, the overall dose was calculated using only existing physical dosimetric equipment. Biologic conversion of this dose has not been measured with the study of organisms in real time. Furthermore, precise information as to the timing of events, dose rate, time between events, and the quality of the radiation during each event (i.e. proportion of protons, gamma rays, and charged particles) is incomplete.

Table 1. Typical Spaceflight-Related Radiation Exposures
(Source: Jones et al. 2018 [1])

Event or Limit	Radiation Dose Level
Skin dose aboard the ISS during solar maximum	0.5 mSv / day
Skin dose aboard the ISS during solar minimum	1 mSv / day
Space Shuttle Average mission skin dose	~4.3 mSv / mission
Exposure during EVA with excessive South Atlantic Anomaly passes	4.5 mSv / event
Skin dose to a Space Shuttle crewmember during the October 1989 SPE (no magnetic storm, no EVA)	10 mSv / event
Apollo 14 (Highest Skin Dose)	14 mSv / mission
Dose estimated during the October 1989 magnetic storm, from crew dosimeters aboard Mir	30 mSv / event
Skylab 4 (Highest Skin Dose)	178 mSv / mission
Exposure limit for U.S. astronaut in any 1-month period Skin exposure during an EVA during a radiation	250 mSv / month 400 mSv / event belt enhancement
Annual exposure limit for U.S. astronauts	500 mSv / year

Values indicate approximate dose to the blood-forming organs unless otherwise noted.
Abbreviation: ISS, International Space Station; SPE, solar particle event; EVA, extravehicular activity.

Table 2: GCR dose estimates during a mission to Mars
(Source: Zeitlin et al., 2013 [2])

GCR flux Model	Pions/included in transport	Dose rate (*m*Gy/day)	Dose equivalent rate (mSv/day)	<Q>
Badhwar-O'Neill 1996	No	0.429	1.69	3.95
	Yes	0.507	1.70	3.53
Badhwar-O'Neill 2011	No	0.366	1.72	4.69
	Yes	0.445	1.80	4.05
RAD measurement		0.481+ 0.080	1.84+ 0.33	3.82 + 0.25

Table 3: Large SPEs during Solar Cycles 19 through 23 Corresponding to $\Phi_{30} > 10^9$ protons/cm^2
(Source: Wu et al., 2009 [3])

Solar Cycle	SPE	Φ_{30} > (protons/cm^2)
19	11/12/1960	9.00×10^9
20	08/02/1972	5.00×10^9
22	10/19/1989	4.23×10^9
23	07/14/2000	3.74×10^9
23	10/26/2003	3.25×10^9
23	11/04/2001	2.92×10^9
19	07/10/1959	2.30×10^9
23	11/08/2000	2.27×10^9
22	03/23/1991	1.74×10^9
22	08/12/1989	1.51×10^9
22	09/29/1989	1.35×10^9
23	01/16/2005	1.04×10^9
19	02/23/1956	1.00×10^9

Radiobiology of High vs Low LET Radiation

What are the Biologic Consequences of Space Radiation?

Some information has been obtained from long-term follow-up of returning astronauts who have completed missions on the Space Shuttle, International Space Station, or other low-Earth orbit spacecraft. Radiation effects have been studied with respect to those known to be associated with proton or high-LET particle total body exposure of experimental animals on Earth. As previously indicated, a major question of ongoing research and investigation is that of relative biological effect (RBE).

Despite many decades of research, a consensus about the RBE of protons and other charged particles has not yet been established. Radiation biologists usually consider the RBE of protons to be somewhere between 1.5 and 2. Thus, 2 Gy of radiation from gamma rays or linear

accelerator generated photons would be equivalent to 1 Gy of protons. If one normalizes the two measurements to a similar dose rate delivering either gamma rays or protons, the data would be comparable. There would be a difference, however, if one beam delivered a higher dose rate, and this would clearly affect the RBE measurement. Information on gamma rays and x-rays reveals a clear dose rate effect. A higher dose rate produces more radiobiologic damage (defined as nuclear DNA double strand breaks, radiation-induced apoptosis of cells, damage to tissues, organs, and organ systems). The volume effect is also clearly relevant and is independent of RBE. With respect to human radiobiology, this refers to the relative percent of surface area and volume of the human body that is exposed. Partial body irradiation, whether from protons, high LET charged particles, or x-rays/gamma rays, is less damaging than total body exposure. A larger volume of exposed tissue will produce more clinically significant side effects than a smaller volume. The clinical sequelae are also determined by the type of tissue affected (e.g. blood forming organs, gastrointestinal tract, etc.)

Volume experiments can be carried out in laboratories with experimental animals (rodents, guinea pigs, hamsters, rabbits, pigs, dogs, and non-human primates), and standardization can be achieved by precisely controlling the radiation beam (i.e. energy and composition), dose rate, and volume of the tissue being irradiated.

The controversy over the precise RBE of protons is minor compared to the controversy concerning high-LET particles from GCR. There is great interest in Iron 59 (Fe^{59}) charged particles, which are a significant component of galactic cosmic radiation (GCR). Here, the controversy regarding RBE derives from the observation that the RBE may differ for each of several tissue types, and may also differ with respect to the event being studied. In the pioneering work of investigators at Brookhaven National Laboratories, Colorado State University, National Aeronautics and Space Administration (NASA), and the Armed Forces Radiobiologic Institute (AFRRI), the RBE of Fe^{59} has been calculated to range from 2 – 20, depending on the model system being studied. Study outcomes have ranged from the lethality of total body irradiation in rodents to the study of lethal esophagitis in single fraction partially irradiated mice [4]. Models of radiation-induced carcinogenesis have also been studied, with one example, among many, evaluating the Fe^{59} induction of leukemia compared to liver tumors in CBA mice [5]. Efforts are under way to develop more advanced models and Earth-based analogs to simulate the complex space radiation environment.

Clinical Effects of Acute and Chronic Radiation Exposure

A comprehensive discussion of all clinical consequences of radiation exposure is beyond the scope of this chapter. In this section, we will summarize the known effects associated with acute and chronic radiation exposure with emphasis on exposures relevant to the spaceflight environment.

