

# Chapter 7

## BEHAVIORAL AND NEURO- PHYSIOLOGICAL CONSEQUENCES OF RADIATION EXPOSURE

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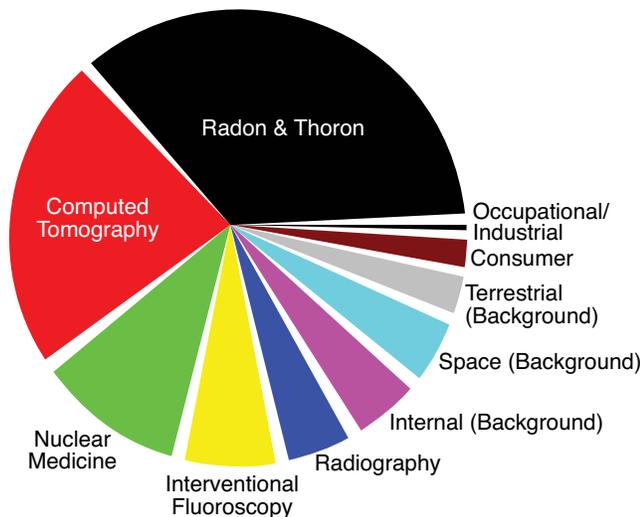
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## INTRODUCTION

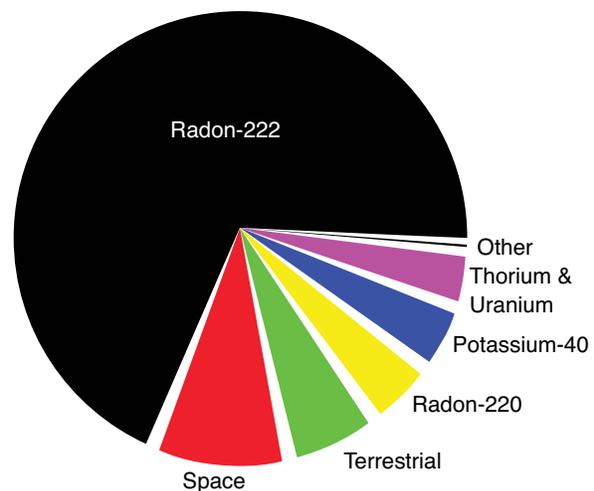
Understanding the behavioral and neurophysiological consequences of radiation exposure are of great importance. Although this chapter in the previously published *Textbook of Military Medicine* covered this topic in great detail, this chapter expands and updates the current understanding of radiation effects, specifically describing new clinical and research advancements in behavioral and relevant noninvasive imaging modalities.

The use of nuclear weapons in military conflicts will significantly challenge the ability of the armed forces to function; the thermal and overpressure stresses of conventional weapons are significantly intensified during a nuclear battle, and military personnel will have to contend with the hazards of exposure to ionizing radiation, which will be the main producer of casualties for nuclear weapons of 50 kt or less. Present projections of nuclear combat operations suggest that between one half and three quarters of the infantry personnel targeted by a tactical nuclear weapon would receive an initial radiation dose of 1.5 to 30.0 Gy.<sup>1</sup> This acute dose of ionizing radiation could dramatically affect a soldier's ability to complete combat tasks successfully, and in turn may ultimately affect the outcome of the armed conflict. In addition to these more acute effects, the long-term effects of ionizing radiation on soldier performance need to be considered.

Information about the consequences of ionizing radiation may be derived from the following: (a) the nuclear detonations over Hiroshima and Nagasaki, (b) clinical irradiations, (c) nuclear accidents, and (d) laboratory animal research (Figures 7-1 and 7-2). The Hiroshima and Nagasaki data are of limited value because there was no scientific assessment of behavior and the reports were anecdotal, often conflicting, and not easily tied to specific radiation doses. Clinical irradiations are also of questionable value because precise measures of behavior are not usually recorded, and patients are behaviorally compromised by their illnesses or the chemical therapy being used. Nuclear accidents have been few and behavioral information that has been obtained from these (ie, Chernobyl) is not consistent. In addition, factors that may affect behavioral disruption after irradiation in the context of a battlefield include (but are not limited to) the physical well-being of the subject (ie, sick or healthy, tired or rested), the presence or absence of physical shielding or pharmacological radioprotectants, and the exposure or nonexposure of the subject to radiation alone or to radiation and other stresses of the nuclear battlefield (such as blast, heat, or flash). Therefore, although information on human radiation exposure is normally preferred, the paucity of data forces significant reliance on animal research.



**Figure 7-1.** Civilian routes of radiation exposure from all sources, including acquired and background radiation sources. Note that medical radiation exposures constitute the largest sources of acquired radiation exposure.



**Figure 7-2.** Distribution of ubiquitous background radiation.

## HUMAN RETROSPECTIVE CASE STUDIES

Humans have been exposed to radiation from environmental and industrial sources, clinical therapy, accidents, wartime detonations at Hiroshima and Nagasaki, and even inadvertently during experiments in research laboratories. Many of these exposures contribute little information about the behavioral effects of ionizing radiation because, in most cases, behavioral data were not collected. Many of the data that were gathered are difficult to evaluate because there is no information about the radiation dose received, the level of baseline performance, or other circumstances. But the data are congruent with animal model findings and also suggest new hypotheses for testing.

### Linear-No-Threshold Dose Response

An underlying tenant of radiobiology, particularly when addressing human risk factors, is the concept of a linear-no-threshold dose response. Because low doses are thought to result primarily in the induction of cancer, extrapolation methods are used to assess potential risk after radiation exposure. The linear-no-threshold dose response has demonstrated excellent concordance with epidemiological studies from survivors of Nagasaki and Hiroshima, with a clear linear relationship between dose and cancer incidence.<sup>2</sup> The linear-no-threshold model for radioprotection has been recently reviewed and suggests that this model is still the most effective method for describing the risks of cancer.<sup>3</sup> While much research supporting the linear-no-threshold model has been derived from genomic instability<sup>4</sup> and radiation bystander-effects studies,<sup>5</sup> the experimental variables between studies do not allow for firm conclusions. More work is required to better understand the relationship between dose, dose rate, and time from the exposure to disease initiation (currently, cancer). While immune responses and sickness behavior (a consequence of cancer-inducing or other properties of irradiation) will affect behavior, it seems that there is a threshold for the effects of irradiation on behavior and cognition, although it is not yet precisely known what this threshold would be.

