A review of ground-based heavy-ion radiobiology relevant to space radiation risk assessment. Part II: Cardiovascular and immunological effects

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Abstract

The future of manned space flight depends on an analysis of the numerous potential risks of travel into deep space. Currently no radiation dose limits have been established for these exploratory missions. To set these standards more information is needed about potential acute and late effects on human physiology from appropriate radiation exposure scenarios, including pertinent radiation types and dose rates. Cancer risks have long been considered the most serious late effect from chronic daily relatively low-dose exposures to the complex space radiation environment. However, other late effects from space radiation exposure scenarios are under study in ground-based accelerator facilities and have revealed some unique particle radiation effects not observed with conventional radiations. A comprehensive review of pertinent literature that considers tissue effects of radiation leading to functional detriments in specific organ systems has recently been published (NCRP National Council on Radiation Protection and

Measurements. Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit. Report #153, Bethesda, MD, 2006). This paper highlights the review of two non-cancer concerns from this report: cardiovascular and immunological effects.

Keywords: Space radiation; Heavy ions; Acute and late radiation effects; Risk assessment; Cardiovascular radiation effects; Immunological radiation effects

1. Introduction

Space exploration is a challenging endeavor requiring an understanding of the biological effects of exposure to a constant, relatively low-dose complex radiation field in an environment of additional stressors. A recent report by the National Council on Radiation Protection and Measurements (NCRP) has comprehensively reviewed what is known about space radiation physics and transport, dosimetry, biology, and risk assessment methodology (NCRP, 2006) and has identified and described major scientific information that is still needed by NASA to make radiation protection recommendations for space missions beyond Lower Earth Orbit (LEO).

Ionizing radiations prevalent in space are complex, comprised of a broad range of radiation types and energies from cosmic and unpredictable solar sources, representing a very diverse range of ionization qualities and biological effectiveness. The linear energy transfer (LET) of the potential radiations can cover several orders of magnitude from <1.0 keV μm^{-1} to > several 100 keV μm^{-1}. Protons are more prevalent and have relatively low-LET values, whereas iron ions for example are relatively more rare, but can have high-LET values.

Typically, astronauts and cosmonauts on the International Space Station (ISS) receive from 0.5 to 1.2 mSv d^{-1}, with 75% coming from galactic cosmic ray (GCR) ions and 25% coming from protons encountered in passages through the South Atlantic Anomaly region of the Van Allen belts. The radiation from GCR is

continuous and at a very low-dose rate, and thus not only cancer, but also non-cancer effects should be taken into consideration in the evaluation of late effects (Schimmerling and Cucinotta, 2006). It is only during large Solar Particle Events (SPEs), such as occurred in 1972, that the dose rates rise to above what is considered low-dose rate (Parsons and Townsend, 2000). The radiation dose in deep space on missions to Mars will be higher than in LEO, due primarily to the increased risk of the longer flight times needed for exploratory missions. There is insufficient information to explain the basis of biological effectiveness of different radiation at inducing late effects in humans at low-dose rates.

The risk of cancer has long been recognized as a potential adverse late effect from exposure to single or multiple doses of ionizing radiation, but with the recognition that many biological and physical variables contribute to radiation sensitivity (Suit et al., 2007). Studies on the effects of ionizing radiation on the risk of specific diseases and aging on atomic bomb survivors have contributed significantly to our understanding of radiation effects on life shortening. Several years after the bombs were dropped, the Atomic Bomb Casualty Commission-Radiation Effects Research Foundation (ABCC-RERF) conducted two longitudinal studies, the Adult Health Study (AHS) and the Life Span Study (LSS). Short-term radiation effects on the Atomic Bomb Survivors (ABS) were not all documented, however by the late 1970s, there was little evidence of a correlation between radiation exposure and late effects like aging. Only life shortening from cancer was observed, and suggestions of radiation-induced atherosclerotic diseases and acceleration of aging in the immune system (Sasaki et al., 1991) has been confirmed in more recent follow-up studies (Shimizu et al., 1999). Correlations have also been made with radiation and increased age changes in hypertension (Sasaki et al., 2002), and decreased T- and B-cell populations (Kusunoki et al., 1988).

