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A review of ground-based heavy ion radiobiology relevant to space radiation risk assessment: Cataracts and CNS effects

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Abstract

Analysis of the numerous potential risks of travel into deep space is critical to future manned missions. Despite the availability of significant new information on heavy-ion radiobiology at high doses and high dose-rates, radiation effects on human physiology during space travel, and later in the career of the space traveler, remain high on the list of what still needs to be known under space radiation scenarios. 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 radiation effects from space radiation 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 functional degradation of specific body organs and systems at risk has recently been published (NCRP Report #153, 2006). This paper highlights the review of two noncancer concerns from this report: cataracts and effects on the central nervous system.

Keywords: Space radiation; Heavy ions; Acute and late radiation effects; Risk assessment; Radiation-induced cataracts; Radiation-induced CNS effects

1. Introduction

One of the challenges of space exploration missions beyond lower Earth orbit (LEO) is an understanding of the biological effects of exposure to ionizing radiation levels that may exceed those routinely received by terrestrial radiation workers, or space travelers in near-Earth orbits such as the International Space Station (ISS). Estimating radiation risks requires a multidisciplinary review of the potential pertinent variables. A recent report by the National Council on Radiation Protection & Measurements (NCRP) has comprehensively reviewed what is known about space radiation physics and transport, dosimetry, biology, and risk assessment methodology (NCRP, 2007), and has identified and described major scientific information that is still needed by NASA to make radiation protection recommendations for space missions beyond LEO. Current space radiation guidelines pertain only to missions in LEO and are not considered relevant for missions beyond LEO.

Evaluation of potential health effects from radiation exposure during and after deep space travel is important for the future of manned missions. The world's experience in human space flight is only about four decades old, inaugurated by the first complete orbit of the earth by Yuri Gagarin of the former Soviet Union, and currently continuing on the International Space Station. To date, manned missions have been limited to near-Earth orbits, with the moon our farthest destination from earth. Historical space radiation career exposures for astronauts from all NASA Missions through December 1999 (including early Mercury, Gemini, STS, and Apollo Missions) involved total exposures of less than about 20 mSv (Cucinotta et al., 2001a). With the advent of Skylab and MIR, total career exposure levels increased to a maximum of nearly

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200 mSv. Missions into deep space, due to the requisite longer duration of the missions planned, may pose greater risks due to the increased potential for exposure to complex radiation fields comprised of a broad range of radiation types and energies from cosmic and unpredictable solar sources. It is not just the total absorbed dose that is important however, but also the type of radiation contributing to the dose (Edwards, 2001). Ionizing radiations prevalent in space such as protons, carbon, argon and iron ions include a broad range of different particle kinetic energies and are capable of a highly diverse range of penetration of tissue-equivalent material with a concomitant variability of radiation quality. The linear energy transfer (LET) range of these particles can be for example from <10 to >200 keV μm^{-1}. Protons are more prevalent and have relatively low LET values, whereas the iron ions are relatively more rare, but will have high LET values. Dose rates measured in LEO are of the order of fractions of a mSv/day, but radiation dose rates will be higher in deep space on missions to Mars. It is an enormous and complex task to assess the biological and clinical effects of all possible space radiation scenarios.

Reminders of the presence of low-fluence particle radiation fields have graphically been visualized in light-flash phenomena experienced by many space travelers (News, 1970). Evidence exists from the accelerator-based human exposures with muons, (McNulty, 1971; McNulty et al., 1976), pions (McNulty et al., 1975), helium ions (Tobias et al., 1971), carbon ions (McNulty et al., 1978) and nitrogen ions (Budinger et al., 1972). Visual phenomena have also been noted by human subjects on exposure to neutrons of several energies (Fremlin, 1970; Budinger et al., 1971; Charman et al., 1971).

It may still be too early in man's exploration of space for the evaluation of late tissue effects in large numbers of crew members, since we do not have a long follow-up period yet from astronauts or cosmonauts, and their radiation exposures during space travel have been relatively low. The first steps in such an evaluation are underway with bio- and physical-dosimetric measurements on both commercial flight personnel and international space crews who have experience on near-earth orbits (see Testard et al., 1996; Obe et al., 1997; Yang et al., 1997; Testard and Sabatier, 1999; Wolf et al., 1999a,b; De Angelis et al., 2001; George et al., 2001a,b) and the necessary theoretical modeling of particle-track traversal per cell, including the contributing effects of δ-rays in exposures to particles (Cucinotta et al., 1998).

The radiation in deep space is complex and different from that on earth but the assumption is made that the biological effects differ quantitatively and qualitatively. Because the dose deposition and density is so different with the heavy-charged particles compared to sparsely ionizing radiations, the assumption requires further testing. In the case of cancer, existing evidence indicates that those that occur naturally or are induced by low-LET radiation are similar and no signature lesions have been found in tumors induced experimentally by heavy ions.

The potential risks resulting from exposure to radiation in deep space are cancer, noncancer and genetic effects. The risk of cancer has long been recognized as a potential adverse late effect from exposure to single or multiple doses of ionizing radiations, but with the recognition that many biological and physical variables contribute to radiation sensitivity (Suit et al., 2007). The risk associated with exposure to low doses (<0.1 Sv) of low LET radiation has recently been very controversial (Tubiana, 2005; Tubiana et al., 2006).