### Radiation Accidents

Two radiation accidents are particularly instructive because both exposures occurred in the early days of fissionable radiation material production for nuclear weapons and involved radiation doses large enough to produce an early transient incapacitation (ETI). Despite safety precautions to ensure that the plutonium-rich holding tanks did not contain enough

fissionable material to permit a critical reaction, such an accidental event took place in 1958 at the Los Alamos Scientific Laboratory,<sup>6</sup> where a worker received an average (and fatal) total-body dose of 45 Gy and an upper-abdominal dose estimated at 120 Gy of mixed neutron-gamma radiation. During the accident, the worker either fell or was knocked to the floor. For a short period, he was apparently dazed and turned his plutonium-mixing apparatus off and on again. He was able to run to another room but soon became ataxic and disoriented. He was incapacitated and drifted in and out of consciousness for over a half hour before he was rushed to a local hospital. Before his death 35 hours after irradiation, the worker regained consciousness and a degree of coherence. From approximately 2 to 30 hours after the accident, he showed significant behavioral recovery and at some points actually experienced euphoria, although his clinical signs were grave.<sup>6</sup>

The 1964 case of an employee at a uranium-235 recovery plant closely paralleled that of the Los Alamos worker. This accident took place in Providence, Rhode Island, when the worker was trying to extract fissionable material from uranium scraps. A criticality occurred and the worker was thrown backward and stunned for a period of time. He received a head dose of 140 Gy and an average body dose of 120 Gy. Unlike the Los Alamos worker, however, the worker did not lose consciousness. After a period of disorientation and confusion, he stood up and ran from the building to an emergency shack; a distance of over 200 yards, but his awareness of his surroundings during this early period has been questioned. Ambulance transport lasted almost 2 hours, during which time behavior was not observed. When the worker arrived at Rhode Island Hospital, he had transient difficulty enunciating words. Significant behavioral recovery occurred from 8 to 10 hours after the accident. During this period, the worker was alert, cooperative, and talked of future activities in a euphoric manner, inconsistent with his terminal diagnosis. In the hours before his death at 49 hours after the accident, the worker's condition deteriorated significantly.<sup>7</sup>

These human sequelae are comparable to animal research suggesting that supralethal radiation produces early performance decrements (EPDs). Both of the accident victims experienced behavioral deficits to some degree quickly after exposure, but they were transient. The behavioral recovery phase was similar in both patients, as were their final behavioral actions prior to death. The data agree with general conclusions reached in a review of several radiation accidents, in which a

remission of early symptoms occurred before the onset of the manifest illness phase was recorded.<sup>8</sup> Compared to these high-dose accidents, lower radiation doses or partial-body exposures may produce milder but more persistent behavioral changes that are characterized by weakness and fatigability. An accident victim exposed to ionizing radiation from an unshielded klystron tube received as much as 10 Gy to portions of his upper torso and experienced fatigue that lasted for more than 210 days after exposure.<sup>9</sup>

The 1986 Chernobyl nuclear reactor accident also produced behavioral deficits in individuals attempting to perform their duties in high-radiation environments. A Soviet firefighter who fought the blaze of the burning reactor core suffered performance deficits and eventually had to withdraw because of his exposure to radiation.<sup>10</sup> Similarly, a Soviet physician who had received significant radiation exposures while treating patients could not continue to perform his duties.<sup>11</sup> Both eventually recovered from their behaviorally depressed states. These accident data add to the growing literature suggesting that sublethal doses of radiation can induce human performance decrements.

In the more than 20 years since the Chernobyl incident, significant data have emerged regarding cancer incidence connected to the accident.<sup>12</sup> The most prominent cancer types from the affected population have been thyroid and leukemia cancers, but bladder, kidney, and breast cancers have also been reported. It is important to note that only thyroid cancers (particularly in children and adolescent populations) have been shown to have a clear relationship to Chernobyl radiation exposure. Worgol et al also reported cataractogenesis as an outcome of Chernobyl radiation exposure, particularly in reactor liquidators.<sup>13</sup> In fact, a recent review suggests that a dose of 0.5 Gy may be sufficient to induce cataract formation, and may have a doubling dose of around 2 Gy.<sup>14</sup> Other data that are emerging include increased incidence of trisomy 21<sup>15,16</sup> and schizophrenia,<sup>17</sup> and potentially accelerated aging (ie, Alzheimer disease).<sup>18</sup> Reports from Chernobyl and other radiation accidents hint at an association between radiation exposure and cardiovascular disease,<sup>19</sup> but more research is required. It is important to remind the reader that while putative associations between radiation exposure and a host of disease states have been suggested, there is only clear epidemiological evidence for a link between radiation exposure and cancer.<sup>20,21</sup> More research is needed to definitively ascribe increased onset of disease with radiation exposure, particularly in those related to low-dose exposures.<sup>22</sup>

There has been scant work on the behavioral effects of radiation exposure in human populations.

Large-scale epidemiological studies on the behavioral effects of radiation exposure are needed. While the Chernobyl accident provided a wealth of data on cancer incidence,<sup>23</sup> behavioral and psychological data collection was only started 7 years after the accident.<sup>24</sup> These behavioral studies focused on three areas: (1) morbidity surveys based on population statistics, (2) cognitive impairment in children, and (3) mental health studies of cleanup workers.<sup>25</sup> Bromet and colleagues reported significant adverse psychological effects in radiation-exposed populations, particularly in depression and anxiety with somatic symptoms.<sup>26</sup> The associated risk factors were being female, having young children (although no psychological effects were found in these children<sup>27</sup>), financial difficulties, and the perception that the Chernobyl accident had an adverse effect on one's health.

Concern about the mental and cognitive performance of children in the affected areas around Chernobyl was expressed given the higher incidence of thyroid tumors in this population.<sup>28</sup> A number of studies have shown no significant link between cognitive performance in children who were exposed to radiation at a young age or in utero.<sup>29-31</sup> Finally, numerous cognitive studies of cleanup workers at Chernobyl were assessed, but the results have not been independently verified. As noted, Loganovksy and Loganovskaja reported an increased incidence of schizophrenia,<sup>32</sup> but this linkage was not definitive. Polyukhov et al reported accelerated aging (radiation progeria syndrome) based on psychological and cardiovascular testing.<sup>33</sup> Although suggestive, the associations between cognitive performance decrements and radiation exposure in humans are tenuous at this time, particularly at low doses.