NCRP Report No. 132 (NCRP, 2000) comprehensively reviewed available information on the biological effects of individual components of the space radiation environment, with a focus on each of the radiation-types prevalent in

near-Earth missions. NCRP Report No. 153 (NCRP, 2006) has updated the review of available information and extended the summary to identify what is still needed to make radiation protection recommendations for travel beyond LEO. The focus of this paper is to highlight key research issues raised in NCRP Report No. 153 that require further research before deep space missions can be safely planned. In particular, radiation effects on the cardiovascular and immune systems of the body are highlighted.

2. Cardiovascular disease

2.1. Radiation-induced vascular change

Cancer and diseases of the cardiovascular system account for the majority of human deaths. Based on the experience of the ABS cohort who received relatively low to intermediate radiation exposures, it has become increasingly evident that this radiation-exposed population is susceptible to chronic multifactorial diseases including coronary heart disease, essential hypertension, and diabetes mellitus (Sankaranarayanan et al., 1999). These pathological effects can lead to non-cancer mortalities ([Kodama et al., 1996], [Shimizu et al., 1999], [Wong et al., 1999] and [Preston et al., 2003]), or at radiation doses below those causing increased mortality, simply a reduced quality of life.

Vascular damage due to radiation exposure has been previously reported. Yang and Tobias (1984) irradiated one-day-old neonatal rats in the head region alone with either X-rays or heavy ions. Doses ranged from 0.5 to 8 Gy. Distinct petechial hemorrhages developed in the cerebral cortex within a few hours after irradiation, reached a maximum about 13–24 h, and decreased exponentially with time. No brain hemorrhage was found in neonatal rats 12 days after irradiation. These results indicated that a dose of a few Gy of X-rays can induce a significant number of hemorrhages in the young brain, and the number of lesions increased exponentially with dose. Heavy ions induced more hemorrhages than X-rays for a given dose, and the RBE for 670 MeV/nucleon

neon particles ranged from about 2.0 for low-doses to about 1.4 for high doses. Histological examination of the hemorrhages revealed that a large number of red blood cells leaked from the blood vessels, indicating that the radiation-induced hemorrhages may be a result of some capillary membrane damages or reproductive death of some blood vessel endothelial cells. The rapid onset of hemorrhage after irradiation suggests that some membrane damage may be involved. Effects of negative pi mesons on vascular permeability of brain in neonatal rats had previously been reported by Landolt et al. (1979). Dose–response relationships were developed for effects on vascular permeability in neonatal rats. The brains were removed and fixed in formalin 24 h after irradiation, and scored from 0 to 5 by number and size of petechial hemorrhage. The RBE was found to be 1.1 for peak and 0.6 for plateau negative pi mesons (peak to plateau ratio of 1.8 compared with 200 kV X-rays). Interestingly, Yang and Tobias (1984) found that hesperetin, a compound of vitamin P, may reduce the formation of brain hemorrhages in X-ray-irradiated rats. Neonatal rats that received a subcutaneous injection of 10 mg hesperetin (dissolved in propylene glycol) about 20–30 min before X-ray irradiation showed fewer hemorrhages in the brain than those in rats that were only irradiated. Control animals receiving the same volume of propylene solution without hesperetin did not show the protection. Late effects of heavy charged particles or neutrons on the fine structure of the mouse coronary artery have been evaluated by Yang and Ainsworth (1982) and Yang et al. (1978), and revealed significantly altered tissue morphologies and damage compared to low-LET radiations. A single dose of only 0.2 Gy ^{20}Ne ions produced significant damage to the smooth muscle cells in the coronary arteries. The major changes included medial smooth muscle degeneration, fibrosis, accumulation of debris, and extracellular matrix.

The development of late somatic lesions in most normal tissues of irradiated mammals has been suggested to be a result of vascular damage, although the true importance of vascular versus parenchymal cell changes is still not well understood (Hopewell, 1980). The heart muscle itself is very radioresistant, with

anatomical changes not observed below 100 Gy. In contrast, the capillaries have been found to be very sensitive to radiation with increased capillary permeability in human skin noted after 1 Gy (Neumayr and Thurnher, 1952). But what about vascular effects at lower particle fluences? (Griem, 1989) and (Griem et al., 1994) and Dimitrievich et al. (1984) developed a tandem scanning confocal microscope (TSCM) to image the capillary network and the surrounding collagen architecture in the papillary dermis of the rabbit ear *in vivo* after exposure to single X-ray doses of 0.5–4 Gy. Serial observations of the microvasculature volume and vascular width were digitally analyzed over a several week period after the exposure. The 0.5 Gy dose showed transient increases in the width of the response that reached a maximum at 20 days post-exposure, and persisted out 50 days. At 4 Gy the vessel width shrank by 2 days after exposure. Particle beam effects on this endpoint are unknown.