The Joint Report of the French National Academies of Science and Medicine (Tubiana et al., 2005) and the BEIR VII report of the American National Academy of Sciences (BEIR, 2006) published contrasting conclusions. The French Report indicated that epidemiological studies have been unable to detect a significant increase in cancer incidence for doses below 100 mSv in human infants, children or adults. BEIR VII concluded that the balance of evidence from epidemiologic, animal and mechanistic studies tends to favor a simple proportionate relationship at low doses between radiation dose and cancer risk. However authors of the BEIR VII report recognized the uncertainties in this judgment and therefore recommended the use of the linear no threshold (LNT) relationship for assessing the risk of small or very small doses.

There is also insufficient information to explain the basis of biological effectiveness of different radiations at inducing late effects in humans at low dose rates. The radiation from galactic cosmic rays (GCR) is continuous and at a very low dose rate, and thus not only cancer, but also the noncancer effects should be taken into consideration in the evaluation of late effects (Schimmerling and Cucinotta, 2006). Significant uncertainties exist in the estimates of the risks of late effects from space radiation (Cucinotta et al., 2004), but the only potential risk of acute noncancer effects is from exposure without sufficient shielding to a large solar energetic particle event (SPE) that could occur during an extra-vehicular activity (EVA). The highest potential dose would be to the skin and lens of the eye because of the abundance of low energy protons. The major change in the radiation to crew members would be in the dose rate. It is only during very large SPEs, such as that which occurred in 1972, that the dose rate rises to above what is considered low dose rate (Parsons and Townsend, 2000).

Due to the extensive literature published on radiation-induced cancer risk, we have chosen in this paper to focus on noncancer late effects, which are less well documented. Studies on irradiated human populations (cancer radiotherapy patients, radiation accident victims or the atomic bomb survivors) have revealed significant noncancer radiation late effects that include cardiovascular changes (e.g., (Sankaranarayanan et al., 1999; Shimizu et al., 1999; Keefe, 2000; Hayashi et al., 2003; Liubchenko et al., 2004; Zonenberg et al., 2006), immunological deficits (Kusunoki et al., 2001, 2002; Hakoda et al., 2006)) and neurodegeneration (Manton et al., 2004). An increased prevalence of cataracts is the only late-occurring detriment currently

associated with radiation exposures in space travel (Cucinotta et al., 2001a,b).

The goal of all manned space exploration is to assure minimal risk to personnel from any hazard. NASA has spent considerable research effort and resources to evaluate and to mitigate risk at all levels and to follow the ALARA (as low as reasonably achievable) rule. Early in the planning for space exploration the potential risks of radiation exposure were perceived to be important to investigate. But what estimates of risk from radiation exposures in missions to deep space can be made currently?

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, 2007) 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 153 that require further research before deep space missions can be safely planned. In particular, the effects on the lens of the eye and the nervous system are discussed here.

2. Cataract

The human crystalline lens is known to be a radiosensitive organ that responds with opacification in a delayed time course depending on the radiation type and exposure level. Historical data for cataract incidence was analyzed for 295 astronauts participating in NASA's Longitudinal Study of Astronaut Health (LSAH) based on individual occupational radiation exposure data. Eye examinations revealed 48 cases of lens opacification in the 295 astronauts, including one case of congenital cataracts. The exposure histories were broken out to reveal the dose components from diagnostic X-rays, aviation experience, and space travel. In this first analysis of space radiation exposures the contribution from individual radiation-types in the space environment was not available. The astronauts were divided into two groups, a low-dose group with doses below 8 mSv (average 3.6 mSv), and a high-dose group with lens doses above 8 mSv (average 45 mSv). This first epidemiological evidence for a late effect of space radiation exposures among astronauts strikingly demonstrates an increased risk of cataract at lens doses of greater than 8 mSv, compared to exposures of less than 8 mSv (Cucinotta et al., 2001a). This suggested that relatively low doses of space radiation are correlated with an increased incidence and earlier appearance of cataracts. A second report of space-radiation-induced cataract has also been reported among cosmonauts and astronauts (Rastegar et al., 2002). It has not yet been determined which specific radiation component is responsible for these observations. Radiation damage to the lens can continue to progress, but is not life threatening. However, if the cataract is severe, it can affect vision unless surgically corrected with synthetic lens replacement. This procedure is invasive and can have side effects. Stable vision during space flight has been reported in one astronaut with bilateral intraocular synthetic lenses (Mader et al., 1999).

Laboratory animal studies of cataract incidence from individual components of space radiation for example: with neutrons (Upton et al., 1956; Bateman and Bond, 1967; Merriam et al., 1984; Riley and Tuck, 1985; Ainsworth, 1986; Worgul, 1986; Laporte and Delaye, 1987; Ross et al., 1990; Medvedovsky and Worgul, 1991; Worgul et al., 1996; Abrosimova et al., 2000) or high-energy particle beams such as protons (Lett et al., 1991), helium (Abrosimova et al., 2000), carbon (Abrosimova et al., 2000), neon (Lett et al., 1980; Abrosimova et al., 2000), argon (Lett et al., 1980; Merriam et al., 1984; Worgul, 1986; Abrosimova et al., 2000), or iron (Worgul, 1986; Lett et al., 1991; Riley et al., 1991) ions had indicated an earlier appearance of cataract and at lower doses than were known from X-rays or γ-rays. The work of Worgul et al. (1996) provides evidence of cataract incidence in mice from neutrons, and from argon or iron ions. At very low doses (0.002–0.25 Gy) of medium-energy (430 keV) neutrons high RBE values for cataracts were reported. More cataractogenesis studies with charged particle beams at very low doses are needed to confirm the risk due to exposure to very low particle doses, and to investigate countermeasures.