The majority of our knowledge regarding the biological consequences of radiation is derived from four sources: the detonation of nuclear weapons, occupational and industrial exposures, medical treatments, and animal experiments & cell cultures. The effects of radiation can be classified as acute or chronic, and can be further subdivided into deterministic effects (i.e. where

outcomes occur predictably as a function of radiation dose) and stochastic effects (i.e. where the outcomes are probabilistic in nature following exposure).

In the spaceflight environment, an acute radiation exposure event would likely take the form of a whole body exposure secondary to a SPE. The largest SPE recorded occurred on August 4, 1972; during peak intensity, the dose equivalent behind 2 g/cm^2 of aluminum shielding is estimated to have been 1.5 Sv/hour [6]. Symptoms of acute total body radiation exposure are generally predictable and dose-dependent, and can be categorized into three distinct syndromes: hematopoietic, gastro-intestinal and central nervous system (CNS), as outlined in Table 4.

Table 4. Selected features of acute radiation syndromes after whole-body exposure
(Source: Jones et al. 2018 [1])

Principal cause of death (latency period)	Lethal dose range, Gy	Underlying cellular event	Characteristic signs and symptoms prodromal phase	Principal phase
Hematopoietic (2–3 weeks)	2.5–10	Necrosis of bone marrow cells	Anorexia, nausea, vomiting	Petechia and purpura, bleeding from mucous membranes, infection
Gastrointestinal (3–7 days)	10–50	Necrosis and mitotic arrest of mucosal stem cells	Anorexia, nausea, vomiting	Fever, bloody diarrhea, loss of fluids and electrolytes
Acute incapacitation (15 min–3 h)	50+	Unknown; perhaps direct injury of endothelial cells, death of neurons and vasculitis at very high doses	Anorexia, nausea, vomiting, confusion, ataxia, anxiety	Apathy, lethargy. somnolence, tremors, convulsions, coma

Chronic effects of radiation exposure can be both deterministic and stochastic. Generally, chronic effects can be divided into three broad categories of interest: radiation induced malignancy, central nervous system effects, and other degenerative effects.

Radiation induced carcinogenesis is a well-established phenomenon, with most epidemiologic data having been derived from accidental and therapeutic radiation exposures. Cancers observed after exposure to radiation include leukemias, as well as solid organ cancers, such as those of the breast, lung, gastro-intestinal tract and others. The latency period between exposure and cancer development can range from years to decades and the risk depends on overall dose. Table 5 details the excess risk of cancer incidence and mortality due to an exposure of 0.1 Sv over a period of 1 year. As outlined in greater detail in the next section, career exposure limits for astronauts aim to contain the long-term risk of malignancy to an acceptable level.

Table 5 Estimated Excess Cancer Incidence and Mortality, in Percent, after an Exposure to 0.1 Sv over a Period of 1 Year.
(Source: Jones et al. 2018 [1])

	----------Mortality----------			----------Morbidity----------		
	Solid Tumors	Leukemia	All Cancers	Solid Tumors	Leukemia	All Cancers
Age at exposure						
35 years						
Male	0.19	0.0666	0.26	0.39	0.044	0.44
Female	0.34	0.023	0.36	0.71	0.031	0.74
45 Years						
Male	0.13	0.039	0.17	0.21	0.049	0.26
Female	0.24	0.032	0.27	0.60	0.061	0.66
55 Years						
Male	0.10	0.028	0.13	0.16	0.041	0.20
Female	0.16	0.021	0.18	0.38	0.03	0.41

Risks to women are higher because of breast and ovarian cancer and higher incidence of lung cancer. (MODIFIED FROM NCRP, 1997).

With very few exceptions, the exposures upon which such figures are based have been photon based (x-rays, gamma-rays). Human data for exposure to proton and heavy ion radiation is limited and extrapolation from animal models is challenging. Legitimate concerns have been raised about the increased carcinogenic potential of particle radiation. Animal models have demonstrated a higher rate of solid tumor induction with exposure to HZE particle radiation, with tumor aggressiveness influenced by both particle energy and type [5,7]. As previously discussed, the RBE of particle radiation remains an area of ongoing investigation and controversy. The nature of the radiation environment beyond low-Earth orbit raises the concerning possibility that risk extrapolation from terrestrial photon-based exposures may be problematic, and that the clinical consequences of exposure to the deep space radiation environment may prove to be more significant than anticipated.

In addition to the risk of malignancy, concerns have been raised about the effects of space radiation on the central nervous system (CNS) of astronauts. It has been estimated that during inter-planetary spaceflight, a proton will traverse every CNS nucleus every 3 days, and that 46% of hippocampal neurons will be hit by at least 1 HZE particle over the course of a 3-year Mars mission at solar minimum [8,9]. Multiple animal models of have demonstrated significant changes in behavioral and cognitive function, as well as neuronal structure, after exposure to proton or HZE radiation [10-14]. Other degenerative effects are well known and include cataract

formation, cardiovascular disease and pulmonary fibrotic changes, among others. Table 6 highlights radiation related non-cancer related deaths in the cohort of the atomic bomb survivors included in the lifespan study.

Table 6 – Estimates of Excess Relative Risk per Sievert for Non-cancer related deaths from Life-span Study of the Atomic Bomb Survivors. Life-Span Study Cause-Specific, Nan-cancer Disease ERR Estimates 1968-1997
(Source: Huff et al. 2009 [15])

Cause	ERR per Sv	Deaths[a]	Estimated number of radiation-associated deaths
All non-cancer diseases (0–139, 240–279, 290–799)	0.14 (0.08; 0.2)[b]	14,459	273 (176; 375)[b]
Heart disease (390–429)	0.17 (0.08; 0.26)	4,477	101 (47; 161)
Stroke (430–438)	0.12 (0.02; 0.22)	3,954	64 (14; 118)
Respiratory disease (640–519)	0.18 (0.06; 0.32)	2,266	57 (19; 98)
Pneumonia (480–487)	0.16 (0.00; 0.32)	1,528	33 (4; 67)
Digestive disease (520–579)	0.15 (0.00; 0.32)	1,292	27 (0; 58)
Cirrhosis (571)	0.19 (–0.05; 0.5)	567	16 (–2; 37)
Infectious disease (000–139)	–0.02 (< –0.2; 0.25)	397	–1 (–14; 15)
Tuberculosis (010–018)	–0.01 (< –0.2; 0.4)	237	–0.5 (–2; 13)
Other diseases[c] (240–279; 319–389; 580–799)	0.08 (–0.04; 0.23)	2,073	24 (–12; 64)
Urinary diseases (589–629)	0.25 (–0.01; 0.6)	515	17 (–1; 39)

[a]Deaths among potential survivors between 1968 and 1997; [b]90% C.I.; [c]Excluding diseases of the blood and BFOs.