Since 1899 radiation injury to blood vessels was recognized as one of the most common effects of therapeutic radiation on normal human tissues (Fajardo and Berthrong, 1988). Alterations in capillaries and arterioles are pathologic hallmarks of delayed damage in many mammalian tissues, primarily thought due to ischemia resulting from microvascular damage. The narrowest (and most prevalent element) of the vasculature is the most radiosensitive due to endothelial radiosensitivity and the fact that endothelial cells constitute the major component of the walls of the smallest vessels.

2.2. Radiation-induced atherosclerotic effects

Atherosclerosis is a multistep process involving injury to the endothelial lining of the arteries, infiltration of arterial intima with plasma lipoproteins, migration of smooth muscle cells (SMCs) from the media into the intima, proliferation of SMCs, and synthesis of connective tissue components. Monocytes in the peripheral blood become fat-filled foam cells through the uptake of low-density lipoproteins (LDL), and high LDL cholesterol is an important risk factor. Radiation-induced coronary disease in humans results in luminal narrowing

([Stewart et al., 1995] and [Virmani et al., 1999]). The morphological changes are different from typical atherosclerosis with more frequent medial destruction and greater adventitial fibrosis and thickening produced post-radiation. These pathological findings are similar to late radiation-induced tissue changes such as areas of necrosis, foam cell deposition, adventitial thickening, and medial thinning and calcification which were only observed in porcine arteries with a stent coated with a radionuclide.

Ionizing radiation is reported to accelerate aortic lesion formation in fat-fed mice via superoxide dismutase (SOD)-inhibitable processes (Tribble et al., 1999) in a dose-dependent manner. The atherogenic effects of radiation appear to be particularly pronounced when the high-fat diet was introduced within 7 days after exposure to radiation. The mean lesion area was the same as that in the control, non-irradiated, high-fat-fed group if the high-fat diet was introduced 14 days after exposure. The primary mechanisms by which radiation promotes atherosclerosis have not been identified, but based on the premise that atherogenic effects of radiation may involve reactive oxygen species (ROS)-mediated promotion of lipoprotein oxidation and vascular inflammation, Tribble et al. (1999) demonstrated that overexpression of the anti-oxidant enzyme Cu–Zn SOD reduced radiation-induced atherosclerotic lesions, and aortic oxygen concentrations. Tribble et al. (2000) found evidence that ionizing radiation promotes changes in the artery wall that enhance the deposition of lipoprotein lipids. Using a trapped ligand methodology, they showed that the LDL is degraded more readily in the irradiated aorta and that the enhanced degradation is affected by anti-oxidants, including α-tocopherol. These results show that LDL degradation products accumulate in the irradiated aorta, but the effect is inhibited by anti-oxidants which reduce the potential for LDL oxidation. The radiation used for these studies was ^{60}Co γ rays at a dose of 2, 4, or 8 Gy. No data are available at lower photon doses, or for HZE particles. Additional research is needed on the late radiation effects of low-doses of radiation types prevalent in space on the

pathophysiology of coronary artery disease, and the potential inhibition of these effects by anti-oxidants and low-fat diets.

Radiation induces several types of damage to the cardiovascular system (Basavaraju and Easterly, 2002). X-rays induced changes in gene expression and distribution of atrial natriuretic peptide (ANP) in different anatomical regions of the heart after acute high doses (15 or 20 Gy) (Kruse et al., 2002). The ANP peptide is associated with a variety of morphological changes in the atria and ventricules, eventually leading to impairment of cardiac function. Circulating levels of ANP in the plasma may provide indications of early cardiac changes. No data exist on the effects of exposure to radiations in space on ANP plasma levels.