Evidence from clinical radiotherapy for the treatment of cancer with X-rays (Nutting et al., 1999), protons (Gragoudas et al., 1995) helium ions (Meecham et al., 1994) or total body irradiation in preparation for bone marrow transplantation (e.g., Dunn et al., 1993; Belkacemi et al., 1996; Frisk et al., 2000; Zierhut et al., 2000; Thomas et al., 2001; van Kempen-Harteveld et al., 2002a,b) has also provided human experience on radiation-induced cataract. In addition, there are analyses of cataract induction among individuals exposed at Hiroshima and Nagasaki (Otake and Schull, 1990; Medvedovsky and Worgul, 1991), in cases of exposure of cyclotron- and reactor-operators (ICRP, 1969) and in populations exposed to environmental radiation contamination (Junk et al., 1999). However, none of the published data on humans allow a prediction of radiation-induced cataract at doses in the mSv range from chronic exposure to low doses of protons or low-fluence heavy ion doses. Proton-induced cataractogenesis studies in non-human primates by Niemer-Tucker et al. (1999) have evaluated late ophthalmological complications after total body exposure. The data reveal increased cataract indices and shorter latencies with increasing doses from 0.31 to 7.5 Gy. Fedorenko (1995) examined the dose-rate dependence of radiation induced cataract in mice after 4 Gy of very high energy (645 MeV) protons and demonstrates dose rate sparing at 0.18 Gy min^{-1} versus 18 Gy min^{-1}. Although 0.18 Gy min^{-1} is a low dose rate, it is not below the limit where biological effects are independent of dose rate, so at lower rates, the effects could still decrease.

In vitro radiation studies using human lens cell models (Blakely et al., 2000) have suggested that molecular markers of radiation-stress can be measured at relatively lower doses than previously documented *in vivo* (Chang et al., 2000; McNamara et al., 2001). The *in vitro* models also may provide more specific evidence for molecular mechanisms underlying the radiation damage that leads to the mal-folding or aggregation of the crystalline proteins associated with cataract, and for potential countermeasures. Current known countermeasures for cataract that require administration prior to radiation exposure include antioxidants, e.g., vitamins, especially C and E (Bantseev et al., 1997; Jacques et al., 1997; Taylor et al., 2002) and sulfhydryl agents (Kador, 1983).

Another important issue with regard to radiation effects, including cataract or cancer, is the radiosensitivity or genetic background of the exposed individual. There are radiosensitive subsets of the human population represented by individuals with cancer-prone phenotypes (Hall and Angele, 1999), presumably due to inherent genetic deficiencies. One well-known but relatively rare autosomal recessive disorder is ataxia telangiectasia (AT) (Lavin and Shiloh, 1999). When there are mutations in both alleles of the ATM (AT Mutated) gene, these homozygous individuals are radiosensitive. More commonly, 1–3% of the human population is thought to be ATM heterozygotes with mutations in only one allele ($ATM^{+/-}$). Although phenotypically indistinguishable from the rest of the population, individuals heterozygous for the ATM gene may have an increased risk of cancer (Bay et al., 1999; Broeks et al., 2000). Two clinical reports indicate severe late radiation responses in AT heterozygotes during and after cancer radiotherapy (Hall et al., 1998; Iannuzzi et al., 2002). Recently results of radiation studies on ATM gene-deficient mice have indicated that ATM heterozygous mice are more sensitive to radiation-induced cataracts than are their wild-type counterparts (Worgul et al., 2002). Worgul et al. (2002) found that the lenses of homozygous mice were the first to opacify at any given dose, and more importantly that cataracts appeared earlier in the heterozygous versus the wild-type animals. It has been suggested that genetic screening of individuals for evidence of radiosensitive genes may become an important future criteria for selection of astronaut candidates for deep space missions, however legal and ethical issues regarding the implementation of such an idea need further consideration.

3. Central and peripheral nervous system

The possibility of radiation-induced effects on the CNS, especially by heavy ions is of concern. There are not sufficient data on the threshold doses for effects on the functions of the CNS despite a considerable number of relevant studies (Nelson et al., 2000) funded by NASA, especially with regard to late radiation damage and its relationship to aging.

The CNS has previously been considered a relatively radio-resistant organ with a very high dose threshold and the effects of high doses of low-LET radiation on the central nervous system (CNS) are known reasonably well. The tolerance dose for the brain for fractionated exposures is expressed in terms of several thousand Grays depending primarily on the volume, and secondarily on anatomical location of the exposure in the brain (Kramer et al., 1972; Fabrikant et al., 1989; Schultheiss et al., 1995). Detailed information on the radiation tolerance of human brain has been obtained from the use of charged particle beams for treatment of pituitary tumors (Kjellberg and Kliman, 1979; Linfoot, 1979), hormone-responsive metastatic mammary carcinoma (Tobias, 1979), brain tumors (Suit et al., 1982a,b; Castro et al., 1985) and intracranial arteriovenous malformations (AVMs) and other cerebrovascular diseases (Kjellberg et al., 1983; Fabrikant et al., 1984, 1985, 1989; Levy et al., 1989; Steinberg et al., 1990).