The human gut microbiota has evolved closely with the human race over the millennia, providing functional activities not encoded by the human genome and allowing its host to derive energy from otherwise inaccessible substrates locked into plant structural and storage polysaccharides, in addition to mediating many co-metabolic processes [16]. The human gut hosts 100 trillion microorganisms, encompassing hundreds of species. Colonic density of bacterial cells is estimated to be 10^{12} per ml, making the colon one of the most densely populated microbial habitats on Earth. Recent bacterial sequencing analysis revealed that the majority (98% of all species) belong to only four bacterial divisions: Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%) and Actinobacteria (3%), whereas other minor taxonomic divisions are quite diverse [17,18]. The genome size of this microbial organ, collectively named 'microbiome', exceeds the size of the human nuclear genome by two orders of magnitude and provides important biological functions for the host. Recent research has highlighted some key aspects of the mammalian host–gut microbial relationship that could link gut microbiome to human infections and diseases, carcinogenesis, and to behavioral and CNS disorders [19-26]

A murine model that mirrors what is seen in humans has recently demonstrated a direct link between the gut microbiome and the development of colorectal cancer [27]. Specifically, germ-free mice colonized with microbiota from tumor-bearing mice were found to harbor a higher relative abundance of populations associated with tumor formation in conventional animals. Furthermore, several recent studies have demonstated a strong correlation between microbiota, inflammation, and genomic instability [23]. For example, a recent study demonstrated that members of the *Enterobacteriaceae* family are upregulated over 100 fold in the colons of IL-10 knockout mice with colitis compared to wild-type control mice without colitis [28].

Additionally, a functional link between bacterial-mediated inflammation and DNA damage was also revealed by a study of RAG-2 knockout mice infected with *Helicobacter hepaticus* in a specific pathogen-free facility. The immume response following the infection resulted in increased production of cytokines and chemokines, as well as nitric oxide, superoxide and a number of ROS that led to DNA and RNA damage products and culminated in colorectal cancer [29].

Additionally, several lines of evidence show that perturbations in the delicate symbiotic host-microbiota relationship may have serious consequences resulting in various disorders of the brain-gut axis [24]. Germ-free mice studies have indicated consistent decreases in anxiety like behavior during exposure to novel and aversive environments (elevated plus maze, light/dark box, open field) [30, 31], social impairments and increased stereotypical behaviors [32], and impairments in non-spatial and working memory tasks (novel object recognition and spontaneous alternation assessed in the T-maze) [33]. Furthermore, chronic stress has been a common denominator in several GI disorders and a key player in microbiota-brain-axis dysregulation of the stress-related CNS diseases [25, 26, 34-37]. Mechanisms of stress-induced alterations have been associated with the compromise of the epithelial barrier, which result in translocation of pathobionts across the mucosal lining to sites where direct interaction with the immune cells and the enteric nervous system can occur and which leads to pro-inflammatory mediators in circulation and the CNS [38, 39]. Additionally, it has been shown that the microbiome can influence behavior via a non-infectious and possibly non-inflammatory mechanism, due to an ability to produce and recognize neurochemicals [40].

Finally, our group has recently investigated the bacterial composition of the intestine in C57BL/6NTac mice and the types of microbes entering the body at two time points after the $LD_{50/30}$ dose (9.25 and 9.25 Gy) of total body irradiation. Our studies indicated a significant shift in the mouse gut microbial speciation in several bacterial families, some of which are known to produce disease in humans, including abscess formation, bacteremia, sepsis, disseminated toxins and even death. Microbial populations in the blood post exposure were found to be similar to those present in the gut, indicating that the epithelial barrier was compromised [41]. Furthermore, multiple spaceflight and simulated microgravity experiments have shown changes in phenotypic microbial characteristics such as microbial growth, morphology, metabolism, genetic transfer, virulence factors, and susceptibility to antibiotics and other stressors [42, 43].

Based on the different lines of evidence demonstrating the impact of the microbiome on cancer and CNS disorders, our group strongly believes that addressing the impact of radiation on the microbiome is important to the general and systemic assessment of the role of oxidative stress mechanisms in carcinogenesis and neurocognitive deficits.

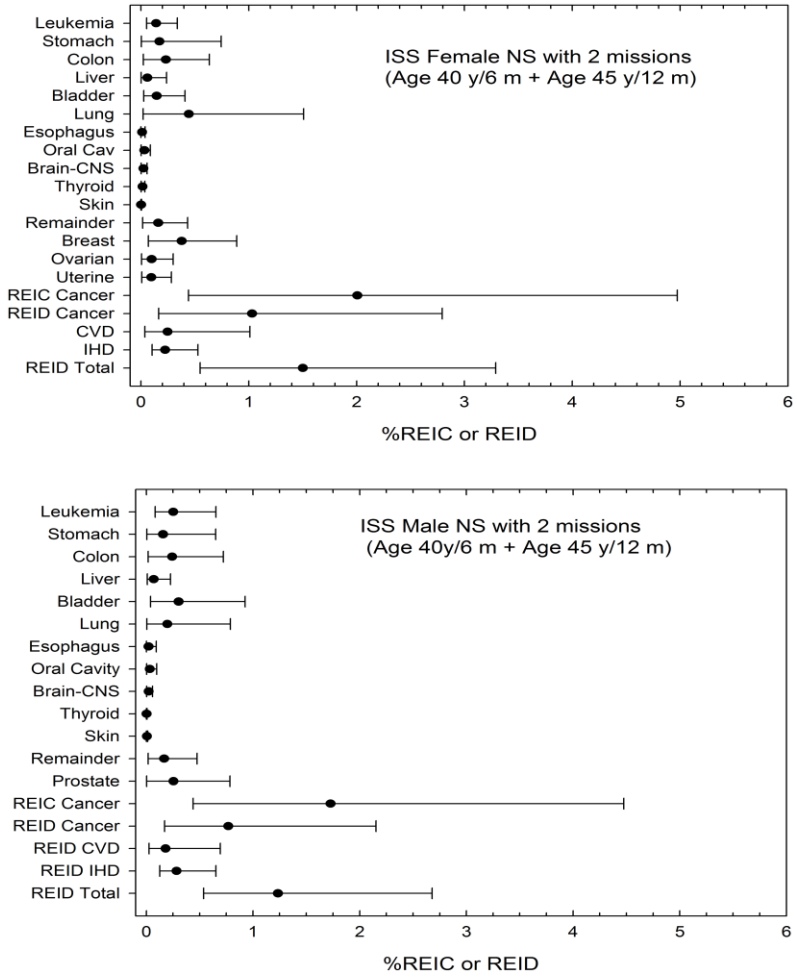
Estimating Radiation Related Health Risks for Astronaut Crews

