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Radiation Hazards and the Colonization of Mars

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Abstract

If human history is a guide, exploration missions to Mars will likely be followed by a continuously occupied base and eventual colonization. However, the harsh radiation environment in space will have to be reckoned with. The annual dose in interplanetary space from galactic cosmic radiation (GCR) is about 0.73 Sv during solar minimum and 0.28 Sv during solar maximum. On the surface of Mars, without significant added shielding, the annual dose is reduced to about 0.33 Sv and 0.08 Sv during solar minimum and maximum, respectively. Such high radiation doses are unsustainable for long-duration habitation and will require considerable shielding. Radiation from solar particle events (SPE) can be very intense, but is easier to shield. For perspective, we have grouped radiation health effects into those that may have a threshold (i.e., a dose below which no effect will occur) and those that are not believed to exhibit a threshold. Threshold effects should be prevented if at all possible and non-threshold effects should be reduced to an acceptable level of risk. For adults, the available data suggest effective threshold for serious health effects in the 0.5-Sv range for high dose rate x rays or gamma rays. These data may be useful to estimate the thresholds for GCR protons, which have similar biological effectiveness as gamma rays. However, they cannot be used to estimate the thresholds for high linear energy transfer (LET) heavy ions. That will require new data from radiobiology and a better understanding of how to extrapolate those data to humans. For long-term habitation on Mars, possible in utero exposures must be considered. Serious health effects from radiation exposures in utero can occur at substantially lower doses than in adults. The threshold (or effective threshold) for developmental abnormalities in the fetus during major organogenesis appears to be about 0.1 Sv acute gamma rays. Again, information is not available from high LET radiation for these effects in humans hence estimating a threshold dose for the high-LET component of GCR would have substantial uncertainty at this time. The critical health effect (most radiosensitive) for human colonization of Mars may turn out to be infertility in women resulting from radiation exposure in utero. Although direct human data are not available for this effect, studies in non-human primates have found that oocytes are extremely radiosensitive during gestation, i.e., 50% killed following only 0.07 Sv of chronic tritium beta rays (similar in biological effectiveness to x rays and GCR protons). This would imply that the threshold for early onset of infertility (menopause) could possibly be in the 0.05 Sv range. Protecting the fetus on Mars should be possible using

available regolith for shielding material, but it would be difficult to achieve the shielding required to protect the fetus during transit. New technologies in shielding and propulsion would be required for the transit of pregnant women and children. Various countermeasure approaches are discussed as well as the need for non-invasive biomarkers to assess risk susceptibility. Finally, an interesting question is whether Phobos can be used as a shielded base near Mars; there may be substantial natural shielding in Stickney crater (perhaps more than 90% reduction in GCR) due to its position relative to Mars.

1. INTRODUCTION

Since the dawn of human evolution on the African continent, our history on Earth has been one of migration and colonization. As people outgrew their place of birth, they set forth to find opportunities in new lands. On a million-year time scale, we have finally colonized the entire Earth. In the not too distant past it was expected that the family remaining behind may never see their loved ones again when they sailed off to America. In less than 100 years, technology has made possible low cost rapid transportation between continents so that what used to require months now requires only hours. So too, will our journey into the cosmos be made increasingly accessible through technological advances. It should be expected as a matter of natural progression that as we outgrew our birthplace we will eventually outgrow our birth planet. Colonization of space is inevitable--just a matter of time. The first colony is likely to be on Mars because of its proximity to Earth and its climate.

Analogous to the early explorers on Earth, the pioneers making the first journeys to Mars and its vicinity to explore and setup a base that eventually will lead to a continuously occupied colony, will face more hazards than those that follow. In addition to the many things that can potentially go awry during such pioneering missions, exposure to space radiation, which is about 500 times greater in space than here on Earth, must be minimized to the extent possible and its effects on human health must be better understood. In this paper, we describe the space radiation environment, the principal health hazards associated with exposure to space radiation, and the implications for human colonization of Mars.

2. A CHALLENGING SPACE RADIATION ENVIRONMENT

The radiation environment in space is complex. It includes charged particles primarily from hydrogen to iron and a myriad of secondary radiations including neutrons produced by charged-particle interactions with materials (e.g., spacecraft, planetary surface, Mars atmosphere, base structures, and even the astronauts themselves). For longer duration missions, the major contributor to dose in deep space or on the surface of Mars is galactic cosmic radiation (GCR). GCR is composed of mostly very penetrating protons (primarily in the hundreds of MeV to many GeV range) and heavier nuclei from He to Fe (Simpson 1983; O"Neil 2006). Due to their high energies, these radiations are very difficult to shield against as seen in Fig. 1 in which we also show data from a large solar particle event (SPE).

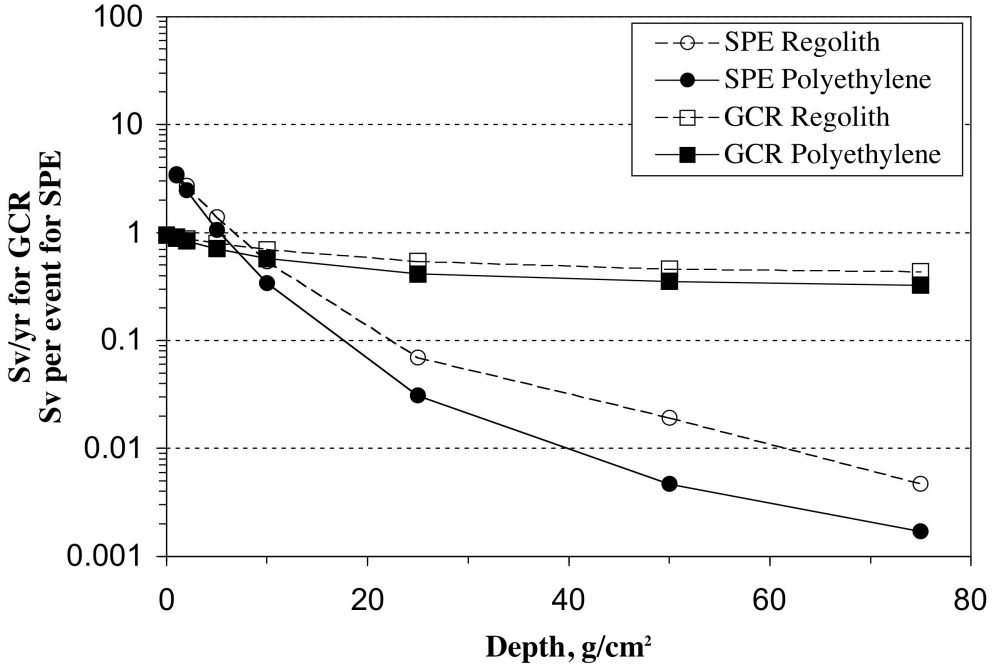

Figure 1. Calculated dose-equivalent to blood forming organs (BFO) as a function of thickness of regolith and polyethylene for galactic cosmic rays (GCR) and radiation from the August 1972 solar particle event (SPE). Aluminum (not shown) is similar to regolith for both GCR and SPE shielding on a g/cm^2 scale. Calculations are based on free-space at 1 AU. Plotted from data in Wilson et al. 1997.

During periods of high solar activity (an approximately 11-year cycle), the probability for a significant solar particle event (SPE) is elevated. A large SPE can release a very high flux of charged-particle radiation—about 98% consists of protons, which are typically less than 150 MeV. Due to their relatively low energies, SPE radiation can be substantially shielded en route and essentially fully shielded on the surface of Mars. However, extended EVA on the Martian surface will require active monitoring and careful planning to always be within safe distance of a solar storm shelter. Reliable forecasting of SPE is not yet possible.

During periods of low solar activity, the dose from GCR is at its maximum. The dose-equivalent rate to the blood forming organs (BFO) in unshielded interplanetary space from GCR is estimated to be about 0.73 Sv/year and 0.28 Sv/year during solar minimum and solar maximum, respectively (Borggrafe et al. 2009). Inside an aluminum shield of 10 g/cm^2 depth the dose-equivalent rate is reduced somewhat to 0.59 Sv/year during solar minimum and 0.24 Sv/year during solar maximum. The dose-equivalent rate on the surface of Mars is lower than in interplanetary space due to planet self-shielding and some attenuation through the thin Martian CO_2 atmosphere. Estimates of the GCR dose equivalent rates listed in Table 1 for interplanetary space with and without Al shielding, on the surface of Mars assuming 16 g/cm^2 CO_2, and on the surface of Mars with 16 g/cm^2 CO_2 plus an additional 20 g/cm^2 regolith were generated using the OLTARIS website (Singleterry 2010). Mars surface dose modeling is complicated due to the production of

secondary radiations (e.g., neutrons) in the Martian atmosphere and surface (which is likely to be location specific due to varying elemental composition and density) so these estimates have substantial uncertainty until measurement validation can be performed.

Table 1. GCR dose-equivalent rates for various shielding conditions.

Shielding Condition	GCR Dose Equivalent Rate (Sv/year, solar max)	GCR Dose Equivalent Rate (Sv/year, solar min)
Interplanetary Space	0.21 (0.28)*	1.07 (0.73)
Interplanetary space with 10 g/cm^2 Al	0.20 (0.24)	0.85 (0.59)
Surface of Mars (16 g/cm^2 CO_2)	0.08	0.33
Surface of Mars (16 g/cm^2 CO_2 + 20 g/cm^2 regolith)	0.07	0.26

*Values in parentheses are from Borggrafe et al. 2009, and illustrate variations due to different versions of computer code used for modeling.

Estimates of dose equivalents for a large SPE are listed in Table 2 for various shielding scenarios. These estimates are based on the October 1989 SPE. It is observed that a very large dose could be received if EVA in interplanetary space during a large SPE. Such a dose would produce severe skin damage and likely be lethal (see Section 3 for a discussion on doses required to produce acute health effects). However, as can be seen in Table 2 (generated using the OLTARIS website, Singleterry 2010), shielding is highly effective for SPE radiation due to the modest energies of the particles. On the surface of Mars doses would be well below those required to produce acute radiation sickness even in a large event such as the one modeled here.

Table 2. Dose equivalent from the October 1989 SPE under various shielding conditions.