2.3. CVD in radiotherapy patients and radiation workers

Several groups of radiation-exposed human populations have shown evidence of increased cardiovascular disease (CVD) after relatively high doses (5–50 Gy) of low-LET radiations, including radiotherapy patients with breast cancer (Seddon et al., 2002), head and neck cancer ([McGuirt et al., 1992] and [Cheng et al., 1999]), Hodgkin's disease (Thomson and Wallace, 2002) and testicular cancer (van den Belt-Dusebout et al., 2006). There is also an observable excess relative risk for CVD among the ABS (Wong et al., 1999) and Chernobyl workers (Ivanov et al., 2001). The effects of radiation on the long-term trends of the total serum cholesterol levels of the Hiroshima and Nagasaki atomic bomb survivors were examined using data collected in the adult Health Study over a 28-year period (1958–1986). The growth-curve method was used to model the longitudinal age-dependent changes. The mean growth-curve of cholesterol levels for the irradiated subjects were significantly higher than for the unirradiated subjects, and the increase was greater for women than for men. No difference in dose response was detected between Hiroshima and Nagasaki. The maximum predicted increase at 1 Gy for women occurred at age 52 years for the 1930 cohort. The corresponding increase for men occurred at age 29 years for the

1940 cohort. The dose range of exposure for the Chernobyl workers and liquidators was 0.005–0.3 Sv. It has been estimated that the liquidators have an excess relative risk per unit dose (ERR Sv^{-1}) for CVDs of arteries, arterioles and capillaries of 0.54 (0.18, 0.91, 95% CI) derived using an external control based on the mortality of the general population in Russia (Ivanov et al., 2001).

Newly discovered is the statistically significant dose risk of ischemic heart disease in Chernobyl emergency workers [Excess Relative Risk (ERR) Gy^{-1} = 0.41, 95% CI = (0.05; 0.78)] (Ivanov et al., 2006). Confirmation is provided for the existence of significant dose risks for essential hypertension [ERR Gy^{-1} = 0.36, 95% CI = (0.005; 0.71)], and cerebrovascular diseases [ERR Gy^{-1} = 0.45, 95% CI = (0.11; 0.80)]. In 1996–2000, the assessed ERR $Gy^{-1}$for cerebrovascular diseases was 0.22 with 95% CI = (–0.15; 0.58). Special consideration is given to cerebrovascular diseases in the cohort of 29,003 emergency workers who arrived in the Chernobyl zone during the first year after the accident. The statistically significant heterogeneity of the dose risk of cerebrovascular diseases is shown as a function of the duration of stay in the Chernobyl zone: ERR Gy^{-1} = 0.89 for durations of less than six weeks, and ERR Gy^{-1} = 0.39 on average. The at-risk group with respect to cerebrovascular diseases are those who received external radiation doses >150 mGy in less than six weeks [Relative Risk (RR) = 1.18, 95% CI = (1; 1.40)]. For doses >150 mGy, the statistically significant risk of cerebrovascular diseases as a function of averaged dose rate (mean daily dose) was observed: ERR per 100 mGy d^{-1} = 2.17 with 95% CI = (0.64; 3.69). The duration of the stay within the Chernobyl zone itself, regardless of the dose factor, had little influence on cerebrovascular disease morbidity: ERR $week^{-1}$ = –0.002 with 95% CI = (–0.004; –0.001). The radiation risks in this large-scale cohort study were not adjusted for recognized risk factors such as excessive weight, hypercholesterolemia, smoking, alcohol consumption, and others. A systematic review of the 26 published epidemiological data <5 Sv however, has concluded that other than the ABS, the US radiological technologists, the Three Countries Study, and the

Study of Chernobyl emergency workers, no other published work has the statistical power to conclude a risk of circulatory diseases from ionizing radiations <4 Sv (McGale and Darby, 2005). No trend in risk of circulatory diseases with increasing cumulative exposure to either radon, external gamma radiation, or long-lived radionuclides was observed in a German uranium minors cohort study with data over 52 years (Kreuzer et al., 2006).