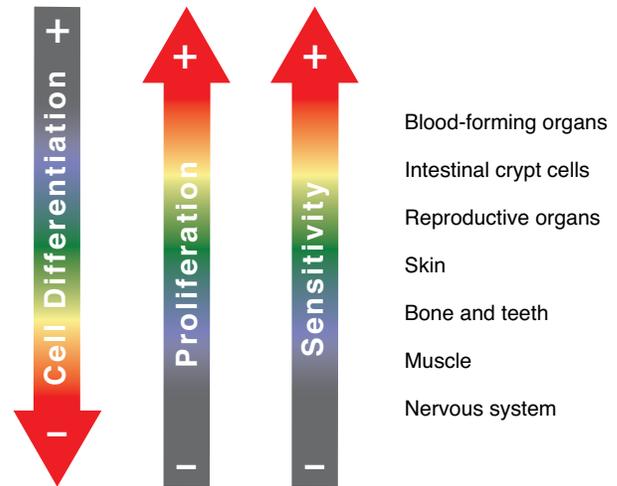
### Clinical Irradiations

Numerous studies have been undertaken to assess human performance after clinical irradiations. The Halsted test battery for frontal-lobe functional deficits was used in four patients exposed to 0.12 to 1.90 Gy of mixed neutron-gamma radiations.<sup>34</sup> Test scores at days 1 and 4 and 1 year after exposure were within the normal ranges. Patients with advanced neoplastic disease received whole-body irradiation with 0.15 to 2.0 Gy given as a single dose, or in 2 to 5 fractions separated by intervals of up to 1 hour.<sup>35</sup> These subjects were pre-trained and served as their own controls in performing tests designed to assess hand-eye coordination. Tests were performed immediately after exposure and at later intervals, but at no time did a performance decrement exist that could be ascribed to these relatively low radiation doses. However, because the behavioral

design of these experiments was secondary to medical treatment, the results are inconclusive. The paucity of radiobiological data on human behavior and the need to predict military performance after ionizing radiation exposure has led to an extensive Defense Threat Reduction Agency (DTRA; formerly the Defense Nuclear Agency) program on the estimation of human radiation effects.<sup>36</sup>

Clinical datasets, particularly from radiotherapy, can provide some understanding of radiation effects on the brain. Treatment of childhood tumors has demonstrated significant late cognitive abnormalities and complications of endocrine dysfunction in long-term survivors.<sup>37</sup> An important caveat is that the type, size, and location of the tumor can effect these complications. Radiotherapy is more closely associated with endocrine dysfunction than cognitive changes<sup>37,38</sup>; however, numerous studies have demonstrated differences in intelligence quotient scores in children treated with radiation for posterior fossa tumors.<sup>39</sup> In adults with low-grade gliomas, there have been some reports of neurocognitive decrements.<sup>40</sup> A cross-sectional study (195 patients) noted that patients who received fractional doses less than 2 Gy did not have adverse cognition, but higher fractional doses than 2 Gy were more likely to result in disability. A recent review confirms this viewpoint.<sup>41</sup> Cofactors such as epilepsy (and use of antiepileptic drugs) correlated more strongly with cognitive deficits than did radiotherapy. In a recent follow-up study of head and neck cancer, patients' tumor localization was a highly significant covariant for cognitive deficits.<sup>38</sup> Such studies underline the difficulty in assessing radiation risks from human radiotherapy studies. An original study by Taphoorn<sup>40</sup> was recently extended to follow up with patients after radiotherapy, with a mean of 12 years after treatment (range 6–28 years).<sup>42</sup> The radiotherapy patients (regardless of fractionated dose) all demonstrated significant declines in attentional and executive functioning and information speed processing. Thus, while early postradiotherapy decrements were not conclusive, long-term, neurocognitive declines are an important factor to consider after radiation exposures.

There are a number of studies that suggest cognitive decrements after radiotherapy even when the treatment site is distant from central nervous system (CNS) structures (Figure 7-3). Cognitive impairments after breast cancer treatment,<sup>43</sup> cervical cancer,<sup>44</sup> and testicular cancer<sup>45</sup> (however, a recent report disputes the testicular cancer results<sup>46</sup>) have all been described, but more study is required to determine the effects of radiation on behavior. In summary, there are no good studies evaluating radiation effects and behavioral out-



**Figure 7-3.** Relative tissue sensitivity. This figure illustrates the concept that highly proliferative organs (eg, blood-forming organs) have increased radiosensitivity, while those regions that are highly differentiated (eg, brain) have the lowest radiosensitivity.

comes. Although radiotherapy studies provide hints at some significant decrements in cognition, further study is needed.

### Predicting Radiation-Induced Changes in Military Performance

In 1984, the Defense Nuclear Agency (currently the DTRA) published a study predicting certain effect distributions for combat personnel exposed to ionizing radiation. For every soldier who receives a radiation dose of greater than 30 Gy (a supralethal and behaviorally incapacitating dose), another will receive a lethal (4.5 Gy) dose that may alter behavior. Two more soldiers will receive doses that are sublethal but greater than the present maximum (0.5 Gy) allowed for troop safety.<sup>47</sup> Given this wide range of expected doses and the ambiguity of the expected outcomes for human behavior, the DTRA has established methods for estimating the behavioral effects of acute radiation doses (0.75–45.0 Gy) on combat troops.

To predict human radiation-induced performance deficits, the DTRA used a survey method, first identifying the physical symptoms expected after various radiation doses, then determining the soldiers' estimates of their own changes in performance while experiencing these symptoms. While the provided examples are somewhat dated, they illustrate the point. Briefly, this involved (a) an extensive review of the literature on human radiation (including radiation therapy patients, Japanese atomic bomb victims, and radiation