Shielding Condition	Event-Integrated Dose Equivalent October 1989 SPE (Sv)
Interplanetary space plus 0.4 g/cm^2 polyethylene (spacesuit approximation)	61
Same plus 5 g/cm^2 polyethylene (approximate dose to BFO)	2.4
Dose to BFO inside 10 g/cm^2 aluminum + spacesuit	1.0
EVA on Mars surface (dose to BFO under 16 g/cm^2 CO_2 + spacesuit)	0.1
Mars surface plus regolith shielding (dose to BFO under 16 g/cm^2 CO_2 + 20 g/cm^2 regolith)	0.03

It is expected that colonization of Mars would be a process requiring many phases, each phase having learned from the ones before. To better understand radiation exposure levels, it is possible to employ relatively low-cost precursor missions to Mars prior to human missions. Radiation measurements in Mars orbit have been performed and surface measurements are scheduled to begin in 2012. Radiation measurements were made by the MARIE instrument onboard the Odyssey spacecraft (launched 2001) while orbiting Mars with additional data on neutron doses coming from the HEND instrument (Tretyakov et al. 2009) also onboard Odyssey. The next radiation instrument that will make measurements on Mars will be the Radiation Assessment Detector (RAD) onboard the Mars Science Laboratory (MSL) planned to launch late 2011. The RAD instrument is a combined charged particle and neutron spectrometer. MSL will land on Mars in 2012, and RAD will provide the first radiation measurements on the surface of Mars.

As measurement technologies continue to advance, particularly in the areas of microelectronics and low-power devices, we expect precursor missions to include measurement stations on the surface of Mars in locations under consideration for a base. These stations could characterize the radiation environment during an entire solar cycle and measure the radiation impact of SPEs. There may also be an interest in such a measurement station on Phobos, possibly in Stickney crater, which is on the side of Phobos facing Mars and therefore shielded by both the crater walls and Mars from cosmic radiation. Knowing the radiation environment in locations where human missions may be planned is of critical importance. To obtain such knowledge it is necessary to perform radiation measurements and validate computational models well in advance of a human mission so that adequate protective measures can be designed into the mission.

It is also expected that the transit to/from Mars would be better characterized by both modeling and validation measurements. A significant issue of concern during transit is how radiation exposures will vary as one moves away from 1AU where the vast majority of radiation measurements have been taken (Mars Architecture Steering Group 2009). For example, missions such as short-term Mars with trajectories closer to the Sun and longer transit duration would result in greater chance for large SPE exposures while in the spacecraft as well as greater chance of a SPE at closer proximity to the Sun. GCR doses are also larger for long transit/short stay missions because dose rate is higher in transit than on Mars. From the radiation perspective, the short-stay mission profile could potentially be higher-risk than the long-stay.

The usual method for estimating the solar energetic proton environment for a Mars mission is to use observations made at 1 AU and extrapolate to other radial distances (NCRP 2006). It was assumed in those extrapolations that the proton fluence rate is confined to a magnetic fluence-rate tube, which behaves in a classical manner with radial distance from the Sun (R). Based on such an extrapolation approach, the peak fluence-rate should fall with increasing distance as R^{-3}, and the fluence should fall as R^{-2}. However, the limited experimental data of measuring the same event at different radial distances (Hamilton 1977) find that the best estimate for peak fluence-rate extrapolations for greater than 1 AU is $R^{-3.3}$ with variations from R^{-4} to R^{-3}. For peak fluence rate

extrapolations for less than 1 AU, the best estimate is R^{-3} with variations from R^{-3} to R^{-2} (Feynman and Gabriel 1988).

These generalizations apply only to well-connected solar-flare-associated events (i.e, the near-sun injection events). They do not always apply to the extended interplanetary shock source events (NCRP 2006). Hence, exposure from a large SPE can be 4 to 8 times greater at a distance of 0.5 AU from the Sun with a functional extrapolation of 5.6 times greater for the short stay mission trajectory. Few measurements exist to estimate the energy dependence of SPE radial gradients.

The above extrapolations are based on simplistic assumptions, which may not prove entirely correct and have only been validated by a few proton measurements in the energy range of a few MeV to tens of MeV. Protons in this energy range are stopped by the vehicle hull and do not contribute significantly to astronaut dose. Data are required for proton energies greater than ~150 MeV where the contribution to crew dose is the greatest. Unfortunately, such data are particularly sparse for distances from the Sun most relevant for a Mars mission and the data that are available do not agree (Reames and Ng 1998; Ruzmaikan et al. 2005; Lario et al. 2006; Mewaldt 2006). To help close these gaps in our knowledge of the space radiation environment, appropriate radiation measurement technologies should be onboard precursor missions to provide validation data to improve accuracy of modeling radiation during transit.

3. HEALTH HAZARDS FROM EXPOSURE TO SPACE RADIATION

Background Information. Since the discovery of x-rays by Roentgen in 1895, the health hazards associated with radiation exposure have been studied extensively, perhaps more than any other potentially hazardous agent. An extensive body of radiobiological and epidemiological investigations (e.g., many summarized in NCRP 1989, 1990; NRC 1990, 2000; UNSCEAR 2000; Preston et al. 2003, 2004; NRC 2006a; UNSCEAR 2006) has revealed both the biological effects produced by radiation and the relative effectiveness of various kinds of radiations commonly encountered on Earth (e.g., x rays, gamma rays, beta rays, alpha particles, and neutrons). Observations from these studies show that radiation does not generally produce new types of health effects (some acute radiation syndromes are exceptions), but rather increases the frequency in a dose-dependent manner of certain kinds of diseases and abnormalities already present in populations. These include various kinds of cancers, genetic effects in offspring, diminished fertility, cataracts, effects on the cardiovascular system, various developmental abnormalities if exposures occur in utero, and central nervous system effects. These are the radiation-induced health effects of concern from exposure to space radiation as well and therefore the available data serve as a necessary but insufficient basis for radiation risk assessment in space. The unique properties of space radiations, particularly heavy ions, require caution when extrapolating health risks from x rays and gamma rays.

Typical dose-response relationships are seen in Fig. 2 for low and high linear energy transfer (LET) radiation, i.e., a measure of the density of ionization produced by the radiation, usually expressed in units of keV/μm. Low LET radiations include x rays,

gamma rays, and protons from GCR and SPE. High LET radiations include neutrons and heavy nuclei in GCR.

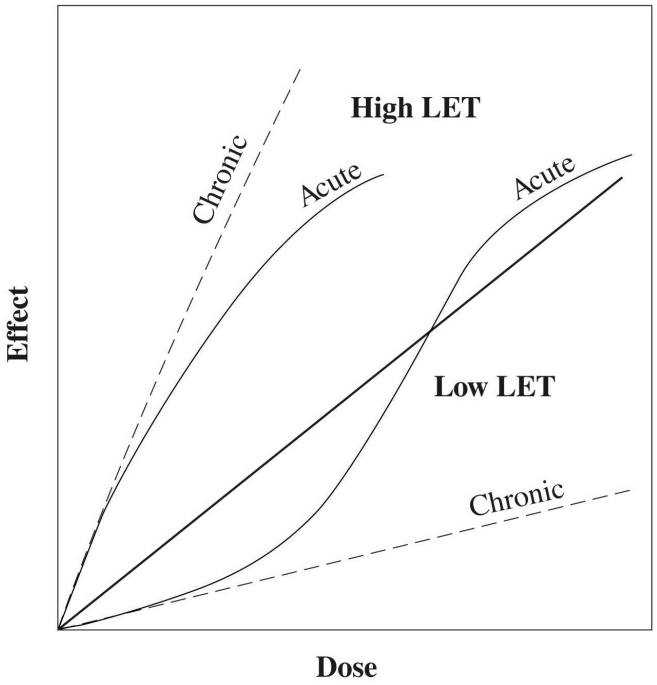

Figure 2. Curves representing dose-response relationships for carcinogenesis and mutagenesis effects in the range 0 to about 3 Gy of whole-body absorbed dose. The high LET curves are for neutrons and heavy ions and the low LET curves are for gamma rays, x rays, and high-energy protons. The solid curves are for single acute (high dose rate) exposures and the dashed curves are for chronic (low dose rate) exposures. The solid straight line is a linear fit to the high dose-rate low LET data, generally referred to as linear-no-threshold (LNT). Modified from Straume and Carsten 1993.

Shapes of dose response curves have been observed to vary substantially for different health effects and different LET radiations. For example, the best dose-response model for solid cancers in humans exposed to high-dose rate (acute) gamma rays appears to be a linear nothreshold (LNT) model, while for leukemia the best fit appears to be a linearquadratic (L-Q) model (NRC 2006a). Such inter-effect differences in dose response relationships are well known from the experimental animal data. The LNT model is generally employed in setting radiation protection standards on Earth due to computational convenience and the lack of consistent and convincing data for other models.

Because it has been observed for many (perhaps most) biological effects that lower doses and dose rates of low LET radiation tend to produce less biological damage given the same total dose, the risk obtained with the LNT model is generally reduced by a dose and dose-rate effectiveness factor (DDREF) when estimating the risk from low dose rate, low LET radiation exposures. The DDREF values have been observed to range from 2 to 10

in laboratory animal studies (NCRP 1980), but nominal values of 1.5 to 2.5 have generally been employed for human cancer, e.g., the recent BEIR VII report adopted 1.5 (NRC 2006a) and the United Nations Scientific Committee on Atomic Radiation (UNSCEAR) has maintained 2.0 (UNSCEAR 2006). The values for DDREF selected by these committees are largely based on curves fitted to the A-bomb survivor cancer data, and do not include the much larger range of values observed in various experimental animal studies. It is not yet clear what DDREF values are most appropriate for the various radiations in space, although high-energy protons from GCR are likely to be similar to gamma rays. DDREF values appropriate for space radiation requires additional radiobiology studies using suitable radiation sources.