2.4. Enhanced long-term CVD-related inflammatory responses in A-bomb survivors

Recent evidence points to significant increases in inflammatory activity demonstrable in long-term A-bomb survivors which may lead to increased risk of CVD and other non-cancer diseases (Hayashi et al., 2003). The inflammatory markers C-reactive protein (CRP) and interleukin 6 (IL-6) were significantly increased in the plasma of A-bomb survivors by 28% after a 1 Gy exposure for CRP and by 9.8% for IL-6, after adjustments for other causative factors such as age, body mass index and history of myocardial infarction. The elevated levels of these proteins were associated with decreases in the percentages of CD4+ helper T-cells in peripheral blood lymphocyte populations. The association with increased CVD risk in this cohort is not proved, but appears likely. Clearly, information about the long-term effects of ionizing radiation on CVD in humans is needed.

2.5. Countermeasures to radiation-induced CVD

Radioprotection of normal vascular endothelium with synthetic aminothiols (such as WR-2721, and WR-1065) has been reported ([Warfield et al., 1990] and [Mooteri et al., 1996]). Presumably the aminothiols are scavenging free radicals and aiding the repair of damaged macromolecules. Mooteri et al. (1996) also suggest that endothelial cell division and morphology are affected by WR-1065. Drab-Weiss et al. (1998) showed that WR-1065 attenuated the inhibition of DNA synthesis caused by lipopolysaccharide exposure by promoting DNA synthesis

and lowering apoptosis in the endothelium. Vitamins E and C are also thought to radioprotect the endothelium (Fajardo and Stewart, 1973). Treatment with certain growth factors such as fibroblast growth factor-2 (FGF-2) can significantly decrease radiation-induced blood vessel stenosis (Fuks et al., 1994).

3. Hematological changes

3.1. Effects on blood cell compartments

Studies on the effects of whole-body proton irradiation on bone-marrow-derived cell types and the highly immunosuppressive cytokine transforming growth factor-β1 (TGF-β1) have been reported by Kajioka et al. (2000a). C57BL/6 female mice were irradiated with a single 3 Gy dose of either 250 MeV or mid-peak stopping protons of 149 MeV. Control animals were irradiated with 3 Gy ^{60}Co γ-rays. Animals were euthanized in a time course of 0.5, 4, 7, 10, 14, and 17 days after exposure. Highly significant decreases in white blood cell (WBC) counts were noted as early as 12 h post-exposure in all irradiated groups, with means being only 32–35% of those for non-irradiated controls. At this same time point, significantly low numbers of lymphocytes (11–17% of control), and monocytes (32–36% of control) were present. The depression generally persisted until the end of the study.

In contrast, neutrophil levels tended to be erratic, and significant differences were observed among the irradiated groups on days 4 and 7. Eosinophils and basophils were noted only rarely in all four groups. Red blood cell (RBC) counts were significantly decreased at 12 h only in the ^{60}Co-irradiated, but not the proton-irradiated animals and the unirradiated control groups. Thrombocyte counts fluctuated showing significant depression for all radiation groups on days 4 and 10–17, but normal levels on days 0.5 and 7. TGF-β1 levels in plasma were significantly elevated at 7 days post-exposure in mice irradiated with ^{60}Co when compared to non-irradiated controls or to either of the proton-irradiated groups.

However, by day 17 all irradiated groups had significantly lower levels of the cytokine than did the control animals.

Dose and dose-rate effects of whole-body γ-irradiation have been reported for lymphocytes and lymphoid (Pecaut et al., 2001) and hematological variables and cytokines (Gridley et al., 2001). C57BL/6 mice were exposed to 0, 0.5, 1.5, and 3 Gy at a low-dose rate (LDR) of 10 mGy min^{-1}, or at a high-dose rate (HDR) of 800 mGy min^{-1} and euthanized 4 days later. A significant dose-dependent loss of spleen mass was observed with both LDR and HDR irradiation; whereas for the thymus this was only true with HDR. Decreasing leukocyte and lymphocyte numbers occurred with increasing dose in blood and spleen at both dose rates. The numbers of CD3+ T lymphocytes decreased in the blood in a dose-dependent manner at both HDR and LDR. Splenic T-cell counts decreased with dose only in HDR groups; percentages increased with dose at both dose rates. Dose-dependent decreases occurred in CD4+ T helper and CD8+ T cytotoxic cell counts at HDR and LDR. In the blood, the percentage of CD4+ cells increased with increasing dose at both dose rates, whereas in the spleen the counts decreased only in the HDR groups. The percentages of the CD8+ population remained stable in both blood and spleen. CD19+ B-cell counts and percentages in both compartments declined markedly with increasing HDR and LDR radiation. Natural killer cell (NK1.1+) numbers and proportions remained relatively stable. Overall, these data indicate that the observed changes were highly dependent on the dose, but not dose rate, and cells in the spleen are more affected by dose rate than those in blood. The results also suggest that the response of lymphocytes in different body compartments may be variable. Significant dose- (but not dose-rate-) dependent decreases were observed in erythrocyte and blood leukocyte counts, hemoglobin and hematocrit.