Taken together, these data highlight the significant potential deleterious effects of radiation exposure in the space flight environment. Such effects can compromise mission outcomes and can affect astronaut health both in the short and long-term, thus emphasizing the need for developing effective radiation protection strategies.

The uncertainties in estimating risks and dose limits for astronauts have been widely recognized, as evidenced by reports from The National Academies of Sciences and The National Research Council. As stated earlier, such uncertainty is largely due to the lack of information regarding the radiobiology of GCR HZE particles, which produce distinct physiological effects from ground-based radiation, such as X-rays or gamma rays, and for which no human data is available. The National Council on Radiation Protection (NCRP) has, as a result, recommended that current methods used for LEO radiation risk assessments are not of sufficient accuracy for long-term exposure to GCR. In response to these recommendations, NASA ultimately developed an approach to estimate the 95% Confidence Level (CL) in cancer risk estimates that was extended to the space radiation exposures. Predictions of tissue-specific Risk of Exposure Induced Death (REID), total cancer REID and the additional REID contributions from cardiovascular disease (CVD) and ischemic heart disease (IHD) are shown in Figure 2 for the case of two ISS missions of 18 month total duration months (6 months for solar median conditions, and 12 months near solar minimum). Central estimates and upper 95% CL of REIC and REID for cancer are slightly reduced (~2%) when CVD and IHD are included in calculations due to the role of competing risks. Risks for females are approximately 20% higher than males due to the added contributions from breast, ovarian, and uterine cancers, and an important difference in lung cancer risks for males and females. Also, organ dose equivalents for females are, when compared to males, larger by a few percentage points due to less body mass. Predictions of CVD and IHD are similar for males and females, non-smokers and U.S. average populations, and increase overall REID by about 40% on average [44].

Figure 2 Predictions of tissue-specific percent Risk of Exposure Induced Cancer (%REIC) or percent Risk of Exposure Induced Death (%REID) for participation in two ISS missions at age

40 and age 45 years (6-months at solar median and 1-year near solar minimum) for Female and Male populations of never-smokers.
(Source: Cucinotta 2014 [45])



Current Radiation Protection Strategies

Exposure Limits

Human beings are naturally exposed to small amounts of background radiation, which originate from their immediate terrestrial environment or, indeed, from the small amounts of space radiation that manages to penetrate the Earth's layers of shielding. Terrestrial sources include air, soil, rocks and water, among others. In the United States, a significant contributor to the overall background radiation dose is radon gas and its decay products, with an overall average background exposure of 3 mSv/year [46].

Individuals in certain occupational settings experience greater exposure to radiation. These include individuals working in certain medical facilities, mining, milling, nuclear facilities or, indeed, astronauts who venture beyond the Earth's protective barriers. The Occupational Safety

and Health administration (OSHA) regulates and sets limits upon occupational radiation exposure; currently, terrestrial workers are limited to a whole-body exposure of 50 mSv/year, while astronauts are limited to 500 mSv/year [46, 47]. The general limits set by OSHA are too restrictive for the spaceflight environment and, as such, unique standards exist for astronauts. Monthly, annual, and career limits are set for crewmembers participating in short or long duration space flight. Deterministic effects of radiation exposure, such as cataract formation, can effectively be prevented by setting appropriate limits. Stochastic effects, however, such as radiation-induced carcinogens, can only be mitigated given that their occurrence is probabilistic in nature. Current career exposure limits for astronauts aim to contain the excess risk of lifetime cancer morality at a maximum of 3% [48].

Table 7 – Dose Limits (in mGy-Eq or mGy) for Non-cancer Radiation Effects
(Source: Wu et al. 2009 [3])

Organ	**30-day limit**	**1-year limit**	**Career**
Lens*	1,000 mGy-Eq	2,000 mGy-Eq	4,000 mGy-Eq
Skin	1,500 mGy-Eq	3,000 mGy-Eq	6,000 mGy-Eq
BFO	250 mGy-Eq	500 mGy-Eq	Not applicable
Heart**	250 mGy-Eq	500 mGy-Eq	1,000 mGy-Eq
CNS***	500 mGy-Eq	1,000 mGy-Eq	1,500 mGy-Eq
CNS*** ($Z \geq 10$)	–	100 mGy	250 mGy

*Lens limits are intended to prevent early (<5 years) severe cataracts (e.g., from an SPE). An additional cataract risk exists
at lower doses from cosmic rays for subclinical cataracts, which may progress to severe types after long latency (>5 years)
and are not preventable by existing mitigation measures; they are deemed an acceptable risk to the program, however.
**Heart doses calculated as average over heart muscle and adjacent arteries.
***CNS limits should be calculated at the hippocampus.
BFO: Blood-forming Organs; CNS: Central Nervous System

Exposure Reduction

Broadly speaking, there are two main protective strategies that can be employed in the setting of ionizing radiation: i) reducing exposure and ii) mitigating the effects of exposure that cannot be avoided or further reduced. In this section we will briefly explore the first of these strategies, while the latter will be dealt with in more detail below.

Radiation exposure can be minimized in one of three ways: i) increasing the distance between the subject and the radiation source, ii) minimizing the time of exposure, and iii) using shielding material to block the radiation. All three of these strategies are used to good effect by terrestrial radiation workers; however, their use in the space-flight environment is more complicated.

Increasing the distance between the crew and the source of radiation is not always a feasible proposition. The solar system is bathed in a relatively isotropic bath of GCRs (although, as previously noted, GCR flux is inversely related to solar activity); SPEs originate from the sun, the distance to which is modifiable to some extent depending on orbital trajectory choice.