Studies also show that different kinds of radiations can exhibit a broad range of biological effectiveness, i.e., produce different amounts of damage when given equal absorbed dose. The relative biological effectiveness (RBE) of radiations is a useful concept to quantitatively compare the hazard potential of different kinds of radiations. The RBE is defined for a specific radiation (A) as: RBE (A) = dose of reference radiation required to produce a specific level of response divided by dose of radiation (A) required to produce an equal response (NCRP 1990). Typically, the reference radiation is x-rays or gamma rays. In radiation protection, both on Earth and in LEO, the RBE provides the basis for the quality factor (QF), which is multiplied by the absorbed dose to obtain the dose equivalent (DE). The objective of the DE is to provide a "dose" that equalizes risk for all radiations such that 1 Sv of gamma rays produces the same health hazard as 1 Sv of neutrons or 1 Sv of GCR radiation or 1 Sv of SPE radiation. The DE approach simplifies radiation protection management, but, of course, the accuracy of this approach is only as good as the underlying data, e.g., see Straume (1995).

A general pattern has emerged from radiobiology that the RBE varies with LET, dose, dose-rate, and endpoint. For a wide variety of biological endpoints (including tumor induction and genetic effects), RBE tends to increase as the dose and dose rate decreases and as the LET increases. For low LET radiation, the effectiveness tends to decrease with decreasing dose rate (NCRP 1990) and for high LET radiations the effectiveness tends to increase with decreasing dose rate (e.g., Thompson et al. 1981, Hill and Elkind 1982; Ullrich et al. 1984; Alpen et al. 1994; Burns et al. 1994). However, this general pattern has exceptions and limitations. The radiobiology data also show that a wide range of RBE values are observed for different health effects and even for the same effect in different strains of the same species (e.g., NRC 1990). For example, the neutron RBE for mammary tumors was observed to vary by a factor of 5 in three different rat strains (Broerse et al. 1982). Such variations translate into large uncertainties when using radiobiological animal data to estimate radiation-induced health risk for humans.

In addition to large inter-endpoint differences in radiation response observed in biological model systems, more recent research has uncovered some rather vexing radiobiological complexities that may have implications for the assessment of health risks associated with radiation exposure generally, and for Mars colonization in particular. It has been assumed in radiobiology that the detrimental effects of radiation result from radiation-induced damage in the irradiated cells, not in adjacent cells that were not hit by the

radiation. However, numerous studies have now observed so-called "non targeted effects" that challenge this assumption. These include bystander effects, radiation-induced genomic instability, and transgenerational effects of parental irradiation that can manifest in the progeny (e.g., Wiley et al. 1997; Baulch et al. 2001; Morgan 2003a; Morgan 2003b; Dauer et al. 2010).

Radiobiological data are also emerging that show qualitative (not just quantitative) differences at low compared with high doses of radiation (see Dauer et al. 2010 for a recent review). For example, genes and molecular pathways seem to differ in radiation damage response at low and high doses of radiation. Analyses of gene expression profiles of mouse brain tissue after gamma-ray irradiation showed that low-dose exposures (0.1 Sv) induced gene expression not affected by high-dose exposures (2 Sv) and that these genes were associated with unique pathways and functions (Lowe et al. 2009). This suggests that different mechanisms may be involved which could result in different response relationships. Because the human data presently used for assessment of radiation-induced cancer and other health effects are primarily obtained from populations that received acute high dose radiation (e.g., Hiroshima/Nagasaki) extrapolating to the lower doses and dose rates in space may be more uncertain than previously believed.

It is important to note, however, that it is not clear how (or if) these emerging observations at the molecular and cellular levels may influence health outcome. Of course, the available health effects data includes non-targeted effects, just not identified as such previously. Hence, dose-response relationships for cancer, transmitted genetic effects, and other health effects would implicitly include such damage mechanisms and therefore the responses are as measured. The real issue is selecting the correct model to extrapolate to the low doses and dose rates where statistically reliable data cannot be obtained experimentally or epidemiologically. Non-targeted effects can potentially influence dose-response relationships in ways not yet understood making such extrapolation models uncertain.

In addition to the complexities described above, a so called "adaptive response" has been observed in some (but not all) experimental systems when a small dose is followed later (within hours) by a larger dose resulting in substantially less biological damage than if the small pre-dose was not received (Wolff 1996, 1998). This small pre-dose appears to enhance repair mechanisms that reduce the effect from the subsequent large dose (see Dauer et al. 2010 for a recent review). The potential impact of this for space radiation risk assessment should be understood, e.g., would constant low-level GCR radiation enhance repair mechanisms and thus result in lower cancer risk in space than estimated from the A-bomb survivor data? Also, would GCR exposure reduce the acute health effects from a large SPE?

The question as to how one extrapolates from these emerging observations to the risk of radiation-induced adverse health effects generally, and to the risk of human space exploration in particular, remains open and in need of further research.

Acute Effects from Large SPEs. Following large doses received in minutes to hours, acute radiation syndrome (ARS) can result. Depending on dose and dose rate, symptoms may include nausea, vomiting, skin damage, and blood cell depletion resulting in infections and bleeding. Following acute doses substantially larger than those expected during space travel, serious gastrointestinal and central nervous system damage may result leading to death within days or even hours depending on the dose and dose rate received (Young 1987, Anno et al. 1989). ARS is expected to be a risk during EVA only. SPE radiation can be shielded in the transit vehicle and modeling calculations indicate that on the surface of Mars the radiation doses from SPEs are unlikely to be more than about 0.1 Sv (see Table 2) if outside in an EVA spacesuit and only about 0.03 Sv if shielded by 20 g/cm^2 regolith. The threshold for ARS for whole-body penetrating gamma rays is at least 0.5 Sv (Young 1987).

High radiation exposures are possible if astronauts are performing EVA during SPE in interplanetary space, on a moon or an asteroid. The dose received depends very much on the proton energy and fluence characteristics of the particular SPE, and of course the time required to seek shelter. Seen in Fig. 3 are proton energy spectra for several prominent SPEs during the past half-century. It is clear that the energy spectra differ substantially for the various SPEs. An SPE often selected for dose modeling purposes is the August 1972 event. This event had exceptionally large proton fluence between 20 MeV and 150 MeV. Depending on EVA spacesuit design, protons above about 20 MeV can penetrate the spacesuit and those above about 70 MeV can reach the blood forming organs (bone marrow) of the astronauts (Wilson et al. 2006).

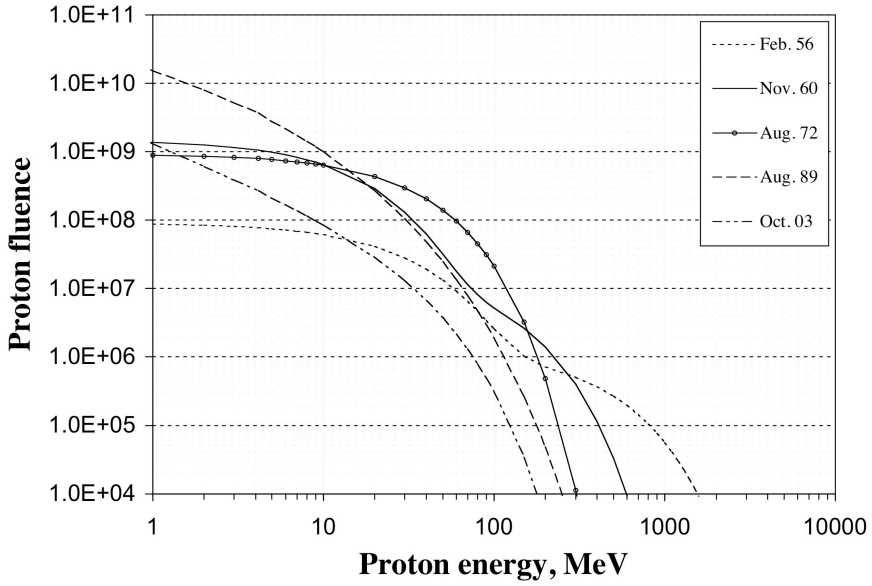

Figure 3. Proton energy spectra for large SPEs. Obtained from the OLTARIS website (Singleterry 2010).

Information on ARS in humans is primarily available from case studies of nuclear accidents, records of patients given total-body radiation therapy for cancer and other

diseases, studies of the survivors of the Hiroshima and Nagasaki atomic bombings, persons accidentally irradiated during a nuclear test in the South Pacific, and Chernobyl. A review and evaluation of those sources of information (Young 1987, Gottlöber et al. 2001) show that about 5% exhibit retching (strong involuntary effort to vomit) 5 to 16 hours following an acute whole-body penetrating dose of 0.5 Sv. This increased to 20% following 1 Sv, 50% following 2 Sv, and 80% following 3.5 Sv. These observations were from high dose rate gamma rays. It is not clear what the thresholds would be for SPE protons, although estimates suggest a DDREF of 4 (Wilson et al. 1999). Based on LET, SPE protons may have similar biological effectiveness to gamma rays. However, the broad spectrum of SPE proton energies would deliver highly non-uniform dose within the body (much higher dose to skin than to bone marrow and other deep organs), which may influence acute responses and their thresholds.

Acute skin response to radiation exposure in humans has been extensively studied following radiotherapy, other medical procedures, and accidents. A whole-body x-ray dose of more than 0.5-1.0 Sv may produce an early erythema reaction (redness of skin) (Conklin and Walker 1987). This early phase will generally subside after 24 to 48 hours. The same dose to a smaller region of the body will also produce erythema but only in the exposed region. Within a few days following 15 to 20 Sv acute x ray exposure of pig skin, a marked reduction has been reported in the mitotic index of basal cells, leading to about 50% depletion within about 20 days (ICRP 1991). Following such large acute doses, dry desquamation may result in 3 to 6 weeks, moist desquamation in 4 to 6 weeks, secondary ulceration after 6 weeks, and dermal necrosis after 10 weeks. The threshold for this more serious late skin reaction is estimated to be in the 5 to 10 Sv range (ICRP 1991). Large doses to skin of whole body (as could potentially be the case during EVA) may result in cutaneous radiation syndrome, which can be fatal (Gottlöber et al. 2001), even if doses to deeper organs are below the threshold. Threshold doses for SPE-type protons are more uncertain due to lack of human data. The dose-response relationships for both early and late radiationinduced damage to skin are significantly influenced by the exposure rate of low-LET radiations. The repair capacity of the dermal tissues is greater than that of the epidermis (ICRP 1991). Hence, we would expect the early response (erythema within about a day) to be reduced more as dose rate is decreased than the late epidermal responses. The DDREF for late epidermal response has been estimated to be about 2 (Wilson et al. 1999).