Recent literature reports extreme sensitivity of adult murine neurogenesis to low doses of X-irradiation. The pathogenesis of long-recognized radiation-induced cognitive injury is unknown, but may involve loss of neural precursor cells from the subgranular zone (SGZ) of the hippocampal dentate gyrus (Mizumatsu et al., 2003) and alterations in neurogenesis (Monje and Palmer, 2003). The inhibition of neurogenesis is accompanied by marked alterations in the neurogenic microenvironment, including disruption of the microvascular angiogenesis associated with adult neurogenesis and a marked increase in the number and activation status of microglia within the neurogenic zone. (Mizumatsu et al., 2003). Such changes in neurogenesis were associated with a significant dose-dependent inflammatory response even two months after irradiation.

Kraft et al. (1979) observed acute necrotic damage in the brain of pocket mice within days after >1 Gy of Bragg peak neon ions. Such changes were not seen after the lower 0.1 Gy. To address the hypothesis that the pathogenesis of heavy-ion particle radiations in space impacts the SGZ, female mice were whole body irradiated with doses of 1 GeV/u iron ion beams (Rola et al., 2004). Histopathology indicated that the iron ions induced chronic and diffuse astrocytosis and changes in pyramidal neurons in and around the hippocampal formation. This is the first evidence showing that high-LET radiation has deleterious effects on cells associated with hippocampal neurogenesis. This work has been confirmed by Casadesus et al. (2005) who noted that these changes are consistent with those found in aged subjects, indicating that heavy-particle irradiation is an adequate model for the study of aging (Casadesus et al., 2005). Results from a follow-up study showed (Rola et al., 2005) that the persistent reductions in proliferating cells and immature neurons were dependent on the exposure dose and LET. Loss of precursor cells was also associated with altered neurogenesis accompanied by a robust inflammatory response. These results indicate that high LET radiation has a significant and long-lasting effect on the neurogenic population in the

hippocampus that involves both cell loss and change in the microenvironment.

Radiation studies of the tolerance of rodent brains to particle beams has been examined by Rosander et al. (1987), Manley (1988) and Richards and Budinger (1988). The decrease in the labeling index of the subependymal layer cells in the unirradiated and the irradiated murine cortices as well as histopathologic changes were determined to be dose- and ion-dependent. *In vivo* surface coil proton spectroscopy demonstrated changes in lipid and phosphatidylcholine peaks, and histology with Evans blue injections revealed blood–brain barrier alterations as early as 4 days after a high dose of 50 Gy. Using NMR imaging and spectroscopy, Richards and Budinger found that at 4–14 days post *in vivo* helium hemi-brain irradiation, image intensity and T1 relaxation time decreased on the irradiated side and increased on the nonirradiated side relative to nonirradiated control animals.

Countermeasures for these effects will involve both protection/replacement of the neural progenitor cell-population, as well as drug-based manipulation of microenvironmental factors regulating microglial inflammation (Monje et al., 2003). Since there is a relationship emerging between hippocampal neurogenesis and associated memory formation, these studies suggest that precursor cell radiation response and altered neurogenesis may play a contributory if not causative role in radiation-induced cognitive impairment.

Rat spinal cord radiation tolerance studies have also been completed with helium-, carbon-, neon- and silicon-ions beams (Leith et al., 1975a,b, 1977, 1981, 1982a,b; Rodriguez et al., 1987; Okada et al., 1998) Cellular changes, degeneration, and necrosis can occur. The dose–effect response of the rat spinal cord to single and fractionated doses of helium ions shows dose-sparing, similar to other low-LET radiations. A recent study using high-precision proton irradiation of relatively high doses to 20 mm sections of cord reports regional differences in radiosensitivity across the rat cervical spinal cord (Bijl et al., 2005). The results indicate that the lateral white matter is more radiosensitive than the central part of the white matter. The gray matter is highly resistant to radiation, with no lesions observable in histology after even 80 Gy.

Biochemical assessment of charged-particle radiation damage on rat spinal cord at 1 year after fractionated exposure to X-rays, carbon- and neon-ions showed no correlation between the activity of alkaline phosphatase (AP), an endothelial cell marker, and dose or radiation modality. Activities of cyclic nucleotide phosphatase (CNP), and γ-glutamyl transpeptidase (GGTP), however both showed a dose- and LET-dependence (CNP increased and GGTP decreased with dose). The reduced GGTP data may reflect depletion of vascular endothelium, whereas increased CNP activity may reflect compensating increased myelin synthesis by oligodendrocytes (Rodriguez et al., 1991). Radiation damage by these enzyme endpoints could not be detected in the dose region below the threshold for paralysis.

Whereas the vasculature and the oligodendrocyte lineage have traditionally been considered the primary radiation targets in the CNS, recently it has been suggested that other phenotypes as well as critical cellular interactions may also be involved in determining the radioresponse of the CNS (Tofilon and Fike, 2000). These authors cited evidence showing that radiation induces an intrinsic recovery/repair response in the form of specific cytokines and may initiate secondary reactive processes that result in the generation of persistent oxidative stress.