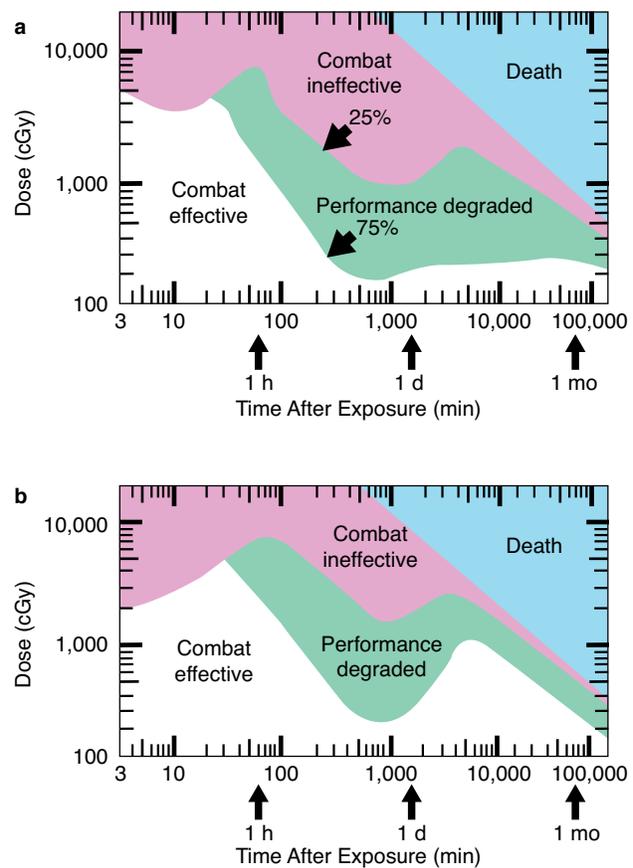
accident victims) to identify the symptoms that might be expected after the radiation doses of interest; (b) the compilation of symptom complexes that reflect various combinations of the expected radiogenic symptoms, including gastrointestinal distress, fatigability, weakness, hypotension, infection, bleeding, fever, fluid loss, and electrolyte imbalance<sup>48</sup>; (c) the development of accurate descriptions of the severity of each symptom category at each postirradiation time of interest; (d) an analysis of tasks performed by five different crews, including a field artillery gun (155-mm self-propelled Howitzer) crew; a manual-operations, field artillery, fire-direction crew; a tank (M60A3) crew; a Chinook helicopter (CH 47) crew; and an antitank guided missile crew in a TOW (tube-launched, optically-tracked, wire command data link, guided missile) armed vehicle; (e) the development of questionnaires that require experienced crewmembers (noncommissioned or warrant officers) to predict task degradation during particular symptom complexes; and (f) the evaluation of monkey performance data from a visual discrimination (physically undemanding) task or a wheel-running (physically demanding) task.<sup>49</sup> The animal data was analyzed in the absence of sufficient human data to estimate the rapid behavioral decrements that follow large (10–45 Gy) radiation doses.

For each crew position, sophisticated statistical techniques made it possible to construct minute-by-minute performance estimates and also smoothed the summary curves as a function of radiation dose and time. The analysis involved grouping the results from individual crewmembers into two categories: physically demanding tasks and physically undemanding tasks. Helicopter tasks were also assessed separately. The degree of performance deficit for each of the five crew positions was described in terms of the following categories: (a) combat effective (performance capability 75%–100% of normal), (b) degraded (performance capability 25%–75% of normal), and (c) combat ineffective (performance capability 0–25% of normal).

This scheme was then used to summarize the expected changes in the performance of combatants after various doses of radiation exposure.<sup>36</sup> In general, the data indicate that the capabilities of crew members performing tasks of a similar demand are similarly degraded. The capabilities of crewmembers performing physically demanding tasks were degraded more than the capabilities of members performing physically undemanding tasks. This latter observation agrees with the data from animal studies on physical effort after irradiation. For example, if crewmembers performing a physically demanding task were exposed to 10 Gy (Figure 7-4), they would be combat effective for only a little over 1 hour. This period would be followed by an

extended time (roughly 1 month) of degraded performance before they became combat ineffective prior to death. The outlook for performance (but not ultimate prognosis) is a little better for a person performing a physically undemanding task after a 10 Gy irradiation. This soldier would remain combat effective for 1.7 hours after exposure. Following this initial period of coping, a transient performance degradation of 2.8 days would ensue before a short recovery and then a gradual decline, ending in death at 1 month after irradiation.

To obtain an independent confirmation of performance degradations predicted for radiation sickness by



**Figure 7-4.** Behavioral responses following radiation exposure. Combat effective: 75%–100% normal capacity; degraded: 25%–75% normal capacity; combat ineffective: 0–25% normal capacity. (a) Expected behavioral response to radiation exposure for persons performing a physically demanding task (1 Gy = 100 cGy = 100 rad). (b) Expected behavioral response to radiation exposure for persons performing a physically undemanding task. Data source: Anno GW, Brode HL, Washton-Brown R. *Initial Human Response to Radiation*. Washington, DC: Defense Nuclear Agency; 1982. DNA-TR-81-237.

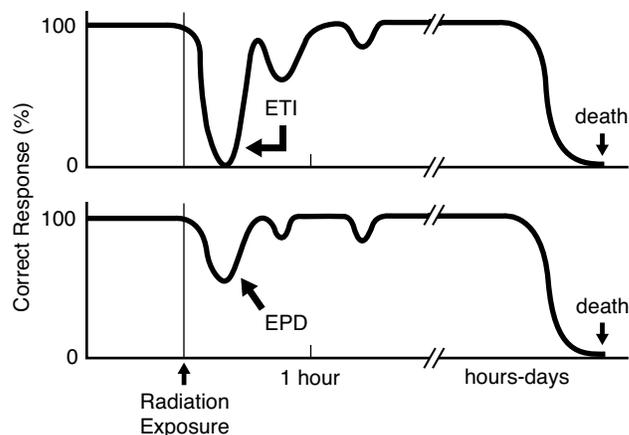
this study, results were compared (where possible) to actual performance decrements measured in members of the US Coast Guard.<sup>50,51</sup> The decrements occurred during motion-sickness episodes with symptoms similar to those of radiation sickness. This comparison revealed that the estimates of radiogenic performance decrements made by responders to the questionnaire were similar to the actual radiation-induced declines in short-term task performance that were measured during motion sickness.

Although these are the best estimates of human radiation-induced behavioral deficits that are currently available, their limitations are recognized. These predictions apply to the physiological effects of a one-time whole-body irradiation. The data do not predict the behavioral effects of protracted radiation exposures that would occur with fallout, nor do they attempt to account for degradation from the psychological effects that are unique to nuclear combat.

For the military, an abrupt inability to perform (ETI) is a potentially devastating behavioral consequence of radiation exposure.<sup>52</sup> An idealized individual ETI profile is shown in Figure 7-5. Prior to irradiation, performance is at maximum efficiency, but 5 to 10 minutes after exposure to a large, rapidly delivered dose of ionizing radiation, performance falls rapidly to near zero, followed by partial or total recovery 10 to 15 minutes later. Delayed ETIs may also occur at about 45 minutes and 4 hours after the initial irradiation.