The available human data are from acute x rays or gamma rays, whereas the SPE radiation would be primarily protons received at a lower, but varying (subacute) dose rate. For comparison, "acute" radiation dose rate is generally defined in radiobiology as 1 Sv/min or 60 Sv/h. The maximum dose rate at 1 AU to skin from the August 1972 SPE was estimated to be 20 Sv/h and a nominal dose rate of about 1 to 2 Sv/h. The maximum dose rate to BFO from this event was only about 0.2 Sv/h (Wilson et al. 2006). Based on the subacute dose rate, and the similar effectiveness of gamma rays and high energy protons observed for many other experimental endpoints, it may be expected that SPE radiation would have effectiveness intermediate between chronic gamma rays and acute x rays. However, there is presently considerable uncertainty in the dose-rate response for SPE protons for these particular endpoints. The dose-rate response for SPE-type protons

may become clearer once results are made available from an ongoing research effort by the Center for Acute Radiation Research supported by the National Space Biomedical Research Institute (NSBRI) at the University of Pennsylvania (Kennedy et al. 2010). Furthermore, there is a substantial difference in dose rate between skin and BFO for the same SPE due to body self-shielding of these low energy protons. It is therefore necessary to consider the dose-rate differences between skin and deeper body organs in SPE risk assessments.

Radiation-Induced Cancer. Cancers induced by radiation appear to be indistinguishable from those arising spontaneously or caused by other carcinogens (although this may not be the case in the future as the field of cancer biomarkers advances). This has limited the assessment of radiation-induced cancer risk to statistical analyses based on large epidemiological studies, which attempt to control for confounding factors such as genetics, cigarette smoke, lifestyle, etc.

Radiation-induced cancer in human populations has been studied extensively for well over half a century and has provided a large amount of data (e.g., NRC 2006a; UNSCEAR 2006). The human database that has provided the majority of whole-body radiation-induced cancer risk estimates is the atomic bomb survivor cohort of Hiroshima and Nagasaki. Cancer data available from human epidemiological studies involve primarily exposures to gamma rays and x rays, which are directly relevant to many Earth-based radiation risk assessments. They do not, however, include high-energy particle radiations such as protons and heavy ions (and their secondary radiations such as neutrons), which are of primary concern in space. Also, the A-bomb survivors were exposed to very high dose rates, whereas Mars colony inhabitants (and those transiting between Earth and Mars) will receive long term, relatively low-dose-rate exposures.

Using available human epidemiological data, the National Academy Committee on the Biological Effects of Ionizing Radiation (NRC 2006a) provided their best estimates of the radiation-induced cancer risk coefficient from low LET, low-dose exposure in a human population. They assumed that a population of 100,000 persons with an age distribution similar to that of the U.S. population was exposed to a dose of 0.1 Sv. They provided mean estimates and 95% confidence intervals for solid cancer and leukemia for both males and females, which accounted for uncertainties in statistical variation, in the extrapolation from high dose and high dose rate to low dose and low dose rate, and the uncertainty in transporting from Japanese Abomb survivors to the U.S. population. They did not include uncertainties in the A-bomb dosimetry, and thus the uncertainties are actually somewhat larger than listed in Table 3. The most recent dosimetry assessment for A-bomb survivors estimated a cohort standard deviation of about 15% of the mean (RERF 2005). Their total lifetime cancer mortality risk coefficients (solid cancer plus leukemia) for low doses of low-LET radiation are 4.8% per Sv for men and 6.6% per Sv for women for a population similar to that of the U.S. The upper 95% confidence limits are about twice the means.

Table 3. Estimates of lifetime cancer risk coefficients for low dose, low-LET radiation of a population similar to that of the U.S. (from NRC 2006a).

	Solid cancer (%/Sv)		Leukemia (%/Sv)	
	Males	Females	Males	Females
Incidence	8.0 (4.0-16.0)	13.0 (6.9-25.0)	1.0 (0.3-3.0)	0.7 (0.2-2.5)
Mortality	4.1 (2.0-8.3)	6.1 (3.0-12.0)	0.7 (0.2-2.2)	0.5 (0.1-1.9)

These observations are compared with results in Table 4 of risk coefficient estimates for Mars missions. Cancer mortality risks have been estimated (Cucinotta et al. 2005) for 600-day Mars mission (600 days transit, 0 days surface) and 1000-day mission (400 days transit, 600 days surface) based on the same human epidemiological data employed in Table 3 (i.e., A-bomb survivors), but in this case, converted to space radiation and an astronaut population. These estimates assume solar minimum, 5 g/cm^2 Al shielding, and that the astronauts are 40 years of age at time of mission.

Table 4. Estimates of space-radiation-induced cancer lifetime risks for selected missions (from Cucinotta et al. 2005).

Mission	Effective dose	Cancer mortality risk, % (95% CI)	
	Sv	Men	Women
Mars orbit (600 d)	1.03	4.0 (1.0-10.5)	4.9 (1.4-16.2)
Mars exploration (1000 d)	1.07	4.2 (1.3-13.6)	5.1 (1.6-16.4)

The following observations are notable: (a) The total radiation doses received during a 600 d and 1000 d mission to Mars are essentially identical. This is because more time is spent in transit during the 600 d mission, which involves the highest radiation dose rates. When on the surface of Mars the astronauts are shielded by both the atmosphere and Mars itself. (b) The upper 95% confidence limits are about 3.3x the means reflecting large uncertainties in these estimates. Comparing uncertainties in Tables 1 and 2 shows that about 2/3 of the uncertainty is from the available human epidemiology data and the remaining 1/3 is from extrapolation to space radiation and an astronaut population. Substantial research efforts are underway (e.g., funded by the NASA Space Radiation Program, as well as space research programs in several countries around the world) to reduce the uncertainties in extrapolation to space, so it is likely that the uncertainty associated with extrapolation to space will be reduced significantly over time. However, the available radiation cancer epidemiology data are unlikely to improve substantially in the foreseeable future, hence we are probably stuck with at least a factor of 2 uncertainty in the cancer risk coefficient unless new approaches can be developed to reliably estimate radiation-induced risk. This would probably require major breakthroughs in personalized risk assessment, perhaps involving risk-specific biomarkers (e.g., see summaries of current biomarker research in Straume et al. 2008).

A particularly important factor influencing the radiation-induced lifetime cancer risk coefficient is age at time of exposure -- the young are at higher risk than the old. This is an important consideration for a permanently occupied base--and subsequent

colonization--of Mars, which could accidentally or intentionally involve pregnancies and childbirth on Mars. The influence of age on radiation-induced cancer risk is seen in Fig. 4, where the total cancer risk coefficient (%/Sv) inferred from the A-bomb data is plotted as a function of age at exposure for a population like that of the U.S. exposed to low dose, low LET radiation (NRC 1990). It is clear that age at exposure is a highly significant factor affecting lifetime cancer risk. Studies of atomic bomb survivors who were exposed either in utero or during the first 5 years of life (Delongchamp et al. 1997, Yoshimoto et al. 1988) suggested that cancer risk estimates in utero were similar to those observed for survivors exposed during the first 5 years of life, which, as seen in Fig. 4, are substantially higher than adults. An unusual aspect of the finding in utero was that 9 of the 10 cancers occurred in females, and significant differences between the sexes persisted even when the three female cancer sites (breast, ovary, and uterus) were excluded. These findings are consistent with girls having higher risk than boys in Fig. 4, but suggest even larger sex differences when exposed in utero. Additional follow-up of the in utero exposed cohort now suggests that their radiation-induced full lifetime cancer risk may actually be lower than that for early childhood exposure, although uncertainties are still quite large (Preston et al. 2008).

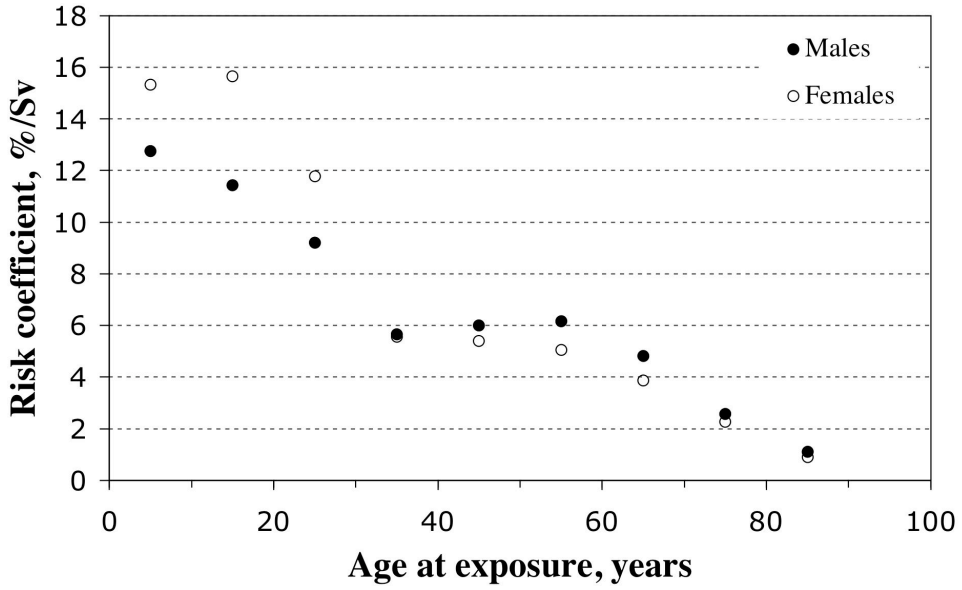

Figure 4. Lifetime cancer mortality risk coefficient as a function of age at exposure in males and females. Plotted from data in NRC 1990 estimated for low dose, low LET radiation exposure.

The approach used by NASA to control risk induced by space radiation is to maintain an estimated upper 95% confidence level below a career limit of 3% excess lifetime cancer mortality risk (NASA 2007). The rationale for such an approach is that the risks for several key health effects have large uncertainties requiring conservative safety standards and also satisfying the principle of as low as reasonably achievable.

Assuming a 3% risk limit, the maximum days in deep space for males and females is estimated as a function of age at exposure. For example, assuming 40-y-old astronaut, 10 g/cm^2 of Al (3.7 cm) shielding, and solar minimum, the maximum time in interplanetary space would be about 180 days (Cucinotta et al. 2005).