In the context of current technology, the choice of orbital trajectory is the most important factor in determining overall exposure time. For a crewed mission to Mars, two basic types of trajectories exist: conjunction and opposition. Conjunction trajectories, which benefit from alignment between the Earth and Mars for both outbound and return legs, have generally been favored due to the fact that they minimize transit times, propellant requirements, and allow for a long-duration stay on the Martian surface. Opposition trajectories, by contrast, would require greater total energy expenditure and would result in less time spent on the Martian surface; however, they would allow for a significant reduction in overall mission time [49]. It should be noted, however, that this reduction would come at the cost of increased transit time and may, depending on the return trajectory chosen, increase the risk form SPEs.

The use of shielding material to block radiation is the most commonly used means of protection for terrestrial radiation workers. In principle, shielding can attenuate the intensity of the incident radiation, change its properties, or both. The effectiveness of shielding depends on both the thickness and composition of the material being used. In the terrestrial setting, shielding against low-LET radiation is fairly easy to achieve by using thick and dense material, such as lead, which readily absorbs photon radiation. In contrast, shielding against high-LET radiation, such as GCR and SPEs, poses a significantly greater challenge. Some degree of protection can be achieved by using small amounts shielding; however, the effectiveness of shielding begins to decline as material thickness or density increases. This is due to the production of secondary particles caused by interactions between the incident radiation beam and the atoms within the shielding material [47]. Such secondary radiation may be more biologically harmful than the original incident beam [50]. Heavier elements, such as aluminum, will produce more secondary radiation than lighter elements such as hydrogen, with shielding effectiveness per unit mass being highest for hydrogen and decreasing as a function of increasing atomic number [51, 52]. While liquid hydrogen is impractical for use as a shielding material, other low-density hydrogen rich materials, such as polyethylene, have been employed in spacecraft shielding and are currently used to line the sleeping quarters of the ISS [53]. Even optimum shielding, however, can reduce effective GCR dose by no more than 35% [54]. As such, other forms of countermeasures will have to be deployed when radiation exposure cannot be avoided altogether.

Countermeasures (Radioprotectors, Radiomitigators, Radiomodulators)

When exposure cannot be avoided or further minimized, pharmacologic agents may be used to mitigate the biologic effects of ionizing radiation. There are many ways to categorize such agents, but one useful framework for classification is as follows: radio-modulators, radio-protectors and radio-mitigators [55].

Radio-modulators serve to increase the baseline radiation resistance of an organism's tissues and are therefore administered in a prophylactic manner. A common family of agents is the anti-oxidants, whose protective effects against radiation-induced biologic damage have been demonstrated in cell cultures as well as in animal models [56]. Exogenous dietary antioxidants

such as N-acetyl cysteine, plant flavonoids, carotenoids, etc., are particularly attractive. These agents may be combined in controlled dosages to ameliorate radiation injury by targeting multiple cellular pathways of radiation damage, thus potentiating their protective effect, while diminishing the risk of side effects associated with high-dose single agents [57]. These formulas may be administered as individual prophylactic doses or may, potentially, be incorporated directly into astronaut diets. A chemo-protective diet may have additional benefits beyond radiation protection alone by potentially mitigating oxidative stress from other environmental exposures.

Radio-protectors are agents that serve to temporarily increase the body's ability to tolerate radiation exposure and are therefore administered immediately before an expected exposure event. The principal mechanism of action for such agents is direct protection of cellular components and/or the neutralization of free radicals. Amifostine (WR-2721) represents one such agent and it is, at present, the only one approved by the FDA for specific use in radiation exposure – specifically, for the prevention of radiation induced mucositis. A number of other agents, however, are currently in various phases of FDA approval [58].

Radio-mitigators are a final class of compounds that serve to prevent radiation related complications and to facilitate healing once an exposure event has occurred. This includes, in the broadest sense, all supportive measures for the irradiated individual such as blood product replacement and intra-venous fluid administration, as well as more specific therapies such as antibiotics, steroids, and growth factors, as appropriate.

Figure 3 – Brief diagramatic representation of radiation injury and the mode of action of radiation countermeasures at advanced stages of development. This simplified response pathway of a subject's irradiation shows that radiation exposure induces free radicals, DNA breaks, and apoptosis. The various radiation countermeasures reduced the injurious effects of irraditiation

through different pathways as indicated by colored arrows. Only the drugs with well-understood mechanism of action are included and may have been indicated at multiple points, as several drugs work through several pathways. Red arrows indicate inhibition of deleterious effects of radiation injury and green arows indicate enhancement of recovery.
GI: gastrointestinal; MPC: myeloid progenitor cell
(Source: Singh et al. 2014 [59])