### Radiation-Induced Brain Damage Based on Clinical Studies

Radiogenic damage to the brain, in the forms of altered performance and neuropathology, may occur after an exposure of less than 15 Gy and is a well-accepted finding at higher doses. A review of many standard radiobiology textbooks reveals the common belief that the adult nervous system is relatively resistant to damage from ionizing radiation exposure.<sup>53</sup> These conclusions have been derived, in part, from early clinical reports suggesting that radiation exposures, given to produce some degree of tumor control, had no immediate observable morphological effects on the nervous system.<sup>54</sup> However, this view eroded when it was demonstrated that the latency period for the appearance of radiation damage in the nervous system is simply longer than in other organ systems.<sup>55</sup> Subsequent interest in the pathogenesis of delayed radiation necrosis in clinical medicine has produced a significant body of literature. Recent studies of radiation-induced brain damage in human patients have used computed tomography to confirm CNS abnormalities that are not associated with the tumor under treatment but occur



**Figure 7-5.** Idealized performance time-course profiles for an acute, radiation-induced behavioral decrement. Soon after a sufficiently large dose of radiation, several animal species exhibit early transient incapacitation (upper panel) or early performance decrements (lower panel). Smaller transient deficits may occur around 45 minutes and 4 hours later. Early transient incapacitation has been reported at doses as low as 3 Gy, while early performance decrements require larger doses of 100–300 Gy.

EPD: early performance decrement

ETI: early transient incapacitation

Data sources: (1) Bruner A. Immediate dose rate effects of <sup>60</sup>Co on performance and blood pressure in monkeys. *Radiat Res.* 1977;70:378–390. (2) Pitchford T. *Beagle Incapacitation and Survival Time After Pulsed Mixed Gamma Neutron Irradiation*. Bethesda, MD: Armed Forces Radiobiology Research Institute; 1968.

because of the radiotherapy.<sup>56</sup>

General (although not universal) agreement exists that there is a threshold dose below which no late radiation-induced morphological sequelae occur in the CNS. In humans, the “safe” dose has been a topic of considerable debate. Depending on the radiation field size, the threshold for CNS damage has been estimated to be 30 to 40 Gy if the radiation is given in fractions,<sup>57</sup> although spinal cord damage may occur with fractionated doses as low as 25 Gy.<sup>58</sup> The difference between a safe and a pathogenic radiation dose to the brain may be as small as 4.3 Gy.<sup>59</sup>

It is clear that the technique used to assess neuropathology can profoundly influence its detection. In an inspection of neutron-irradiated brain tissue stained with silver to detect degenerating neural elements, punctate brain lesions were found within 4 days after exposure to 2 to 8 Gy protons and electrons.<sup>60</sup> The degeneration was linear through this dose range and the cellular profile suggested that beta astrocytes were the primary targets. At higher doses (20–100 Gy), the findings suggested a saturation effect. The lesions were

not detectable using standard hematoxylin and eosin stains. These effects are similar to a multiinfarction syndrome in which the effects of small infarctions accumulate and may become symptomatic. This pathology was observed at a dose of radiation previously believed to be completely safe, suggesting that the brain is radiosensitive.

In an organ like the brain, different topographical regions may vary in their susceptibility to ionizing radiation. The most sensitive area is the brainstem.<sup>61</sup> The brain cortex may be less sensitive than the subcortical structures,<sup>62</sup> such as the hypothalamus,<sup>63</sup> the optic chiasm, and the dorsal medulla.<sup>64</sup> Although radiation lesions tend to occur more frequently in brain white matter,<sup>65-67</sup> the radiosensitivity of white matter also appears to vary from region to region.<sup>62</sup>

In this regard, researchers have produced measures of the functional sensitivity of some brain areas and the insensitivity of others.<sup>68,69</sup> The activation of behaviors through electrical stimulation of the lateral hypothalamus (but not the septal nucleus or substantia nigra) is still possible after 100 Gy.<sup>70,71</sup> However, years after clinical irradiations, dysfunction of the hypothalamus remains prominent even without evidence of hypothalamic necrosis.<sup>72</sup> Local subcortical changes may exist in the reticular formation and account for radiation-induced hyperexcitability of the brain.<sup>73,74</sup> Similarly, postirradiation spike discharges are more likely to be seen in hippocampal electroencephalographs than in the cortical electroencephalographs.<sup>75</sup> The idea of selective neurosensitivity is further supported by experiments in which electrical recordings were made from individual nerve fibers after irradiation.<sup>76</sup> These data reveal a hierarchy of radiosensitivity in which gamma nerve fibers are more sensitive than beta fibers, and alpha nerve fibers are the least sensitive.

A recent series of papers described the use of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy to monitor radiation damage in the CNS.<sup>77,78</sup> Noninvasive imaging modalities allow temporal and spatial assessment of tissue alterations. Adult rodents were assessed over the course of 1 to 18 months after a single exposure of 1 to 4 Gy iron-56 (a component of cosmic radiation). Although no visual abnormalities were reported from anatomical MRI, the authors reported that quantifiable MRI and magnetic resonance spectroscopy results allowed identification of biophysical changes in all memory-related regions of interest prior to evident histological damage. As early as 1 month after brain-only radiation exposure, they reported no neuronal loss, but damage to the non-neuronal cells was indicated by decreased quantitative measures of brain water mobility (diffusion-weighted imaging) and increased edema (T2-weighted imaging;

Figure 7-6). These findings were supported by immunohistochemical data, suggesting that apparent diffusion coefficients, computed from diffusion-weighted imaging, are one of the most sensitive MRI biomarkers to monitor early disturbances within brain tissue after radiation exposure. Evaluation of the dynamic nature of radiation effects within the brain showed that up to 18 months after a single exposure to radiation, MRI can demonstrate temporal changes that correspond to evolving glial cell changes.<sup>79</sup> These studies demonstrate that quantification of noninvasive imaging modalities can delineate short- and long-term radiation effects. While many imaging studies are animal investigations, these reports could be readily translated to the clinical setting if needed.