The approach of controlling risk using the upper 95% confidence limit places a substantial premium on defining and reducing the uncertainties. Figure 5 illustrates various "what if" assumptions---3% controlled at upper 95th percentile, 3% controlled at mean, and 5% controlled at mean. It is observed that the selection of a risk limit has a large effect on the maximum days permitted in deep space.

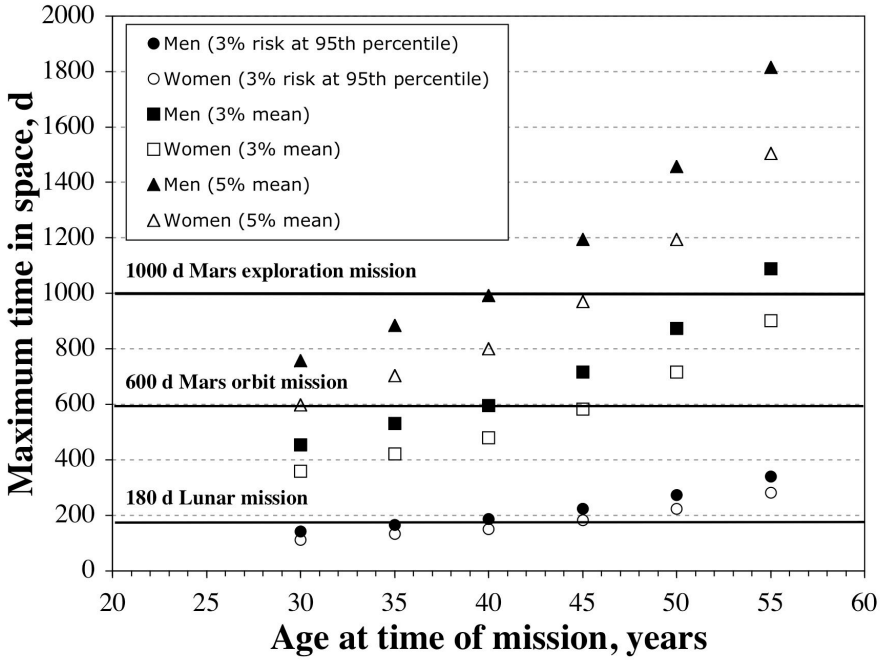

Figure 5. Projections of age-dependent maximum days in deep space for males and females based on "acceptable" risk level for space radiation-induced cancer mortality assuming aluminum shielding of 10 g/cm^2 and solar minimum conditions. The "3% risk at 95th percentile", which is the current standard for LEO (NASA 2007), was plotted from data in Cucinotta et al. 2005, and the others were scaled from those data.

Cataracts. Radiation-protection guidelines have assumed a dose-effect threshold of 5 Gy for vision-impairing cataracts in humans (ICRP 1991). However, recent studies (Chylack et al. 2009, Cucinotta et al. 2001) suggest an increased risk of cataract among astronauts with higher space radiation doses (0.045 Sv average) to the lens of the eye compared to astronauts with lower lens doses (<0.008 Sv average). These data suggest that the relatively low doses of radiation in LEO may be associated with an increased incidence and earlier appearance of cataracts in astronauts. The latest study (Chylack et al. 2009) included 171 astronauts who flew at least one mission in space and the comparison group consisted of 53 astronauts who had not flown in space, 95 military aircrew personnel, and 99 non-aircrew ground-based comparison subjects. Adjustments were made for age,

demographics, smoking, medical history, nutrition, and sun exposure to eyes. The results show that the frequency of cortical cataracts was significantly higher for exposed astronauts than for unexposed astronauts and control subjects of similar ages. An extensive review and summary of the radiation cataract data provided by Blakely et al. (2010) indicates that the threshold for radiation cataractogenesis may be substantially lower than previously believed. The most recent evaluations of A-bomb survivors now provide a threshold range for radiation-induced cataracts from 0 (i.e., no threshold) to 0.8 Gy (Neriishi et al. 2007) and the Chernobyl cleanup worker studies from 0 to 0.7 Gy (Worgul et al. 2007). These results, together with the findings in astronauts receiving average lens dose of only 0.045 Sv, are beginning to provide a rather strong argument for a cataract threshold within the dose range expected for a Mars mission.

Cardiovascular Effects. There is clear evidence that therapeutic doses of radiation can cause harmful effects to the cardiovascular system in humans. It is well established that patients exposed during radiotherapy may develop enhanced plaque formation in arteries in the radiation field and may develop heart disease if the heart is directly exposed (Glanzmann et al. 1998, Darby et al. 2005).

However, more recent evaluations of the A-bomb survivor data (Preston et al. 2003) show statistically significant radiation-induced mortality from heart disease and stroke in the dose range 0.5 Sv to 2.5 Sv. This observation has raised concern that such effects may also occur at lower doses, including doses relevant to long-duration human space travel. Radiation effects at doses below 0.5 Sv were not statistically significant. Given these observations, it is important to better understand the cardiovascular radiation risk and how it may translate to astronaut risk on long-duration missions; particularly the potential combined effects from stress, microgravity, immobility, and continuous long-term exposure to GCR.

Central Nervous System. The adult brain has generally been thought to be insensitive to radiation because of the resistance of neurons to cell killing (Belka et al. 2001). It is well known from radiotherapy that large doses of gamma rays or x rays to the brain can be tolerated. In fact, for over 50 years whole brain radiotherapy (WBRT) has been the standard for palliative treatment for brain metastases. The typical dose regimen is 12 daily fractions of 2.5 Sv each for a total dose of 30 Sv. However, a randomized controlled trial was recently stopped at MD Anderson because it became clear that 30 Sv WBRT was causing detectable impairment in learning and memory function when tested 4 months after treatment (Chang et al. 2009). It appears there is a substantial dose per fraction and dose-rate effect for CNS damage. For example, the dose per fraction appears to be largely responsible for the development of late neurotoxicity (Klein et al. 2002). RT to the brain with doses above 2 Sv per fraction were found to be more detrimental than doses below 2 Sv per fraction. Also, A-bomb survivors who survived acute radiation sickness (and therefore received less than 5 Sv acute gamma rays) showed deficits in memory and intellectual capacity when evaluated 5 years later (CCMDC 1981).

Research using experimental animals has focused on the potential damage to neuronal stem cells and precursor cells, which have been shown to be sensitive to radiation,

including space-type radiation (Rola et al. 2004; Rola et al. 2005; Limoli et al. 2006; Limoli et al. 2007; Mizumatsu et al. 2003; Rabin et al. 2007). For example, Mizumatsu et al. (2003) exposed the whole brains of mice to graded doses of acute x-rays and evaluated hippocampal tissue for apoptosis, numbers of proliferating cells, and immature neurons. They observed that 2 Sv reduced the numbers of proliferating cells by 93%. This is a large effect, suggesting that detectable effects are likely to occur at much lower doses. Furthermore, high LET ^{56}Fe particles have been observed to be highly effective in producing what appears to be an acceleration of Alzheimer's disease-related neurological deficits (Vlkolinsky et al. 2010). Taken together, the concern is that space radiations could potentially interfere with the ability of astronauts to successfully meet mission requirements on a deep space mission.

It is not possible to determine at present whether these observations in experimental animals translate into functional impairments in humans or to mission-relevant human risk. The 50- year history of WBRT shows that the human brain can withstand a fractionated dose 30 times larger than those expected from a Mars mission without serious (albeit detectable) functional impairments, but that dose consists entirely of low LET radiation. What is not known is the effectiveness of high LET radiation in causing damage in the human brain. In particular, it is not known whether the high LET component from GCR, which would be received at low dose rate--but for prolonged periods of time--will produce significant functional impairment such that astronauts would have difficulty with the many complex tasks required during a Mars mission.

Combined Effects. Astronauts on long-duration missions to Mars will experience many stressors simultaneously, e.g., radiation, variable gravity, variable oxygen concentration, long-term confinement, etc. Of particular concern are possible combined (additive or synergistic) effects of radiation and microgravity, e.g., what if space radiation enhances bone loss due to microgravity or prevents subsequent skeletal recovery from microgravity? It is well known that astronauts lose bone mass during long duration, low Earth orbit missions, caused by musculoskeletal disuse in the microgravity environment. Recovery after return to Earth occurs slowly and incompletely and thus bone loss poses a long-term health risk (Lang et al. 2004; Lang et al. 2006). Space radiation exposure outside the protection of Earth's magnetosphere may also cause bone loss, albeit by a different mechanism than microgravity. Pioneering research underway in Dr. Ruth Globus' lab at NASA Ames Research Center shows that radiation exposure may enhance the bone loss effects induced by microgravity alone (Alwood et al. 2010; Kondo et al. 2010; Yumoto et al. 2010). Gamma irradiation of mice causes bone loss similar to changes observed in skeletal diseases associated with oxidative stress (Hamilton et al. 2006; Kondo et al. 2009). The authors hypothesize that increased oxidative stress mediates radiation-induced bone loss (Kondo et al. 2009), and that musculoskeletal disuse causes cancellous tissue to be more sensitive to radiation exposure (Yumoto et al. 2010). Interestingly, treatment with an antioxidant mitigates the damage caused by gamma radiation (Kondo et al. 2009). Furthermore, ^{56}Fe exacerbates the adverse effects of musculoskeletal disuse on osteoprogenitors, which are needed for skeletal recovery from disuse (Yumoto et al. 2010). Thus, the combination of radiation and microgravity may cause greater skeletal damage during and after spaceflight than either would alone.

In-Utero Development. Long-term missions to Mars will require the consideration that pregnancy may occur, unless steps are taken in advance to prevent it. Multi-generation colonization will require healthy pregnancy and childbirth. Substantial data exist on the effects of prenatal radiation exposures in experimental animals and humans. The effects observed include gross structural malformations, growth retardation, embryo lethality, sterility, and central nervous system abnormalities (NRC 1990). The developing central nervous system has been observed to be particularly sensitive to radiation exposure in both experimental animals and humans. The ICRP evaluated the data from animal experiments and concluded that the threshold for radiation-induced developmental effects of the fetus was about 0.1 Gy acute low-LET radiation (ICRP 1991).