Particle radiation effects have been investigated on adult rat neural precursor cells from the hippocampus, retinal explants and primary cultures of mouse and rat brain cells *in vitro* in order to contribute further to our understanding of fundamental mechanisms. Persistent dose dependent apoptotic responses accompanied by an increase in reactive oxygen species (ROS) was measured in the adult rat neural precursor cells after particle radiation (Limoli et al., 2004). The radiation effects also included the activation of cell cycle checkpoints associated with Trp53 phosphorylation and the induction of Trp53 and p21 proteins. Vazquez et al. (Vazquez and Kirk, 2000) has exposed retinal explants from chick embryos, to determine the dose response relationships for neurite outgrowth with morphometric techniques. Neurite outgrowth is responsive to low doses of iron ions with a maximal effect at a dose of 1 Gy. Neurite generation is a more sensitive parameter than neurite elongation, suggesting a different mechanism of radiation damage. These results showed that low doses/fluences of iron particles could impair the capacity of the retinal ganglion cells to generate neuritis indicating the high neurotoxicity of iron ions. Nojima et al. (2000) irradiated primary mixed cultures of astrocytes and microglia from neonatal mice with high energy carbon ions. Immunohistochemical staining showed that there was a greater survival of astrocytes than microglia. It appears that embryonic microglia are more sensitive than astrocytes to carbon ions and X-rays, and that the radiosensitivity of microglia depends on both differentiation or proliferation status and radiation quality. Mamoon et al. (Mamoon, 1969) incubated small explants of neonatal rat cerebellum and midbrain embedded in plasma clots as a model of myelination response to radiation. Freshly dissected explants were irradiated with X-rays, deuterons, or helium ions and examined for evidence of myelin formation. All the radiation types produced observable differences compared to the unirradiated controls at 4 Gy. Myelination was inhibited at 40 Gy. The ED_{50} for all the experiments was 17.27 ± 1.15 Gy with no statistically significant variation between different types of radiation.

An early comparison was made of radiation necrosis and edema in canines, hemi-brain irradiated with either helium or neon ions using positron emission tomography (PET) and magnetic resonance imaging (MRI) (Brennan et al., 1993). All dogs receiving 7.5–11 Gy of neon showed no signs of radiation injury 3 years after irradiation. Dogs receiving $\geqslant 13$ Gy neon or helium succumbed to radiation

necrosis and died 21–32 weeks after irradiation. The earliest CNS changes seen only 3–6 weeks before death were decreased metabolic activity in the cortex of the irradiated hemisphere with an increase in signal intensity in the periventricular white matter. The PET, MRI and histopathological evidence indicated that both cellular and vascular mechanisms were involved in the radiation necrosis observed.

Late functional changes in the normal adult rat brain after single carbon-ion Bragg peak doses between 15.2 and 29.2 Gy were evaluated by T1- and T2-weighted MRI (Karger et al., 2002). The work was compared to earlier studies involving stereotactic irradiation of the right frontal lobe of rats using a linear accelerator and single doses between 26 and 50 Gy (Karger et al., 2002). The results of the carbon studies showed MRI changes were progressive in time up to 17 months and remained stationary after that time. The relative biological effectiveness (RBE) was calculated based on the previous photon results. Tolerance RBEs at the 50% effect probability level were 1.95 ± 0.20 and 1.88 ± 0.18 for the T1 and T2-weighted MRI. A comparison with data in the literature for the spinal cord yielded good agreement, indicating that the RBE values for single-dose irradiations of the brain and the spinal cord are the same within the experimental uncertainty. However it is not possible to extrapolate the effects observed to the much smaller particle doses expected in space in order to estimate risk. Unlike the clinical situation, most traversals of human brain tissue by heavy ions in space travel are expected to be composed of a distribution of different particle types, to be protracted at low-dose fluences, and to involve much smaller brain volumes. Further work is necessary to expand ongoing investigations of clinically relevant effects from low fluences of components and mixtures of the space radiation environment.

Radiotherapy applied to the CNS can cause neurological complications. These effects generally follow from extremely high doses below the threshold for necrosis, but also occasionally from relatively low doses (Goldberg et al., 1982; Keime-Guibert et al., 1998). Dementia has been reported following treatment of adult brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy (Vigliani et al., 1999). The clinical picture in a retrospective study of 4 patients after a course of cerebral conventional radiotherapy consisted of a progressive "subcortical" dementia occurring 3–12 months after a course of cerebral radiotherapy. Examination revealed early bilateral corticospinal tract involvement in all patients and dopa-resistant Parkinsonian syndrome in two. The main features in CT and MRI scans consisted of progressive enlargement of the ventricles associated with a diffuse hypodensity/hyperintensity of the white matter. The course was progressive over 8–48 months in 3 patients while one patient had stabilization of his condition for about 28 years. Post mortem pathological examination revealed diffuse white matter pallor with sparing of the arcuate fibers in all patients. Despite a common pattern on gross examination, microscopic studies revealed a variety of lesions that took two basic forms: (1) a diffuse axonal and myelin loss in the white matter associated with tissue necrosis, particularly multiple small foci of necrosis disseminated in the white matter which appeared different from the usual "radionecrosis"; (2) diffuse spongiosis of the white matter characterized by the presence of vacuoles that displaced the normally stained myelin sheets and axons. Despite a rather stereotyped clinical and radiological course, the pathological substratum of radiation-induced dementia was not uniform. Whether the different types of white matter lesions represent the spectrum of a single pathological process or indicate that the pathogenesis of this syndrome is multifactorial with different target cells, remains to be seen (Vigliani et al., 1999).