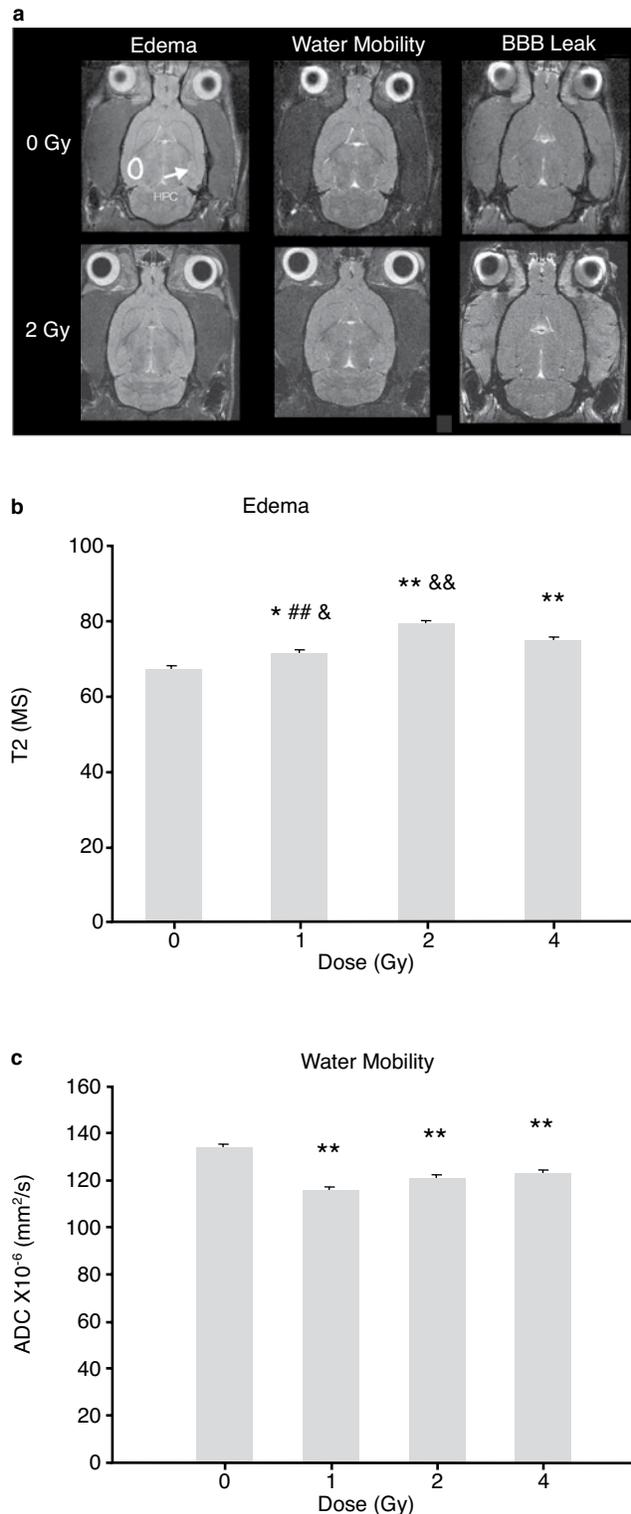
### Latent Central Nervous System Radiation

The phenomenon of latent CNS radiation damage with doses above threshold has been well documented.<sup>53,80,81</sup> The long latent period has led to considerable speculation on the likely pathogenesis of late radiation lesions: (a) radiation may act primarily on the vascular system, with necrosis secondary to edema and ischemia, and (b) radiation may have a primary effect on cells of the neural parenchyma, with vascular lesions exerting a minor influence.<sup>54</sup>

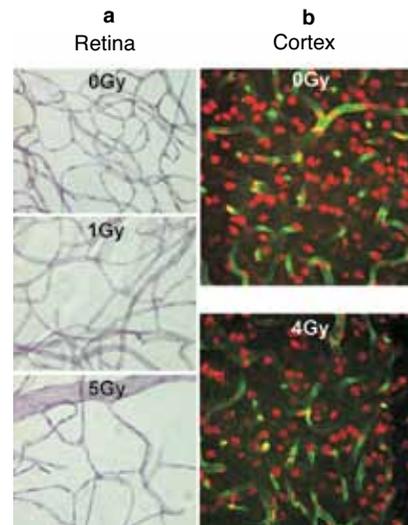
The first evidence in support of a vascular hypothesis was obtained when human brains that had been exposed to X-rays were examined.<sup>55</sup> It was suggested that delayed damage of capillary endothelial cells may occur, leading to a breakdown of the blood-brain barrier (Figure 7-7). Mao and colleagues<sup>82,83</sup> demonstrated a time- and dose-dependent loss of the vasculature following gamma and proton radiation exposure in rodents. Significant decrements in vessel growth were found<sup>83</sup> and could be observed as long as 12 months after a single 8- or 28-Gy exposure.<sup>84</sup> The microvascular loss within the eye could be prevented by treatment with a metalloporphyrin antioxidant mimetic.<sup>84</sup> Together, these findings strongly suggest that radiation exposure results in long-term alterations in vascular function.

Further evidence for vascular dysfunction has shown that radiation-induced blood-brain-barrier breakdown results in vasogenic edema, elevated blood pressure leading to impaired circulation of cerebral spinal fluid, and eventually neuronal and myelin degeneration.<sup>85,86</sup> The finding that hypertension accelerates the appearance of vascular lesions in the brain after irradiation with 10 to 30 Gy also supports a hypothesis of vascular pathogenesis.<sup>87</sup> The occlusive effects of radiation on arterial walls may cause a transient cerebral ischemia.<sup>88</sup>

**Figure 7-6.** Quantitative analysis of magnetic resonance imaging data reveals alterations 1 month after brain-only radiation exposure. (a) No visual anatomical changes were observed in rats on either imaging for edema (T2-weighted imaging), in water mobility (diffusion-weighted imaging), or enhanced blood-brain barrier leak. (b) However, quanti-



fication of water content (edema) within the hippocampus and entorhinal cortex (data not shown) revealed increased tissue edema. (c) Decreased water mobility (quantitative diffusion-weighted imaging, the apparent diffusion coefficient) revealed restricted water mobility in the irradiated brains compared to control. The decrements in water mobility are reflective of the differential neuropathology in microstructure evolving with radiation dose.  
 \*:  $P < 0.05$ ; \*\*:  $P < .01$  vs 0 Gy; ##:  $P < 0.01$  vs 2 Gy; &:  $P < 0.05$ ; &&:  $P < 0.01$  vs 4 Gy; ADC: apparent diffusion coefficient; BBB: blood-brain barrier; T2: T2-weighted imaging  
 Data source: Huang L, Smith A, Cummings P, Kendall EJ, Obenaus A. Neuroimaging assessment of memory-related brain structures in a rat model of acute space-like radiation. *J Magn Reson Imaging*. 2009;29:785–792.