The in-utero data from Hiroshima and Nagasaki A-bomb survivors provide particularly relevant information on radiosensitivity in humans as a function of gestational age and dose for several CNS endpoints, including severe mental retardation, head circumference, intelligence test scores, and school performance. It should be kept in mind that these doses were acute gamma rays and the response to chronic GCR radiation may be different.

Severe mental retardation in A-bomb survivors exposed during various gestational ages is seen in Fig. 6 (Otake et al. 1996). It is observed that the incidence of severe mental retardation increased with radiation dose and was greatest for those exposed 8 to 15 weeks of gestation. The incidence was elevated but decreased at 16 to 25 weeks. Prior to 8 weeks and after 25 weeks there was no detectable mental retardation observed.

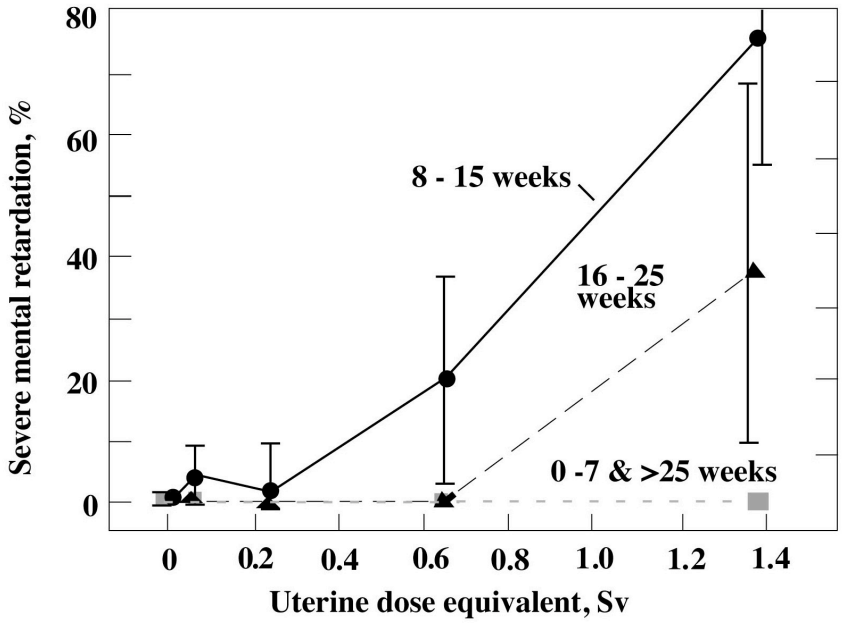

Figure 6. Severe mental retardation detected in children of A-bomb survivors exposed to the bomb radiation during various stages of pregnancy. The error bars are 90% confidence intervals (from Otake et al. 1996; figure kindly provided by Dr. Roy Shore of the Radiation Effects Research Foundation, Hiroshima, Japan).

From these data some important conclusions can be drawn for high dose rate low LET radiation: (1) about 70% of those exposed to a mean dose of 1.38 Sv between 8 and 15 weeks of gestation had severe mental retardation; (2) the estimated threshold for this response is in the range 0.06 to 0.31 Sv (95% confidence interval) based on analyses by Otake et al. 1987, 1996. Although a threshold is suggested, other dose-response relationships are also possible. There are insufficient data to determine how dose rate or high LET radiation would modify this response.

The data from A-bomb survivors exposed in utero during 8 to 15 weeks after conception also show dose-dependent decreases in intelligence quotient (IQ) scores of about 21 to 29 points per Sv (Schull et al. 1988) and the data appear to fit a linear model with no apparent threshold. This was also the case for school performance scores. As cautioned previously, the RBE of high LET radiation for these health effects is not known.

Fertility Effects. The germinal cells of mammals, including humans, exhibit a broad range of radiosensitivity depending on stage of development and degree of maturation and differentiation. In the human male, the seminiferous epithelium of the testis maintains spermatogenesis throughout life, which involves the active proliferation and differentiation of spermatogonial stem cells that sequentially give rise to Type A and Type B spermatogonia spermatocytes, spermatids, and finally sperm. A substantial body of data is available on radiation-induced fertility effects in males. Type A spermatogonia are the most sensitive to radiation. In the human male, temporary infertility is observed after only 0.15-Sv acute xrays (NRC 1990). An acute dose of 3 Sv and chronic or fractionated dose of 5 Sv may result in permanent sterility (UNSCEAR 1982). There seems to be a rather large dose rate effect. For example, dogs exposed indefinitely to about 0.0015 Gy/day of x rays (similar to dose rates expected inside a nominally shielded vehicle in interplanetary space) did not show detectable affects on sperm production (Casarett and Eddy 1968, Fedorova and Markelov 1978). Mice exposed to 4 Gy total gammaray dose at a rate of 0.018 Gy/day showed reduced spermatogenesis after 16 weeks (Fabrikant 1972). This is about 10 times higher dose rate than expected from GCR in interplanetary space.

In contrast to the male, the female is born with her full compliment of germ cells, the oocyte. Oocytes are produced from oogonia in utero and there is no cell division after birth. Oocytes are constantly depleted mostly through natural atresia until the end of reproductive life (menopause). The vast majority (99%+) of the oocytes are in the resting immature stage of development. At any time, only a very small fraction of oocytes are maturing follicles getting ready for ovulation.

Temporary infertility in adult women is observed following 0.65 – 1.5 Sv acute x rays or gamma rays to the ovaries and permanent sterility requires at least 2.5 Sv acute or 6 Sv fractionated or chronic gamma rays (ICRP 1984, NRC 1990). Thus, for this group, we would not expect decreased fertility from exposures to the radiation received during transit to/from Mars or living in a Martian base. However, because immature oocytes in some primates do show extreme radiosensitivity in utero, similar to those seen in juvenile mice (Table 5), the possibility that human females may also have a sensitive prenatal

stage should be given serious consideration. The primate studies showing very high sensitivity in-utero involved exposing the animals continuously to low LET radiation during the second half of pregnancy and therefore did not determine if a narrower window of sensitivity exists within the second half of pregnancy. Such a study should be done in primates to narrow the window of extreme vulnerability.

Experiments have been performed in the mouse using low and high LET radiations, including space-type radiations (Straume et al. 1989a). It was observed that during the most radiosensive stages of these cells, the LD_{50} was 0.05 Gy, 0.07 Gy, and 0.12 Gy, for 450 MeV/n Fe, 570 MeV/n Ar, and 670 MeV/n Si, respectively. The range of RBEs obtained for these radiations was obtained by comparing with chronic gamma rays and is 1.2 – 2.8, the highest being for Fe. These are comparatively low RBEs for these high LET heavy ions. However, similarly low RBEs have also been observed for neutrons in this endpoint (Straume et al. 1987), reflecting the special vulnerability of these cells to killing by low LET radiation. Oocytes are killed by interphase cell death (apoptosis).

Emerging studies suggest that other sensitive cell systems killed via apoptosis, e.g., hippocampal tissue in the mouse brain (Mizumatsu et al. 2003), may also have particularly high sensitivity to low LET radiation. If so, it would be important to test their high-LET radiation response to determine if they also exhibit low RBE. During their most vulnerable stage in the mouse, oocytes are killed nearly equally by low and high-LET radiations. Given that a similar radiosensitive stage has been identified in non-human primates, but in that case prior to birth, it may be reasonable to expect a similar LET dependence as well. If so, protons, high LET particles, and secondary neutrons would have similar biological effectiveness for oocyte killing in utero in non-human primates and perhaps in women.

Table 5. Radiosensitivity of female germ cells.

Species	Radiation	LD_{50} (Gy)	References
Mouse (prenatal)	Gamma rays	1.75	Straume et al. 1987
	Neutrons	0.15	Straume et al. 1987
Mouse (juvenile)	Gamma rays (acute)	0.05	Straume et al. 1987
	Gamma rays (chronic)	0.15	Dobson & Kwan 1977, Dobson et al. 1984
	Neutrons (0.43-15 MeV)	0.038-0.065	Straume et al. 1987
	Si (670 MeV/n)	0.12	Straume et al. 1989a
	Ar (570 MeV/n)	0.07	Straume et al. 1989a
	Fe (450 MeV/n)	0.053	Straume et al. 1989a
Mouse (adult)	Gamma rays	0.12	Dobson et al. 1986
	X rays	0.115	Straume et al. 1989b
	0.43 MeV neutrons	0.056	Straume et al. 1989b
	Fission neutrons	0.095	Straume et al. 1989b
Squirrel monkey (in utero)	^{3}HOH (chronic)	0.07	Dobson et al. 1984, Dobson et al. 1986
Bonnet monkey (in utero)	^{3}HOH (chronic)	0.15	Dobson et al. 1984, Dobson et al. 1986
Rhesus monkey (in utero)	^{3}HOH (chronic)	0.50	Dobson et al. 1984, Dobson et al. 1986
Squirrel monkey (adult)	^{3}HOH (chronic)	2.25	Straume et al. 1989b

Transmitted Genetic Effects. To date there have been no radiation-induced mutations detected in the children of irradiated parents. This has been the case even for the largest and most extensively studied human population, the A-bomb survivors of Hiroshima and Nagasaki. Therefore, only upper-limit radiation-induced mutation frequency estimates are obtainable from human epidemiological studies, i.e., the maximum radiation-induced mutation frequency that would not be detected from the radiation doses received. Such estimates are highly uncertain. Because direct observations of radiation-induced transmitted mutations have not been observed in humans, primary reliance for genetic risk estimation has been on radiation-induced genetic effects obtained from animal experiments, primarily from the mouse (NRC 1990; NRC 2006a). A number of large radiation experiments have been performed using mice to measure genetically transmitted effects from either irradiated male mice mated with nonirradiated females or irradiated females mated with non-irradiated males (Russell 1977; Russell and Kelly 1982). For irradiated male mice, the data provide a genetic doubling dose (DD, the dose that would double the spontaneous mutation frequency) for acute x rays or gamma rays of about 1 Sv. For irradiated female mice, however, the results were more complex. Mutations were observed if mice were mated within 6 weeks of irradiation, but not in mice mated more that 6 weeks after irradiation. Because oocytes require 6 weeks to mature and ovulate, these findings meant that mutations were only seen in maturing oocytes and not in immature oocytes. Subsequent experiments solved this dilemma and substantially strengthened genetic extrapolation from the female mouse to women (Straume et al. 1991). Results indicate that the DD from the female mouse immature oocytes (which make up the genetic pool in both female mice and in women) is consistent with maturing oocytes and the male when the oocyte lethality target (the plasma membrane) is avoided by special dose delivery methods (Straume et al. 1989b, Straume et al. 1991).