4. Immune deficiencies

The immune system is affected by a number of stressors including exposure to radiation and microgravity. A brief description of the effects of radiation alone is

provided here, as well as a brief summary of the combined effects of microgravity and radiation on the immune system.

The study of low-dose (<1.5–2 Gy administered in numerous low-dose fractions of 0.1–0.25 Gy) low-LET radiation effects on the immune system is important, but its therapeutic value in inducing long-term remissions of tumor by stimulating the immune system has been controversial (Safwat, 2000). Numerous signs of immune system dysfunction in radiation-exposed populations have been reported. Since an impaired immune system promotes disease progression, and initiation, both acute and late effects of radiation on the immune system have been investigated. Kusunoki et al. (2001) found that the reduction in the PHA response in heavily irradiated atomic bomb survivors is dependent on a decrease in IL2-producing CD4 T-cells. When exogenous IL2 was added to the peripheral blood lymphocytes of the heavily exposed individuals, the proliferative response to the mitogen was restored. In a follow-up study, the T-cells of Atomic Bomb Survivors who received doses between <0.005 and 1 Gy were found to respond poorly to stimulation by *Staphylococcus aureus* toxins *in vitro*. The results clearly indicated that A-bomb irradiation led to an impairment of the ability of exposed individuals to maintain their native T-cell pools ([Kusunoki et al., 2002a], [Kusunoki et al., 2002b] and [Hayashi et al., 2003]).

Immunophenotyping of PHA-activated mononuclear cells (MNCs) in Chernobyl liquidators who received between 150–500 mGy 13 years prior showed impaired T-cell function, but currently are healthy. Suppression of CD8+ T-cell propagation and augmentation of CD8+ T-cell propagation *in vitro* were both noted compared to control individuals (Kuzmenok et al., 2003). DNA synthesis in the MNCs was markedly inhibited after activation for 3 days with suboptimal concentrations of PHA, pokeweed mitogen and PMA. In contrast to control individuals, the monocytes of cleanup workers were able to stimulate the proliferation of T-cells from healthy individuals but inhibited the proliferation of T-cells from cleanup workers. Two recent papers have examined the acute effects of iron-particle radiation on immunity in population distributions (Pecaut et al., 2006), and with

regard to leukocyte activation, cytokines, and adhesion (Gridley et al., 2006). Both papers indicate significant dose-dependent changes in cell-based immunity 4 days following single doses of 2 or 3 Gy, with fewer effects observed at 0.5 Gy.

Kajioka et al. (1999) compared the effects of proton and ^{60}Co-γ radiation on cell-mediated and humoral immunological parameters. C57BL/6 mice were exposed to a single dose of 3 Gy protons (mid-peak of 3-cm 149 MeV protons) or γ-rays and intraperitoneally injected 1 day later with sheep red blood cells (sRBC). Subsets from each group were euthanized (along with non-irradiated controls with and without the sRBC injection) in a time course 4, 10, 15, and 29 days after exposure. Body and relative spleen weights, leukocyte counts, spontaneous blastogenesis, lymphocyte populations, and anti-sRBCC titers were evaluated. The data showed that whole-body irradiation with protons, or γ-rays at this relatively high-dose resulted in marked, but transient immunosuppression in nearly all assays involving leukocyte populations as well as the spleen. On days 4 and 10 after irradiation B lymphocytes (CD19+) were the most radiosensitive, although reconstitution back to normal levels was observed by day 15. T-cell (CD3+) and T helper cell (CD4+) recovery was evident by day 29, whereas the T cytotoxic cell (CD8+) count remained significantly below normal. NK1.1+ were relatively radioresistant. Anti-sRBC antibody production was slow and low titers were obtained after irradiation compared to the unirradiated controls. However, overall, no significant differences were noted between the two types of radiation. Kajioka et al. (2000b) report little differences with higher energy protons at the entrance of the 250 MeV proton beam, compared to the mid 3 cm peak 149 MeV proton energy. Gridley et al. (2002), however have reported the effects of 0.1, 0.5, and 2 Gy iron ions on lymphoid cells and organs of C57B/6 mice days 4 and 113 after whole-body exposure. The data collectively show that lymphoid cells and tissues are markedly affected by high-LET radiation at relatively low-doses, that some changes persist long after exposure, and that different consequences may be induced by various densely-ionizing particles. The authors conclude that