**Figure 7-7.** Vascular alterations following radiation exposure. (a) Rat retinal vascular morphological changes at 12 months following iron-56 irradiation of 0, 1, and 5 Gy of the rodent eye. Significant endothelial cells and vessel loss at 1 and 5 Gy was observed late after a single radiation exposure. (b) Cranial irradiation evoked morphological microvessel changes in the rat brain cortex at 12 months following iron-56 irradiation. In an unirradiated, age-matched control, the microvessels were normal, of uniform size with smooth contours. However, 12 months following 4-Gy radiation exposure, the microvessels within the cortex were torturous with nonuniform contours (see also Archambeau JO, Mao XW, McMillan PJ, et al. Dose response of rat retinal microvessels to proton dose schedules used clinically: a pilot study. *Int J Radiat Oncol Biol Phys*. 2000;48:1155–1166; Mao XW, Crapo JD, Mekonnen T, et al. Radioprotective effect of a metalloporphyrin compound in rat eye model. *Curr Eye Res*. 2009;34:62–72).  
 Slides courtesy of Dr V Mao, Loma Linda University, Loma Linda, CA.

## ANIMAL STUDIES

Animals, such as mice, share many features with humans at the anatomical, cellular, biochemical, and molecular levels. They also share brain functions, such as anxiety, hunger, circadian rhythm, aggression, memory, sexual behavior, and other emotional responses with humans; therefore, many studies use animal models to approximate human behavioral responses following irradiation and to develop therapeutic interventions for radiation-induced CNS impairments. In laboratory animals, single doses of radiation up to 10 Gy did not produce any late morphological changes in the brain or spinal cord.<sup>62,89</sup> However, necrotic lesions were seen in the forebrain white matter from doses of 15 Gy.<sup>85,90</sup>

In a series of reports, Kiani and colleagues demonstrated that there are significant alterations in the vasculature of the hamster cremaster muscle following a single dose of radiation.<sup>91-93</sup> Both vascular density (capillaries) and blood flow were reduced at 3 to 30 days after irradiation<sup>92</sup> and these effects remained evident for as long as 6 months after a single 10-Gy dose.<sup>91</sup> Mao and colleagues reported similar decrements in the retinal vasculature after components of space irradiation, such as proton and iron-56 irradiations.<sup>82,83</sup> Perfusion and oxygenation deficits in the mouse brain were reported recently after a single 20-Gy exposure.<sup>94</sup> Kiani and colleagues demonstrated that the numbers of anatomical and perfused vessels were decreased up to 30 days after radiation.<sup>94</sup> In conjunction with these findings, they also reported that there was an increase in the distance to the nearest perfused vessel (irradiated approximately 45  $\mu\text{m}$  at 3 days postirradiation, controls approximately 20  $\mu\text{m}$ ).<sup>94</sup> Although there was some return toward control intervessel distances, they never completely returned to control values.

A supportive finding for this apparent decrement in perfused vessel distance was the discovery that local tissues had a 200% increase in tissue hypoxia levels at 3 days postirradiation.<sup>94</sup> Although these very elevated levels of tissue hypoxia slowly declined over the next 120 days, they never reached control levels. Oxygenation pattern modeling also showed significant differences in irradiated tissues compared to age-matched controls.<sup>93</sup> No studies have examined the role of tissue hypoxia after brain radiation.

The hippocampus, like all regions of the brain, is dependent upon an intact and functioning vasculature to deliver oxygen and nutrients. Radiation has short-term (less than 1 month) and long-term (greater than 1 month) effects on brain function. In rodent studies, long-term effects can evolve over 1,

3, or even 12 months following irradiation. Cognitive effects are defined as effects on learning and memory. As behavioral changes can influence performance on cognitive tests, potential effects of irradiation on noncognitive behavioral measures need to be carefully considered in the interpretation of the cognitive effects. For example, potential alterations in measures of anxiety, sensorimotor function, motivation, social hierarchy, and vision can affect performance on tests of spatial learning and memory. Behavioral and cognitive performance are also influenced by genetic and environmental factors; therefore, they need to be carefully considered when assessing effects of irradiation on the brain. Thus, even after a comparable radiation exposure, the genetic makeup of an individual might critically modulate the impact of the irradiation on brain function. As was noted in the introduction, the effects of irradiation on brain function are also sex-dependent and different in female and male C57Bl6/JWT mice.<sup>95</sup> Female and male C57Bl6/J mice express different forms of genetic risk factors for age-related cognitive decline and show differences in developing cognitive impairments following challenges such as traumatic brain injury and cardiac bypass surgery.<sup>96</sup> Various studies have pooled behavioral data from male and female mice to increase statistical power. However, because of the sex differences in irradiation effects and increased variations within female mice due to individual differences in the estrous cycle, it is best not to pool male and female data. With the increase of women in the armed forces, it is important to consider sex differences in evaluating the potential effects of irradiation on brain function.

In addition to sex, age can also influence susceptibility to changes in brain function after irradiation exposure. Some impairments might become detectable or more profound in aged animals following irradiation earlier in life, and animals of different ages are likely to show different susceptibilities to altered radiation-induced changes in brain function following a specific time interval.

Efforts in elucidating the mouse genome have dramatically accelerated human-mouse comparative research. Over 90% of mouse and human genes are syntenic. Employing an automated alignment of rat, mouse, and human genomes, it was shown that 87% of human and mouse-rat sequences are aligned, and that 97% of all alignments with human sequences larger than 100 kb agree with an independent 3-way synteny map.<sup>97</sup> Finally, nearly 99% of human genes have mouse equivalents.<sup>98-114</sup>

## Radiation Dose

A variety of radiation parameters, including dose, can significantly influence EPDs (see Figure 7-5). Low doses of radiation can sometimes produce behavioral changes, such as locomotor activation,<sup>69</sup> that contrast with the locomotor depression observed after high doses.<sup>71</sup> Beyond a certain threshold, more radiation tends to produce increasingly depressed measures of performance.<sup>104,115,116</sup> The radiation dose-response curves for measures of behavior in some ways parallel the curves observed for a number of end points, such as emesis and lethality.<sup>117</sup>