After reviewing the radiation genetics data, the radiation protection community has adopted a DD of 1 Sv (ICRP 1991, NRC 2006a, UNSCEAR 2006). A DD of 1 Sv results in a total genetic risk of 0.41 - 0.64%/Sv in the first generation and 0.53-0.91%/Sv in second generation (NRC 2006a). As the number of space farers increase, the genetic risk becomes more important and should be included in the total risk coefficient for stochastic effects. Genetic effects have been shown to exhibit large RBEs for high LET radiations in a variety of experimental systems (e.g., NCRP 1990), so the high LET dose component of GCR and secondary neutrons would likely be substantially more effective in producing genetic damage than the protons.

4. PERSPECTIVES ON THRESHOLDS AND DOSE LIMITATION

The potential radiation-induced health effects associated with extended missions to, and eventual colonization of, Mars have been grouped into two classes: (1) nonstochastic effects--those whose severity is a function of dose and may have a threshold (real or practical) below which radiation may not induce detectable health effects, and (2) stochastic effects--those whose probability of occurrence in an exposed population (rather than severity in an affected individual) depends on dose. Stochastic effects are commonly regarded as having no threshold and therefore may result in health effects proportional to dose at any dose (NRC 2006a).

Nonstochastic effects are listed in Table 6 and should be prevented if at all possible. These include acute radiation syndromes, cataracts, central nervous system effects, effects on development in utero, cardiovascular effects, and impairment of fertility. The effective threshold for serious health effects in adults appears to be in the 0.5 Sv range for acute low LET radiation. These data may be useful to estimate the thresholds for GCR protons, which appear to have similar LET as gamma rays. However, they cannot be used to estimate the thresholds for these effects from high-LET heavy ions or from lower energy SPE protons, which produce very inhomogeneous dose distribution in the human body. That will require new data from radiobiology and a better understanding of how to extrapolate those data to humans.

Table 6. Nonstochastic effects: Estimates of threshold doses for low-LET radiation in humans.

Effect	Dose, Sv	References
Acute Radiation Syndromes:		
Nausea and vomiting	0.5 acute	Young et al. 1987
Early skin reaction	0.5-1 acute	Conklin and Walker 1987
Late skin reaction	5-10 acute	ICRP 1991
Gastrointestinal syndrome	~7 acute	Young et al. 1987
CNS syndrome	~50 acute	Young et al. 1987
Cataracts:		
Detectable opacities Recent emerging data	0.5 acute, 5 fractionated <0.8 (?) acute & chronic	ICRP 1991 Neriishi et al. 2007 Worgul et al. 2007 Chylack et al. 2009 Blakely et al. 2010
Vision impairing opacities	5 acute, >8 fractionated	ICRP 1991
Central Nervous System:		
Adult (cognition)	<30 fractionated, <5 acute	Chang et al. 2009 CCMDC 1981
In utero (severe mental retardation)	~0.15 acute	Otake et al. 1987, 1996
In utero (IQ)	~0.1 acute	Schull et al. 1988 ICRP 1991
Malformations in Fetus:	~0.1 acute	ICRP 1991
Cardiovascular:	~0.5 acute	Preston et al. 2003
Fertility:		
Man temporary infertility Man permanent sterility	0.15 acute 0.4 Sv/year chronic* 3 acute, 5 fractionated 2 Sv/year chronic*	ICRP 1984 NRC 1990 UNSCEAR 1982 ICRP 1991
Woman temporary infertility Woman permanent sterility Woman premature menopause If exposed as adult If exposed *in utero*	0.65 -1.5 acute 2.5 acute, 6 fractionated >0.2 Sv/year chronic* ~0.05 (?) chronic	ICRP 1984 NRC 1990 ICRP 1991 Straume, this paper

*If exposed continuously over many years as would be the case during colonization of Mars.

The following is a summary of non-stochastic effects as they may relate to space radiation exposure:

• Data on acute radiation syndromes are available for low-LET radiations in humans and provide threshold estimates for the various responses. The data show that it is very unlikely to experience any acute radiation effects below 0.5 Sv of acute gamma rays. The most serious skin reactions (late skin reaction, including cutaneous radiation syndrome) require at least 5 Sv high-dose rate low LET radiation. Dose estimates from a large SPE (Table 2) suggest that acute radiation effects are possible if exposed during EVA and in a lightly shielded vehicle (10 g/cm^2 Al), but not on the surface of Mars. Acute radiation effects will not result from GCR radiation.

• It has generally been thought that radiation does not induce vision-impairing cataracts below about 5 Sv of acute low LET radiation (NRC 1990). It is known that small detectable opacities (not vision impairing) may be observed following lower doses (above 0.5 Sv acute and 5 Sv fractionated x rays). New data are emerging that appear to question these thresholds----suggesting vision impairing thresholds in the 0 to 0.8 Sv range, which are much lower than previously believed and could potentially include no threshold. Such doses are likely to be received during early missions to Mars.

• Fifty-year history of whole brain radiotherapy shows that the human brain can withstand large doses of low-LET radiation, especially when doses are given in many fractions. For example, fractionated high-energy x-ray doses of 2.5 Sv per day for 12 days (total of 30 Sv) are routinely administered without serious functional impairments, although some impairment in learning and memory has been recently detected in such patients. As discussed above, significant impairment in cognitive functions may occur at much lower doses following acute low-LET radiation. For a Mars mission, the concern is whether the high-LET component from GCR, for which we have no human data, would result in significant functional impairment at the much lower doses and dose rates received.

• Serious health effects from radiation exposures in utero can occur at lower doses than in adults. The threshold for developmental malformation of the fetus during major organogenesis is about 0.1 Sv acute low LET radiation. The threshold (or effective threshold) for severe mental retardation estimated from the A-bomb survivor studies appears to be in the 0.06 to 0.31 Sv range of acute low LET radiation. Intelligence quotient (IQ) scores and school performance scores did not show responses consistent with a threshold but are estimated to have an effective threshold of 0.1 Sv acute gamma rays. Given that these are for high dose rates, they could possibly overestimate the risk for low-dose rate GCR protons. However, information is not available from high LET radiation for these effects, hence estimating a threshold dose for the high LET component of GCR is not possible at this time.

• Cardiovascular effects from high therapeutic doses of radiation have been well established. However, recent observations from the A-bomb survivor studies show a radiation dose-related response that is statistically significant at acute gamma ray doses of

0.5 Sv and above. These are doses in the range likely to be received by the early Mars explorers, but at much lower dose rate and a high LET component from GCR. The lower dose rate would likely reduce the effectiveness of GCR protons for this effect, but the high LET component of GCR would likely increase the effectiveness. Experimental animal studies are required to determine how that would balance out.

• Temporary sterility in men can occur following about 0.15 Sv acute low LET radiation; experimental data suggest that chronic exposures to low LET radiation are likely to be less effective for this endpoint, which would probably be the case also for GCR protons. Temporary reduced sperm count would be possible during a Mars mission. Permanent sterility in men requires at least 5 Sv chronic low LET radiation, which is not anticipated for Mars missions.

• There is a serious question about the radiosensitivity of human oocytes in utero. Human data are not available, but data from non-human primates suggest high sensitivity during gestation with LD_{50} as low as 0.07 Sv chronic low LET radiation. The critical question for fertility is how much reduction in reproductive lifespan would be caused by a given decrement of the oocyte pool in utero? It is known that following radiation killing of oocytes in mice the rate of oocyte depletion through natural atresia is increased compared to that in unirradiated mice. This would suggest that if 50% of the oocytes were depleted by radiation exposure in utero the woman may have substantially less than half of her normal oocyte supply at age of sexual maturity. The impact of this on premature menopause in women exposed to space radiation is uncertain. Based on mouse and nonhuman primate data (Dobson et al. 1986), it is possible that 0.07 Sv chronic low-LET radiation received in utero could result in early menopause. This would argue for a low threshold dose during gestation, perhaps in the 0.05 Sv range or even less. Based on available information, the female ovary in utero could possibly be the critical (most sensitive) organ and therefore a dose limit protecting the fetal ovary may also protect the central nervous system and other developmental risks associated with radiation exposures during pregnancy.

Stochastic effects are listed in Table 7. These should be maintained below adopted limits and reduced further consistent with the ALARA principle (NCRP 1999). These effects include cancer induction and transmitted genetic abnormalities and are summarized as follows:

• The data from A-bomb survivors show a strong response with age at exposure for radiation-induced cancer (greater lifetime cancer mortality risk when exposed at younger ages), as was seen in Fig. 4. Based on those data, radiation during childhood results in more than twice the cancer risk compared with those exposed as middle age adults. The most recent follow-up of the A-bomb survivors exposed in utero suggests they may have lower lifetime cancer risk than those exposed in childhood, although those data are uncertain. Also, there appears to be a rather large difference between males and females exposed in utero or during childhood. Girls appear to have higher risk than boys.

• To date, no transmitted genetic effects have been detected with statistical significance above spontaneous rates from any of the irradiated human populations. Best estimate risks for first and second generations exposed to chronic low LET radiation may be suitable for GCR protons but may not be suitable for the high LET component of GCR. Additional research is required to measure the transmitted genetic response following simulated high LET radiation.

Table 7. Stochastic effects: Estimates of risk coefficients for chronic low-LET radiation in humans.

Effect	Risk (%) /Sv	References
Cancer mortality (lifetime)		
Exposed as adults (40 y)	~5-6	NRC 2006a
Exposed as children	~12-15	NRC 1990
Exposed *in utero*	<12	Delongchamp et al. 1997, Yoshimoto et al. 1988, Preston et al. 2008
Genetic effects		
First generation	0.41 - 0.64	NRC 2006a
Second generation	0.53 - 0.91	NRC 2006a

5. WHAT CAN BE DONE TO MITIGATE HEALTH HAZARDS?

Shielding. As colonization of Mars advances the human population on Mars would be expected to grow, analogous to our colonization of Earth during the past million years. Pregnancies and childbirth will become commonplace. The ability to keep exposures lower than that for earlier exploration missions will be required. Shielding comes in two types, active and passive. Active shielding approaches would generally generate electromagnetic fields in order to deflect the charged particle radiation. Currently, active approaches are not technologically feasible but may become so in the future (Adams 2005).