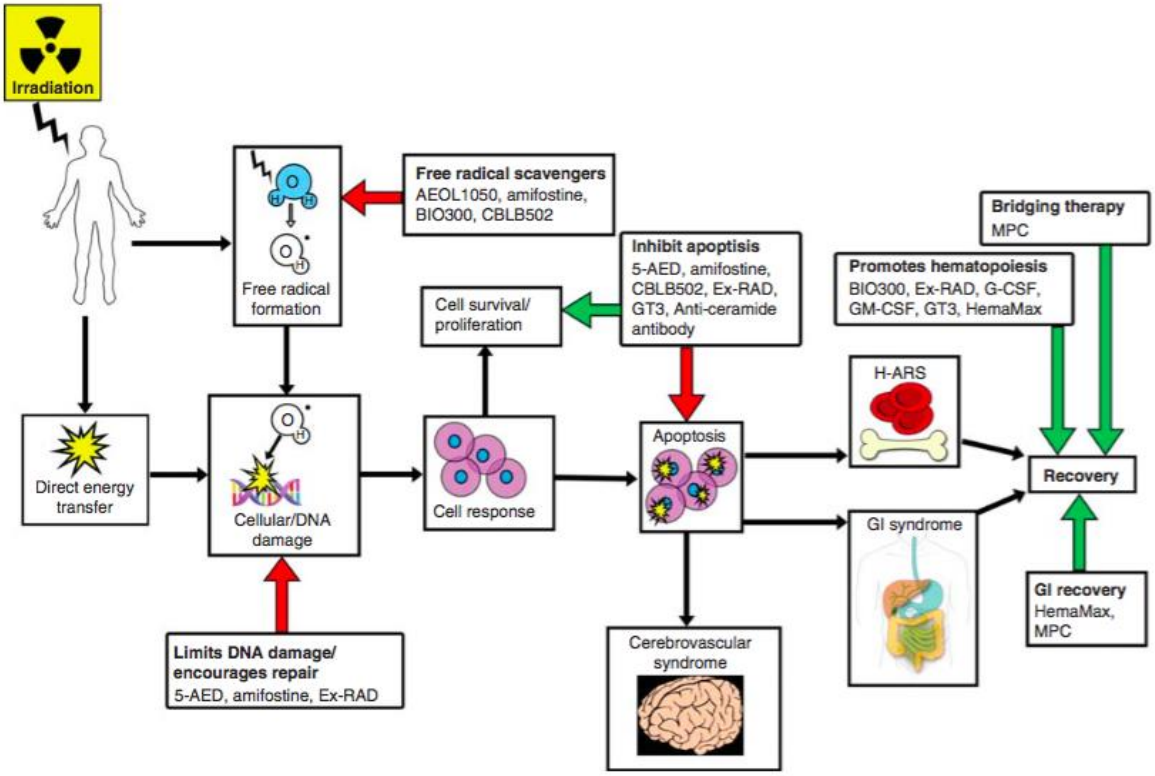
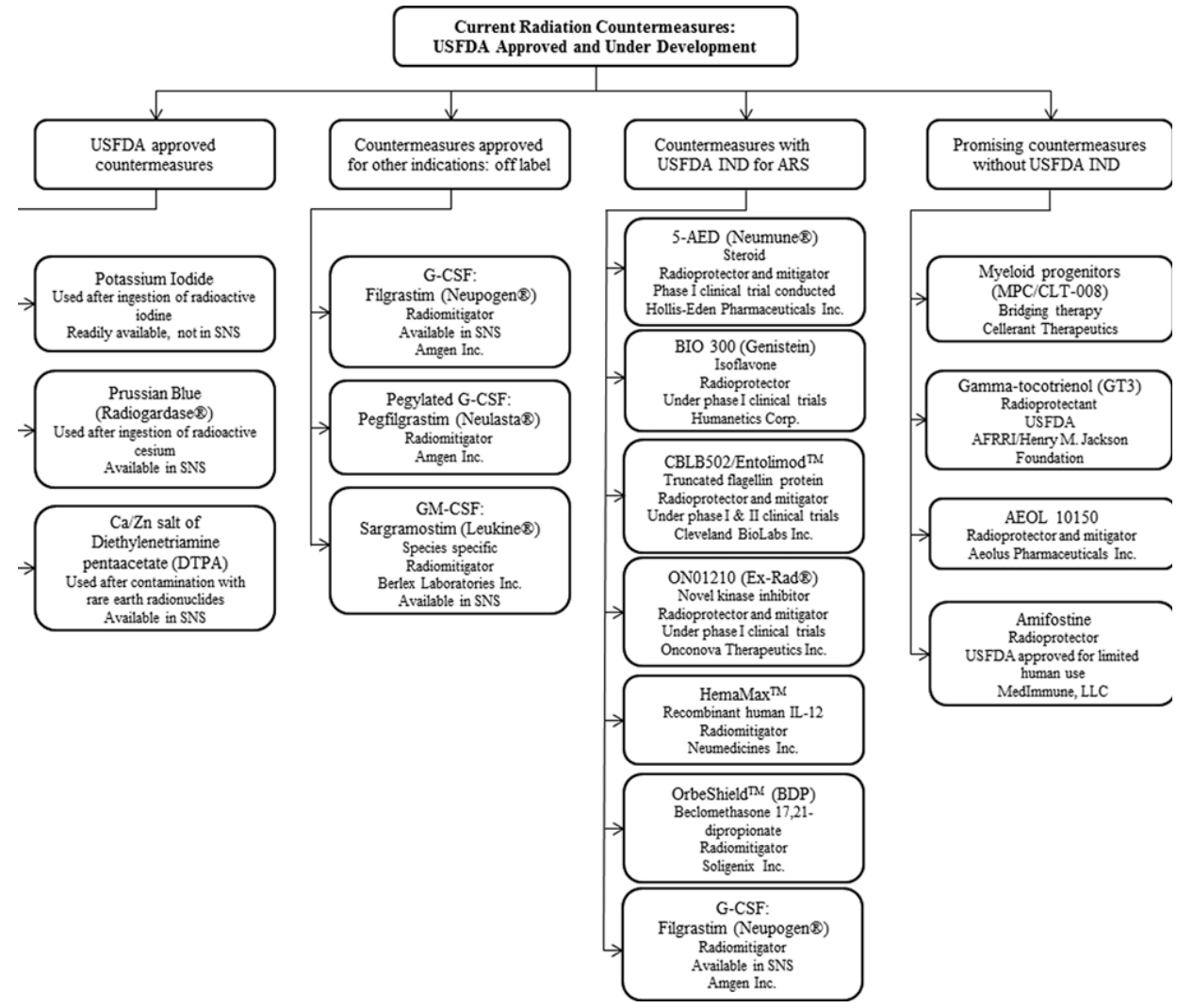


Figure 4 – Current list of potential radiation countermeasures, approved and under development (Source: Singh et al. 2014 [59])



Applying Medical Countermeasures to Ameliorate the Effects of Space Radiation

NASA has expressed serious concern regarding the potential deleterious effects of space radiation, particularly in the setting of long-duration missions outside of the Earth's protective magnetosphere. A manned Mars mission will result in significant sporadic and unpredictable exposure of the spacecraft and its occupants to high LET radiation from both SPEs and GCR.