In another study, 12 patients who received daily fractions of 3–6 Gy up to a total dose of 25–39 Gy whole brain radiotherapy given as sole treatment or in combination with surgical resection were included (De Angelis et al., 2001). Within 5–36 months, all patients developed progressive dementia, ataxia, and urinary incontinence causing severe disability in all and leading to death in 7. No patient had tumor recurrence when neurologic symptoms began. Cortical atrophy and hypodense white matter were identified by CT in all. Contrast-enhancing lesions were seen in 3 patients; 2 of the lesions yielded radionecrosis on biopsy. Autopsies on 2 patients revealed diffuse chronic edema of the hemispheric white matter in the absence of tumor recurrence. These results suggest that the fractionation schedules used can predispose patients to delayed neurologic toxicity, and that more protracted schedules may be a safer and more efficacious treatment regime.

The behavioral neurosciences literature is replete with examples of major differences in behavioral outcome depending on the animal species, strain or measurement method. For example, compared to unirradiated controls, X-irradiated mice show hippocampal-dependent spatial learning and memory impairments in the Barnes maze, but not the Morris water maze (Raber et al., 2004) which can be used to demonstrate deficits in rats (Shukitt-Hale et al., 2000, 2003). Particle radiation studies of behavior have been accomplished primarily in rodents, with some differences in the outcome depending on the endpoint measured.

Behavioral and brain neurochemical changes induced by exposure to iron ions resemble those associated with the aging process (Joseph et al., 1992, 1993). Low doses of iron ions in the 0.1–1 Gy range reduce motor performance using the "wire suspension" test. This is paralleled by the reduction of the K^+-evoked release of dopamine in the irradiated animals, resulting in alterations in the coupling/uncoupling of the receptor G protein interface on the membrane surface, impacting responses via the second messenger pathway (Joseph et al., 1994). Oxidative damage may be the common mechanism relating radiation effects to the aging process. Behavioral deficits are observed as early as three days after radiation exposure and the neurochemical alter-

ations (decreased dopamine release) are still found at 80 days post-exposure (Hunt et al., 1990). In contrast to the particle-induced deficits reported with rats on sensorimotor skills, open-field, rotorad or acoustic startle tests of whole body iron-irradiated C57BL/6 mice whole body showed few significant effects during a 2–8 week period immediately after radiation exposures (Pecaut et al., 2004). Mickley et al. (1988) compared behavioral performance in rats after exposure to either electrons, Bremsstrahlung, gamma rays, or fast neutrons and found that complex and physically demanding tasks are some of the most radiosensitive behavioral tasks. They also found that although classic radioprotectant compounds (e.g., WR 2721) proved effective in reducing the lethal effects of radiation, most also potentiated the radiation's behavioral toxicity. In contrast, antihistamines under certain circumstances had the ability to reverse the radiation-induced performance deficits.

Exposure to iron particles may produce unique effects beyond that attributable to its LET (Hunt et al., 1989a,b; Rabin et al., 1989). Conditioned taste aversion (CTA) learning which involves the dopaminergic nervous system was disrupted by exposure to iron ions while exposure to equivalent or higher doses of other types of radiation (e.g., gamma or neutrons) do not show a similar effect (Rabin et al., 1991). Decrements were observed in muscarinic-stimulated low-K_m GTPase in striatum, but not in hippocampus, and iron particle irradiation did not affect a_1-adrenergic low-K_m GTPase activity in either type of brain tissue (Villalobos-Molina et al., 1994). Iron particles were also found to be potent modulators of thermoregulation (Kansadamy et al., 1994).

It has been known for some time that changes in behavior of rodents could be detected after low doses of heavy ions (Hunt et al., 1989a,b; Rabin et al., 1989, 1991, 1994, 2000). Rabin et al. (1989, 1991) have established that the degree of CTA due to radiation is LET-dependent and that iron ions are the most effective of the various low- and high-LET radiations that have been tested. Rabin et al. (2002) studied CTA in rats maintained on diets containing either 2% blueberry or strawberry extract or a control diet for 8 weeks prior to being exposed to iron ions. In contrast to the control animals, rats maintained on antioxidant diets (strawberry or blueberry extract) continued to show the development of an amphetamine-induced CTA following exposure to iron ions. The results are interpreted as indicating that oxidative stress following exposure to iron ions may be responsible for the disruption of the dopamine-mediated amphetamine-induced CTA in rats fed control diets; and that a reduction in oxidative stress produced by the antioxidant diets can reinstate the dopamine-mediated CTA. The study was extended to examine CTA responses 12 months after exposure (Rabin et al., 2005). The results indicated that diets containing strawberry extract provided significant radioprotection.