simultaneous exposure to multiple radiation sources could lead to a broader spectrum of immune dysfunction than currently anticipated.

There is a major need to investigate the effects of exposure to low-LET radiations at lower doses and dose-rates. Only a very small literature could be found on the effects of exposure to heavy particle beams on the immune system. This is a serious deficiency. The combined hazards of exposure to radiation and microgravity are also a potential issue.

4.1. Combined microgravity and radiation effects

Space flight affects immune function ([Sonnenfeld, 1998] and [Sonnenfeld, 2001]) in astronauts exposed to the conditions of long-term space flight and its rigors of isolation, containment, microgravity, radiation, microbial contamination, sleep disruption, and insufficient nutrition. In a review article, Sonnenfeld and Shearer (2002) summarized information gleaned from both *in vitro* and *in vivo* studies. Early human studies indicated that space flight changed human cell culture activities, such as leukocyte blastogenesis ([Cogoli et al., 1980], [Cogoli et al., 1984], [Bechler et al., 1992] and [Cogoli, 1993]), production of cytokines ([Talas et al., 1983] and [Bechler et al., 1992]) and signal transduction in leukocytes ([Limouse et al., 1991] and [Schmitt et al., 1996]). Studies on animal cell cultures have shown alterations in cytokine production (Chapes et al., 1992), and macrophage hematopoiesis and function (Armstrong et al., 1995). There is also a recent report of changes in neutrophil functions in astronauts (Kaur et al., 2004). The study indicates that neutrophil phagocytosis and oxidative functions are affected by factors associated with space flight and this relationship may depend on mission duration. Decreased non-MHC-restricted (CD56+) killer cell cytotoxicity has also been reported in astronauts after spaceflight (Mehta et al., 2001).

The effects of microgravity on leukocyte blastogenesis were very intriguing. Leukocytes from astronauts were placed in culture during a Space Shuttle

mission, and challenged with a mitogen to induce cell division (or blastogenesis). Blastogenesis of leukocytes is a requirement for a functional immune response. The leukocyte blastogenesis in flight was dramatically decreased compared to ground controls, or 1 g controls centrifuged in space flight. This was among the first demonstrations that microgravity could affect cell culture in space flight. However, when the cells were immobilized on beads, allowing lymphocytes undergoing division during blastogenesis to interact with accessory macrophages required for blastogenesis, the blastogenesis proceeded in a normal fashion. This led to the observation that factors that occur in space flight conditions other than microgravity, such as changes in shear stress and fluid dynamics that would interfere with interactions between cells, also play a role in the effects of space flight on leukocyte blastogenesis (see (Sadhal, 2002) for an overview).

In vivo studies of effects of microgravity on the immune system have not always yielded results similar to those data obtained *in vitro*. Talas et al. (1983) had cosmonauts in space flight obtain and culture leukocytes, and then challenged the cultures to produce interferon-α/β. The interferon production was greatly enhanced compared with controls. However, when the same cosmonauts who had donated the cells used for cultures in space had leukocyte samples challenged after they returned from space, interferon-α/β production was dramatically decreased compared with controls. The lymphocytes in culture would have experienced different fluid shear forces as well as a lack of neuroendocrine signals compared to the lymphocytes *in vivo* (Sonnenfeld and Shearer, 2002).