As previously discussed, one proposed strategy for limiting crew exposure is to shield the spacecraft. Shielding against protons can be achieved with relatively inexpensive materials. However, the weight of such materials might be impractical for the construction of a space vehicle. In contrast, shielding against the high LET particles of GCR would be more complex, and particle transmission through the composite materials in the space vehicle would alter the characteristics of the beam. Irradiation of astronauts within a space vehicle might consist of multiple isotopes of multiple atoms, some of which would be absorbed or dismutated by the materials in the spacecraft, resulting in secondary radiation or a "dirty beam". This concept suggests that attempts to measure the effects of a single high LET particle beam on Earth in the experimental rodent, pig, dog, or monkey models might not be translatable to a situation where multiple isotopes of multiple atoms constitute the beam. The potential modulating effects of the microgravity environment further complicate this picture. NASA has proposed experimental conditions in which to test complex radiation beams in the microgravity environment, but these experiments cannot duplicate the sporadic, unpredictable, and complex dose rate exposures of periodic SPEs and GCR events during long duration interplanetary spaceflight. Nevertheless, as briefly outlined, it is still possible to formulate a set of radiation countermeasures, which may also have practical applications for the management of other complications related to space flight, such bone loss and oxidative stress caused by microgravity, as well as psychological stress from prolonged isolation in an enclosed environment.

Dietary alteration or supplementation for astronauts may be a simple initial step via which to provide radiation protection. Recent experiments have demonstrated that antioxidant/chemopreventive diet models can extend longevity and reduce both acute and late side effects of ionizing radiation, including carcinogenesis and CNS-related sequelae [60-63]. While these original experiments were carried out with photon beam radiation on rodent models, the principles appear sound and have been confirmed by several research groups. Dietary supplements designed to increase antioxidant stores in cells and tissues of astronauts could provide radiation protection. The role of changes in the intestinal microbiome [23, 24, 27] as a result of exposure to radiation, microgravity and other factors in the spaceflight environment remains an area of active investigation, as outlined earlier in the chapter. The role of diet for the purposes of engineering the microbiome remains largely unknown and unexplored, but this may represent a future hypothetical target for radio-protective efforts.

One radiation protector and mitigator drug (MMS350) has been shown to be water-soluble and easily administered in rodent models [64]. Daily liquid supplementation with MMS350 is expected to raise baseline antioxidant stores and provide a significant radiation countermeasure. Readers should refer to Chapter XIV on radiation countermeasures and antioxidants for further details.

Increasing levels of cell and tissue glutathione and endogenous levels of antioxidant enzymes including Manganese Superoxide Dismutase (SOD2), Catalase, and Glutathione Peroxidase (GPX) – principally mitochondrial GPX4 – would be expected to increase radiation resistance. Recent studies have demonstrated that DNA double-strand breaks caused by ionizing irradiation can be decreased by elevating levels of the antioxidant enzyme: MnSOD [4].

It is important to consider that elevation of antioxidants above baseline – secondary to dietary and small molecule dietary supplements – may be counteracted by down-regulation of other radiation protective mechanisms. Such a phenomenon has been observed in transgenic mice overexpressing MnSOD or other radiation protective enzymes [65-67]. This counter-balancing technique of cells and tissues may not completely negate the benefits of supplementation, but down-regulation of other DNA repair mechanisms may dampen some of the efforts to protect against SPEs and GCR.

Radiation exposure from SPEs may occur in the presence or absence of high LET particles from GCR. There is no known "warning system" for detection of GCR although GCR intensity does fluctuate predictably with solar activity and is lower when solar activity is high. A method for predicting SPEs, however, does exist. Gamma ray bursts are detected on Earth and precede proton SPE associated with solar storms (sunspots). One approach to astronaut radioprotection is to administer a radio-protective drug acutely, in addition to baseline antioxidant diet/supplements, in the event of an imminent SPE. Such an event would be detected in the form of gamma ray bursts by observers on Earth, who could then transmit a warning to the crew aboard an inter-planetary spacecraft. The GS-nitroxide, JP4-039, a radiation protector and mitigator drug [68] that targets the mitochondria and minimizes radiation-induced apoptosis, could be administered by Epi-pen intradermal/intramuscular injections prior to the SPE, thus elevating blood levels and preparing organs and tissues for the radiation exposure event. Experimental models to test this hypothesis exist; however, they currently deliver acute countermeasures to experimental animals in the setting of an already elevated baseline of antioxidant stores, beyond what is achieved with dietary measures.

Would Administration of Acute Radiation Countermeasures Alter Late Radiation Effects?

A major concern about space radiation is the spectrum and magnitude of late radiation effects in returning astronauts. Data is available from flight attendants [69], radiation workers [70, 71], and other terrestrial sources [72]. There also exists significant information regarding certain late radiation effects in the astronaut population. Cataracts, secondary tumors, neurodegenerative diseases, and accelerated aging have all been studied in the cohort of over 100 returning astronauts over the past several decades. In female astronauts, there is concern regarding a potential increase in the incidence of breast cancer; an increased incidence of colorectal cancers has been raised as a concern in in both male and female astronauts. An equally important concern is that of the potentially increased risk of neurodegenerative diseases, as well as early onset Alzheimer's and other forms of dementia. Experimental models have demonstrated the deleterious effect of modest doses of high LET radiation on a panel of neurocognitive tests in a rat model [73]. Several experimental model systems are evaluating the hypothesis that prolonged administration of radiation countermeasures may decrease these late radiation effects

[56, 74, 75]. Further studies with large animal models are required to fully test these countermeasures.