With readily available shielding material on the surface of Mars it is unlikely that active shielding will be the main source of shielding. However, it may be useful in transit vehicles on the surface of Mars, particularly if it can be made sufficiently portable. Also, as transit between Earth and Mars becomes more common, i.e., multiple trips and all ages, combinations of active and passive shielding may be required. The principal concerns about active shielding include the need for very high power requirements (perhaps nuclear fission or fusion), which could influence electronics, produce added health effect risk, as well as various reliability issues (NRC 2008).

Passive shielding consists of placing mass between the external radiation and the sensitive targets whether they are humans or electronics. For transit to Mars, mass is very expensive so shielding needs to be optimized. It has been found that the lower the atomic number of a material, the better shielding properties it has for GCR and SPE. Mass will be a major constraint for transit vehicles so it is important to take full advantage of all

existing mass before adding "parasitic" shielding. The development of multifunctional materials with improved shielding properties is required. Also careful consideration of radiation shielding needs throughout the design process is essential to achieving an optimal design since how the mass is distributed throughout the vehicle can be a very important consideration, particularly for SPE. It is also noted that uncertainties in the radiation-induced health risk estimates influence the optimization of shielding materials (Cucinotta 2006), which places substantial premium on reducing those uncertainties. On the surface of Mars, shielding material will be readily available in the form of regolith. It would be expected that as a base is developed on Mars, surface assets would become available as needed over time to process the regolith into shielding material.

Indirectly, one of the best ways to mitigate radiation risk is through improvements in propulsion. Better propulsion could reduce transit time, which would decrease GCR exposure during transit as well as risk from SPE. Also, more mass would be possible for transit vehicle shielding. For example, nuclear thermal propulsion could shorten round trip times from 900 days to less than 500 days (NRC 2008). Radiation exposure to crew from the reactor can be minimized by design (Nealy 1991).

An intriguing question is: can Phobos serve as a shielded base close to Mars? One of the two moons of Mars, Phobos, orbits closer to a major planet than any other moon in the solar system. It is 9,377 km from the center of Mars, or only about 5,981 km from the surface of Mars. Phobos is only about 22 km in diameter and its main features are a very large crater (Stickney crater) near its equator and its irregular shape. Stickney crater is on the side facing Mars. Due to the close proximity, Mars occupies about 25% of the celestial hemisphere of Phobos. On the surface of Phobos facing Mars (i.e., not in a crater) the cosmic ray shielding would be about 75%. However, if inside Stickney crater, the shielding may be 90% or more depending on location. A challenge with using Phobos as a base is the very small gravitational field. Due to its small size and irregular shape, the g-force is 1.9×10^{-3} to 8.6×10^{-3} m/s^2 depending on location (about 0.1% of that on Earth). A person weighing 75 kg on Earth would weigh only about 75 g on Phobos. This means that a base on Phobos would face some challenges regarding how to work in such an environment, although we have substantial experience on the ISS, which has even lower g-force. An advantage would be the low escape velocity from Phobos, only about 10 m/sec.

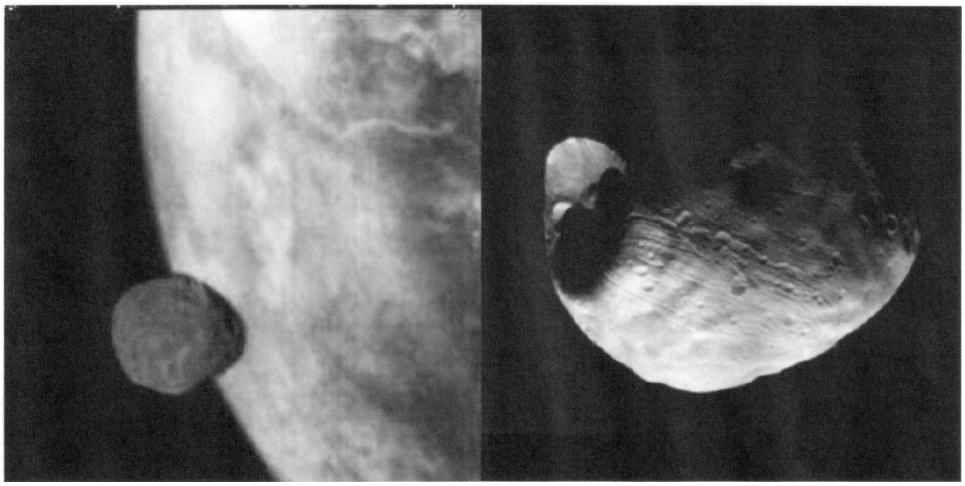

Figure 7. Left image: The moon Phobos orbiting Mars (photo by Phobos-2). Right image: The moon Phobos with its large crater (Stickney) facing Mars (photo by Viking orbiter).

Biological Countermeasures. Biological or pharmaceutical methods to mitigate the long-term effects of space radiation are not currently available. Several FDA approved countermeasures against nausea and vomiting are available and have low risk of adverse side effects. These are commonly used during radiotherapy (Maranzano et al. 2005). These drugs do not degrade cognition, psychomotor skills (Benline et al. 1997a), or performance of complex tasks (Benline et al. 1997b). In the ferret--the principal model used to test emetic (vomiting) response from radiation exposure--these agents have been shown to effectively reduce the emetic response from gamma rays, neutrons, and 200-MeV protons (King et al. 1999). There are no FDA-approved countermeasures for radiation effects on the hematopoietic system. Non-FDA approved drugs such as Neupogen and Amifostine have been used following radiation accidents and radiotherapy, but have side effects. Recent research on Genistein, a soy-derived isoflavone, suggests that it may have some promise as an effective radiation countermeasure with low toxicity (Landauer et al. 2003; Landauer 2008). Genistein appears to have a number of biological properties that are associated with radioprotection, including antioxidant and free radical scavenging.

There is also the concern that the combination of radiation exposure and reduced gravity may result in enhanced damage to the skeletal system requiring countermeasures. Existing FDA-approved medications for osteoporosis, bisphosphonates, inhibit the activity of bone resorbing cells, osteoclasts (Kennel, 2009). Bisphosphonates are currently under serious consideration for use in the astronaut population to prevent weightlessness-induced bone loss, although adverse side effects must be seriously considered (Kennel and Drake 2009). Irradiation also increases resorption by osteoclasts (Kondo et al. 2009, Willey et al. 2008), and in mice, treatment with a bisphosphonate prevents acute radiation-induced trabecular bone loss (Willey et al. 2009), leading to the suggestion that bisphosphonates (or other antiresorptives) may prevent bone loss caused by space radiation alone, or when combined with weightlessness. As attractive as a single treatment modality for preventing bone loss caused by both weightlessness and space

radiation may be, there is considerable evidence that radiation also irreversibly damages stem/progenitor populations within bone marrow, which includes cells that ultimately give rise to bone-forming osetoblasts {Yumoto et al. 2010), needed for replacement of bone tissue throughout life. Thus, a second approach to protect skeletal health over the long term from both radiation and weightlessness may be needed. Treatment with a potent anti-oxidant, alpha-lipoic acid, prevents radiation-induced bone loss in a mouse model (Kondo et al. 2009), and may also protect bone marrow stem and progenitor cells. Much more work is needed in this area to extend our understanding of mechanisms, determine the severity of the weightlessness-radiation effect in humans, and develop effective countermeasures when needed.

Biomarkers. By the time human missions to Mars are feasible, it is likely biomarkers will be available that can be used for astronaut selection and risk management (examples of emerging research in this field are summarized in Straume et al. 2008, and Ramakrishnan and Brenner 2008). It would be particularly helpful for long-duration human space exploration to have biomarkers that can be used to measure individual susceptibility to the major health risks associated with radiation exposure in space: carcinogenesis, acute and late CNS risks, chronic and degenerative tissue risks, acute radiation risks, and possibly combined radiation/microgravity induced risks. Such markers could be used, for example, to select astronauts for long-duration missions who may have lower susceptibility to the major radiation-induced health risks. At present, biomarkers are not available that can be used to measure radiation-induced risk in an individual astronaut, and therefore cannot be used to select less susceptible individuals. However, available biomarkers can be used to identify individuals with unusually high radiosensitivity, such as those with certain known DNA repair deficiencies (e.g., Sanford and Parshard 1990).

Although physical radiation monitoring is employed on all human missions in space and more sophisticated technologies will certainly be available for missions to Mars, advantages of biomarkers include measurement of the biological response to radiation in the individuals themselves while in the Martian environment. This would provide powerful information on the health status of each individual, which would be needed to evaluate their response to the many combined stresses expected while living in a colony on Mars. For radiation, contributions from dose, dose rate, radiation quality and biologically based modifiers of response such as DNA repair would be included in the biomarker measurement. Biomarkers, therefore, can provide a measurement that would be expected to correlate better with health risk than a physical dosimeter. Also, an accurate biomarker measurement could be critical for treatment management if an astronaut has received a large acute exposure from a SPE. Such biomarkers, and the compact devices to detect them using non-invasive means, should be developed so they can be ready for human missions to Mars.

In conclusion, there is clear recognition at the national and international levels that the health hazards associated with radiation exposure during a mission to Mars or other deep space destination must be solved through research and technology development (e.g., NRC 2006a,b; NRC 2008b, Augustine et al. 2010). A critical gap that must be closed to

the extent feasible is the uncertainty in extrapolating radiation-induced health hazards from available ground-based data to the conditions in space.

Radiobiology research is advancing with emphasis on space radiation, relevant doses and dose rates, and the application of the many new biotechnologies that permit a better understanding of the mechanisms of radiation action (e.g., the NASA Space Radiation Program is supporting substantial research in this area including a facility at the Brookhaven National Lab that provides simulated space radiation, the NASA Space Radiation Laboratory). It is the hope that many of the limitations of presently available biological data for space radiation assessment will be solved in advance of a Mars mission and certainly prior to long-term habitats and colonization.

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