An operant order learning test, where animals were required to press a lever in order to obtain food pellets, was used to evaluate the ability of rats to respond to increasing demands of work. The rats exposed to 4 Gy of protons or 1 Gy of 1 GeV/u iron particles responded similarly to controls by increasing their rate of responding as the fixed ratio for food pellet rewards increased (Rabin et al., 2002). However, rats exposed to higher iron doses failed to respond appropriately to increasing work requirements many months after radiation exposure (Rabin et al., 2005). Diets containing strawberry, but not blueberry, extract are effective in preventing operon disruption but this disruption appears transient since there was no difference in performance between the irradiated rats maintained on control, strawberry or blueberry diets at 13–18 months after irradiation. These observations suggest that the beneficial effects of antioxidant diets may be dependent upon the age of testing. Investigations of the effects of exposure to iron particle irradiation on spatial learning and memory behavior (Shukitt-Hale et al., 2000) using the Morris water maze 1 month after whole-body irradiation showed that irradiated rats demonstrated more cognitive impairment when compared to the control group. These findings are similar to those seen in aged rats, suggesting that an increased release of ROS may be responsible for the induction of radiation- and age-related cognitive deficits. Denisova (Denisova et al., 2002) exposed rats to 1.5 Gy of 1 GeV/u iron ions and tested their spatial memory in an 8-arm radial maze (RAM). Radiation exposure impaired cognitive behavior, since irradiated rats committed more errors than control rats in the RAM and were unable to adopt a spatial strategy to solve the maze. To determine whether these findings were related to the brain-region-specific alterations in sensitivity to oxidative stress, inflammation, and neuronal plasticity, three brain regions (striatum, hippocampus, and frontal cortex) known to be linked to behavior were isolated and levels of dichlorofluorescein (DCF), heat shock and synaptic proteins (e.g., synaptobrevin and synaptophysin) were measured. The results show differential brain-region-specific sensitivity induced by iron ion irradiation. These findings are similar to those seen in aged rats, suggesting that increased oxidative stress and inflammation may be responsible for the induction of both radiation and age-related cognitive deficits. These experiments warrant further evaluation of the behavioral and neurochemical effects of high LET particles, as well as the exploration of potential nutritional modification (e.g., antioxidants or anti-inflammatories) to offset the deleterious effects of heavy particles in space.

An important unanswered question is whether surviving neurons, after being traversed by HZE particles, develop changes as a late consequence of the damage they incurred. This question has been addressed using retinal photoreceptor rods as a surrogate for neurons in the CNS. There are several clinical reports of late retinal complications of conventional and proton radiation therapy for cancer therapy (Boozalis et al., 1987; Gordon et al., 1995; Takeda et al., 1999). The mechanisms responsible for delayed radiation effects to most tissues is unknown, but has long been

thought that it involves damage to the vessels, particularly to endothelial cells as a primary cause, since increased radiation dose to the optic nerve correlates with smaller numbers of endothelial cells (Levin et al., 2000). Retinal photoreceptor cell loss has also been reported (Cibis et al., 1955; Gragoudas et al., 1979), and the risk of neuropathy and maculopathy is reported to be enhanced among those with underlying vascular disorders (Gragoudas et al., 1999).

The retinas of primates exposed to oxygen ion beams from an accelerator have been examined by Bonney et al. (1974). Color fundus photographs and fluorescein angiograms were taken of the retinas prior to irradiation and up to 5 weeks post exposure. Animals were sacrificed at post exposure intervals for histopathologic examination of the retinas. A series of animals were exposed to X-rays and examined on the same regime as the first series. The results showed retinal damage at a low equivalent dose of ^{16}O as compared with X-rays, and a marked compression of the latency between exposure and onset of the retinal pathology. The early changes within the monkeys were retinal hemorrhages and altered capillary permeability, indicating that the oxygen nuclei irradiation, like other forms of irradiation, produced changes first in the retinal vasculature. At 5.5×10^7 particles cm^{-2} and below, there is no evidence of changes in the angiograms. The histopathological evidence at 3.9×10^7 particles cm^{-2} indicates that some cellular alterations in the outer segments had occurred. A longer post-exposure following of these animals might have revealed changes following a latent period. The evidence available indicates however, that these animals were near the threshold of damage. It would be useful to have these kinds of studies completed with ion beams of higher atomic number and at lower fluences.

Lett and his coworkers (Lett et al., 1987; Williams and Lett, 1994, 1996) found changes in the DNA of retinal photoreceptor cells in rabbit retinas as a function of time after irradiation. After exposure to low-LET radiation or HZE particles, the initial radiation-induced damage was repaired, but a subsequent breakdown of DNA occurred with age. Exposure to HZE particles resulted in the secondary changes occurring at a younger age than after exposure to low-LET radiation. Loss of rods occurred with age but more markedly after exposure to irradiation, especially iron ions. Mao et al. (2003) reported quantitative architectural and population changes in the rat retinal vasculature after high doses of single or split doses of proton irradiations to the whole eye. Progressive time- and dose-dependent cell loss over a period of 15–24 months were observed in retinas after doses of 20 or 28 Gy.

The expression of inflammatory gene products has been shown as one of the acute phase molecular responses in the brain after whole or mid-brain irradiation (Hong et al., 1995). Levels of TNF-α, IL-1β, ICAM-1, EB22/5.3, and to a lesser extent IL-1α and GFAP, messenger RNA were increased. The responses were dose dependent and temporally regulated with most of the responses peaking within 4–8 h after exposure. Although the ultimate consequences of these transient changes in gene expression are not known, Cytokines have been associated with several pathologic conditions of the nervous system, including multiple sclerosis (MS) and subacute sclerosing panecephalitis (Hofman et al., 1989), lymphocytic choriomeningitis (LCM) (Campbell et al., 1994). Cytokines can influence the proliferative characteristics of stem cells and may also be important to memory loss in other neurodegenerative disease. Irradiation of rodent brain has also demonstrated increased expression of transcription factors associated with injury such as the DNA-binding activities of AP-1, Sp-1, p53 and NFκB after sparsely ionizing radiation doses as low as 5 Gy which does not produce detectable histological damage or result in any eventual toxicity and thus may be associated with radioprotective mechanisms (Raju et al., 2000) . Similar studies on molecular factors produced in the brain in response to radiation exposure are lacking for radiation types and dose rates found in space. Since these radiations frequently have higher effectiveness, it will be important to study doses less than 2 Gy and to have parallel assessments of acute and late functional consequences in order to allow evaluation of the risks involved.