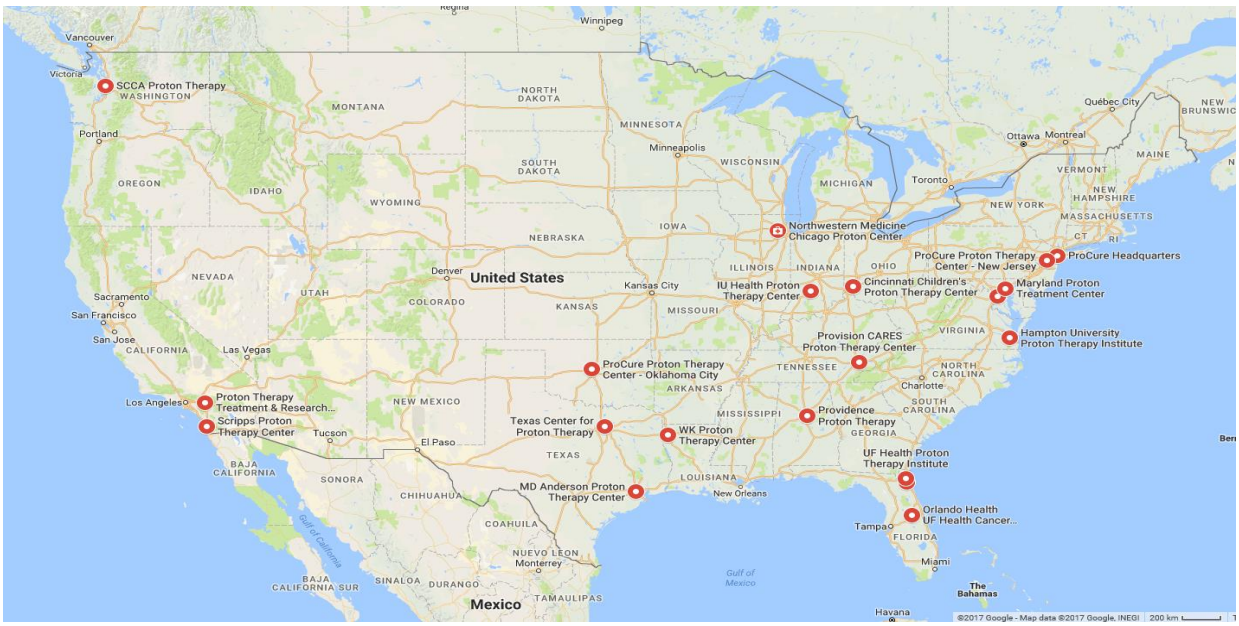
Methods for Studying the Effect of Radiation Countermeasures on Space Radiation

The methodologies for experiments evaluating radiation countermeasures against SPEs and GCR are complex. Brookhaven National Laboratories are currently recognized as the most technologically advanced facility in which to duplicate the complex "dirty beam" of GCR. Proton irradiation facilities are available in 20 medical centers throughout the United States. Proton beam radiotherapy has become potentially important as an option for patients with a wide variety of cancers. In 2015, there were 3500 patients who received proton radiotherapy, approximately 2000 of which were treated for prostate cancer. Proton facilities are available throughout the United States (Figure 5), and investigators wishing to carry out animal experiments using proton beam have the option of collaboration with one of these medical centers. The cost of using the proton beam may be prohibitive, however, and careful planning and utilization are paramount.

In addition, a new neutron beam laboratory at Colorado State University was recently established in Fort Collins, CO, with support from a NASA grant. The facility is intended to mimic the long-term, low-dose-rate exposures to highly energetic radiation that astronauts would encounter on a multi-year space mission that extends beyond the protective geo-magnetosphere.

The above mentioned facilties allow for irradiation of rodent models with complex beams, sporadic proton exposure, and sporadic high LET particle radiation and, while any given model may be imperfect, these efforts can ultimately shed more light on the radiobiliogy of these forms of radiation. The experimental methods for use of proton beam and mixed high LET particle beam at Brookhaven National Laboratories are available online [76, 77].

Figure 5 – Proton Therapy Centers in the United States
(Source: Google Maps)



Radiation Experiments in the Microgravity Environment

Complex radiation experiments in the microgravity environment are more difficult to plan and control. Since the early days of space exploration, the study of the combined effects of radiation and microgravity have been a topic of interest by the scientific community. Many experiments either conducted in space or on the ground have been carried to elucidate the potential synergistic effects of radiation and microgravity and was recently reviewed [78]. Space flight investigations started during the Gemini era (1961-1966) and are still ongoing onboard the ISS [79, 80]. However, access to space is sparse and infrequent therefore several ground based platforms have been developed to simulate the effects of microgravity. One analogue experimental model is the "hind limb elevation" model. In these studies, one hind limb in the rodent is kept elevated to simulate weightlessness. However, this model is obviated by the fact that the rest of the animal is experiencing gravity, and studies of the bone marrow stem cell populations in the elevated limb are complicated by the fact that circulating stem cells repopulate the elevated limb from the general circulation. Similarly, most of the ground based cell biology looking at the biological effects of radiation and microgravity have been based on the use of the Rotating Wall Vessel developed by NASA or similar variation such as 2D and 3D clinostats [81]. Despite several lines of evidence evaluating DNA damage and oxidative stress induced by exposure to the low dose and dose rate radiation environment of LEO, results from ground based platforms and space flights evaluating the combined effect of radiation and microgravity on repair processes have been conflicting [78]. While several investigations have reported increased sensitivity to radiation and decreased DNA repair under simulated microgravity, most of space flight studies, using different models, have shown no effects of spaceflight on the cell's repair mechanisms. In some instances, investigations that studying same endpoints have demonstrated opposing correlations. Therefore, more studies conducted in space are needed. The use of a 1-g centrifuge could alleviate some of the conflicting findings and resolve the potential concern of synergistic effects of microgravity and radiation. Ground based analogs for microgravity are shown to produce some but not all biological effects induced by space environment. Nevertheless, some techniques are available to carry out the above studies and, while imperfect, they are likely to yield useful results and insights.

Conclusions

Space radiation is characterized by trapped particles in the Van Allen belts, solar source energetic protons and ionizing wave radiation, and high-LET, relativistic speed heavy ion galactic cosmic radiation. This represents a unique exposure for astronauts and a considerable challenge for radiation safety officers. Beyond primary space vehicle system failures, space radiation may ultimately prove to be the greatest long-term health risk associated with exploration class space travel. The full spectrum of biological effects associated with radiation of this quality and type remains uncertain. To date, the number of space travelers and their exposure duration, especially beyond low earth orbit, have unfortunately been too limited to yield sufficient statistical power to define the epidemiological risk of exposure to space radiation. Strategies to reduce risk include: 1) exposure reduction ALARA via shielding, EVA limitations during space weather conditions, and rapid interplanetary transit; 2) acute exposure measures, such as confining the crew to storm shelter, acute pharmacologic countermeasures and anti-prodromal effect agents; 3) chronic exposure measures, such as mission design, prophylaxis via

nutrients and nutraceuticals, and 4) post-exposure rehabilitation. Ongoing research is needed to better understand the radiobiological effects of space radiation, the effectiveness and safety of countermeasure agents against space radiation, and the epidemiology of chronic diseases in astronauts exposed to space radiation. The authors feel that the ongoing work to understand and mitigate the effects of space radiation is an exciting and mission-enabling effort that may prove to be a critical element in allowing the space frontier beyond LEO to be opened up for human exploration.

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