Early ground studies on immune function in mice maintained in an environment in which barometric pressure was altered in a similar way to space flight, revealed greater susceptibility to mengovirus infection than did mice maintained under normal barometric pressure conditions (Giron et al., 1967). Hind-limb unloading (anti-orthostatic 15°–20° head-down tilt, with hypokinetic, and hypodynamic-no load-suspension by raising the tail, or suspension with a harness) has been an effective model for some conditions that occur during

space flight (e.g., Ilyin, 2000). With this model, muscle, and bone changes occur that are similar to those after exposure to microgravity in the space flight environment. Involution of the thymus also occurs, but does not appear to have an effect on antibody production ([Caren et al., 1980] and [Steffen and Musacchia, 1986]).

Rats and mice have been used to investigate the effects of hind-limb unloading on cell-mediated immunity (Steffen et al., 1984). Interferon-α/β production was severely inhibited in rats and mice subjected to hind-limb unloading ([Sonnenfeld et al., 1982] and [Rose et al., 1984]). The mice required the head-down tilt for the inhibition effect to be seen, whereas the rats did not. The mice and rats regained the ability to produce interferon when they were allowed to recover in normal caging conditions. Interferon-γ production by spleen cells of hind-limb-unloaded rats also was inhibited (Berry et al., 1991). Numerous studies have investigated how the hind-limb unloading model of microgravity affects the ability to combat infection. Evidence such as decreased production of superoxide and impaired killing of phagocytosed bacteria (Fleming et al., 1990), susceptibility to encephalomyocarditis virus D variant which correlated with the loss of interferon, and other pathogens ([Gould and Sonnenfeld, 1987], [Miller and Sonnenfeld, 1993], [Miller and Sonnenfeld, 1994] and [Belay et al., 2002]) led to the conclusion that the hind-limb unloading model correlated to actual alterations in resistance to infection in space travel and can even lead to mortality. This is potentially a serious issue since threats to health normally combated by the immune system are enhanced in space flight due to a combination of enclosed environment and low gravity which can promote the growth of bacteria (Todd et al., 1999).

Sonnenfeld and Shearer have summarized effects of space flight on the immune system that have been observed from both studies *in vitro* and *in vivo* that followed the hind-limb unloading ground-based studies. The results of human studies are very limited. Human ground-based models of space flight can mimic some of the conditions that occur during space flight, but none can re-create all

space flight conditions. Delayed hypersensitivity skin test responses to common recall antigens which are a measure of cellular immune system function were determined during space flight and were found to be inhibited during short-term and long-term space flights ([Taylor and Janney, 1992] and [Gmunder et al., 1994]). Recent studies in humans have investigated the effects of space flight on herpes virus and Epstein-Barr virus reactivation and have shown increases in urinary catecholamine excretion ([Stowe et al., 2001a] and [Stowe et al., 2001b]). Persistent viruses have been associated with non-Hodgkin's lymphoma tumors (Vilchez et al., 2002) and raise concerns with regard to susceptibility of crew members to cancer. A short-term space flight study on the Space Shuttle showed no change in total immunoglobulin levels of astronauts compared with ground-based controls (Voss, 1984), but long-term space flight on a Soviet mission has indicated small increases in total immunoglobulin levels (Konstantinova and Fuchs, 1991). Significant levels of research on the effects of space flight on the antibody response to specific antigens have not yet been done, and are definitely needed to determine the true sensitivity of antibody responses to space flight conditions.

5. Summary

The published literature on the effects of low-doses of radiation on cardiovascular and immunological systems of the human body are primarily based on what has been observed in atomic bomb survivors, radiotherapy patients, radiation workers and radiation accidents. It is becoming increasingly evident that individuals exposed to low-dose radiation exposures can in addition to cancer, be susceptible to chronic multifactorial diseases including coronary heart disease, essential hypertension, and changes in immune competence. Additional new information is coming from the laboratory using animal models and accelerator-based radiation exposures, but there is currently very little data upon which to base estimates of radiation dose limits for protection from adverse acute and late effects on cardiovascular and immune function due to deep space radiation exposure scenarios. The effects of additional stressors in space such as

microgravity, and catecholamines triggered by working conditions in space may independently impact cardiovascular and immune tissues, and present confounding factors to the analysis of radiation-induced effects. It is important to understand the mechanisms underlying these physiological effects in order to set appropriate dose limits during deep space travel, and in order to devise appropriate countermeasures to prevent loss in the quality of life during and following deep space missions.

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