There is biochemical evidence for LET-dependent premature aging and CNS degeneration (Joseph et al., 1992, 1993, 1994) and unique enhanced behavioral toxicity from particle radiation exposures (DeAngelis et al., 1989; Hunt et al., 1989a,b, 1990; Kastan et al., 1991). But is there any information regarding acute or chronic motor-neural effects of radiations found in space? Exposure to conventional sources of penetrating radiations usually does not indicate sensory perception of radiation. However the retina is very sensitive to X- or γ-rays and exposure to less than 1 R can cause an alteration in the absolute threshold to light sensation (Lipetz, 1955; Kameyama et al., 1956). Single millisecond pulses in excess of 400 Gy or pulse trains of less than 1 s duration elicited the corneal blinking reflex when delivered to the cornea of unanesthetized rabbits (Tobias, 1962). Radiation-induced stimulation of motility on exteriorized intestines of rats, rabbits and guinea pigs has been reported (Conard, 1951). In contrast, appreciable dose rates of 10 Gy min^{-1} of high energy alpha particles failed to stimulate frog sciatic nerves, and persistent alterations of ionic balance in peripheral mammalian nerves occurred only after irradiation by many thousands of Gy (Bachofer and Gautereaux, 1959; Gaffey, 1960). Early performance decrement (EPD) after radiation exposure is often produced by exposure to rapid, super-lethal ionizing radiation (Bogo, 1988), however this appears to be species-dependent since non-human primates show more radiosensitivity to this endpoint than rodents (Bruner, 1977) and dependent on the radiation quality (Bogo et al., 1989). Gauger et al. (1986) reported that movies taken of neurons exposed to particle radiation fields show a dendritic retrac-

tion phenomena in real time. All of this work has led to the conclusion that there are widely varying limits of excitability of nerve or of muscle action, that different radiation qualities are not equally effective at disrupting performance, and the data suggest that high-energy electrons potentially possible in space during solar events could disrupt behavior at lower doses than other radiations, regardless of the doses needed to produce EPD. Fission neutrons were the least effective, and the work of Joseph et al. (1992) indicate high effectiveness for very low doses (less than 1 Gy) of iron ions. This work needs further research into dose-rate effects of the most effective beams for more nerve and muscle endpoints.

While no reliable estimate of risk of important damage to the CNS can yet be given, there are enough data to indicate much more must be known before risk estimates of the effects of exposures in deep space can be made with any confidence. The accumulated evidence from the reported studies on DNA damage, loss of neurons, altered behavior, and motor function is sufficient to require a careful assessment of the total risk to the CNS from exposure to HZE particles.

4. Summary

The probability of health effects due to radiation exposures of humans during and after exploration missions into deep space are presently not completely known. Future research is needed to complete the estimation of risk. This review summarizes the biological and medical information available for effects on the nervous system and cataract formation from flight and accelerator-based studies with radiations prevalent in space. In addition, brief summaries of radiation health effects from investigations of conventional radiations, but not yet completed with space radiations, have also been reviewed. New facts have emerged from the study of radiation-exposed populations that have added to our understanding.

As is the case for radiation workers on Earth, the aim is to prevent noncancer effects, and limit the risk of cancer to acceptable levels. It is hoped that adequate shielding can do so, however, not enough is known. For example, it is not known what special risks are posed by protracted exposures to heavy ions, neutrons and protons. Similarly, there is a need for better estimates of the risk of cataracts. An increased incidence of cataract has been reported among astronauts with higher space radiation dose exposures, but more research is needed to understand which radiation type is responsible, and what can be done to prevent the cataracts. The imminent problem of unexpected solar flares, and the potential of a rapid and progressive exposure to charged particles representing a wide array of atomic numbers, energies and fluences (and any resulting secondary radiation cascades) is a daunting issue that requires extensive further study. Microgravity in space is well-known to be associated with nausea in some individuals after short-duration spaceflight, and most individuals after long-duration spaceflight (Meck et al., 2001; Ziegler and Meck, 2001). With what is known today, there are no reported concerns among space-flight crew members about space radiation-induced acute effects on the brain and peripheral nervous system, such as nausea or emesis. However there are effects that have been reported in experimental animals on behavioral end points that are mediated by the peripheral nervous system that show increasing RBE with increasing LET. In contrast, behaviors mediated by the central nervous system such as learning that involve the dopaminergic nervous system are disrupted by exposure to iron ions, while exposure to equivalent or higher doses of other types of radiation (e.g., γ or neutrons) do not show a similar effect. These adverse behavioral and neuronal effects are similar to those seen in aged animals, and the cognitive deficits are dependent on the individual dose-response or age at exposure, and are unique to radiations found in space. The concern here is that with increasing age there may also be more vulnerability to deficits in neural function from space radiation damage.

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