## Radiation Dose Rate

Another radiation factor that can influence behavior is exposure dose rate.<sup>118</sup> Fractionated (or split) doses have been used to model the cumulative effects of radiation or to model radiation exposure over an extended period of time. As such, these studies may be useful in describing the impact on behavior after radiation exposure. Most studies report that a single dose results in more effective disruption of behavior than to split doses.<sup>113,119-127</sup>

## Radiation in Space

As military operations move to space, new radiation hazards will challenge humans' abilities to carry out missions.<sup>128,129</sup> The behavioral effects of ionizing radiation (such as from protons and high-Z particles) in space are being actively explored.<sup>130,131</sup> A unique feature of the space radiation environment is the presence of high-energy charged particles, including protons, which comprise approximately 90% of the cosmic rays and fully ionized atomic nuclei, such as iron-56. These radiations may pose a significant hazard to space flight crews not only during military missions but also at later times when slow-developing, adverse effects might become more apparent. The hazards associated with the space environment will likely impact many organs and systems, and in the CNS, exposure to such radiation may directly affect structure and function within the brain (eg, behavioral performance), but also may change the tissue sensitivity to secondary insults such as trauma, stroke, or degenerative disease.

The effects of space irradiation on behavior and cognition might be more profound than that of earth irradiation for a few reasons. First, the energy of the irradiation is much higher in space than on Earth. In addition, there are other environmental stresses in space that might affect performance and interact with the effects of irradiation, such as the lack of circadian

variations in light encountered on Earth, weightlessness, and being confined to a relatively small space for prolonged periods of time.

Similar to the sex-dependency of effects of cesium-137C irradiation described above, the effects of space irradiation on cognitive performance might also be sex dependent. When female and male mice were exposed to iron-56 irradiation at a dose of 1, 2, or 3 Gy and fear conditioning was assessed, male mice showed enhanced cognitive performance, while female mice showed reduced cognitive performance, as compared to sex-matched, sham-irradiated mice.

## Irradiation and Sensory and Perceptual Changes

Sensory and perceptual processes are distinct, yet interrelated. The sensory process involves stimuli that impinge on the senses, such as vision, audition, olfaction, gustation, and skin sensation.<sup>132</sup> The perceptual process involves the translation of these stimuli by the brain into appropriate overt or covert interpretation or action. Ionizing radiation can be sensed and perceived, and radiation-induced sensory activation can in fact occur at extremely low levels.<sup>133</sup> For instance, the olfactory response threshold to radiation is less than 10 mrad, and the visual system is sensitive to radiation levels below 0.5 mrad. Ionizing radiation is as efficient as light in producing retinal activity, as assessed by the electroretinogram. The visibility of ionizing radiation was reported shortly after the discovery of X-rays and is now firmly established.<sup>114</sup>

### Vision

Although the visual system can detect a low radiation dose, large doses are required to produce pathological changes in the retina. This is especially true for the rods, which are involved in black and white vision.<sup>134</sup> Necrosis of rods has been reported after irradiation doses of 150 to 200 Gy in rats and rabbits, and after 600 Gy in monkeys. Cone (color vision) ganglion cells are even more resistant to radiation. At these high radiation doses, cataracts occur.<sup>135-139</sup>

Although pathological changes in the visual system occur only at high doses, visual function is affected at lower doses. Rats trained to a brightness discrimination task are not able to differentiate between shades of gray after 3.6 Gy or to make sensitivity changes after exposure to 6 Gy of whole-body X-rays.<sup>114</sup> In mice, low-rate, whole-body irradiation adversely affected brightness discrimination tested 3 to 5 months after exposure. Humans experienced temporary decrements in scotopic visual sensitivity 1 day after being exposed to 0.3 to 1.0 Gy of X-radiation.<sup>140</sup> Long-term

(20–36 days) changes in dark adaptation are reported in patients exposed to 4 to 62 Gy of X-rays.<sup>141</sup>

With regard to visual acuity, only long-term deficits were reported in monkeys at 1 to 3 years after whole-body exposure to 3 to 60 Gy of radiation.<sup>114,142</sup> However, the potential effects of irradiation on attention may have caused some of these effects.<sup>143</sup>

### **Audition and Vestibular Function**

Few adverse auditory changes have been noted after radiation exposure. Two grays of X-ray irradiation to the head produced no changes in cochlear microphonics in rats examined up to 90 days after exposure.<sup>138,144,145</sup>

The physiological substrate of hearing deficits might involve changes in the mouse ear, reported following 20 to 30 Gy of whole-body X-rays, which included cellular necrosis in the organ of Corti and in the epithelial cells of the ear canals.<sup>114</sup> Rats exposed to a whole-body dose of 1 to 30 Gy of gamma or X-radiation showed damage in the cochlea but not in the cristae of the vestibular inner ear or the middle ear. Human patients who received 40 to 50 Gy of therapeutic gamma radiation developed inflammation of the middle ear but only a temporary loss of auditory sensitivity and temporary tinnitus.<sup>146,147</sup>

Vestibular function may be more radiosensitive than audition. Depression in vestibular function may exist at doses close to the LD<sub>50</sub> and symptoms of vestibular disruption may last longer at higher than at lower doses.<sup>148,149</sup>

### **Other Senses**

Olfactory and gustatory changes have been reported in patients exposed to therapeutic radiation.<sup>150</sup> There are altered taste perceptions in patients exposed to 36 Gy of X-rays, with a metallic taste being the most common report. Transient changes in taste and olfactory sensitivity are also reported in radiotherapy patients and in rats.<sup>114</sup>

Radiation may affect the skin senses, but it is often difficult to distinguish the direct receptor changes due to secondary changes arising from effects on the vascular system.<sup>135</sup> Radiation-induced changes in pain perception may be species dependent; gamma photons produce a dose-dependent analgesia in mice,<sup>151</sup> but gamma or X-rays may not alter the analgesic effects of morphine or the anesthetic effects of halothane in rats except under certain conditions.<sup>152,153</sup>

In summary, whole-body radiation doses below LD<sub>50</sub> do not appear to produce permanent sensory changes. However, there may be transient alterations

at doses of 1 to 5 Gy. High levels of radiation can cause longer-lasting sensory impairments and impair perceptual function.

### **Effects of Irradiation on Naturalistic Behaviors**

Naturalistic behaviors (spontaneous locomotion, anxiety, social interaction, consumption behaviors, taste aversion, and emesis) are often evaluated in the study of radiation effect may affect performance on cognitive tests.<sup>75,103,107,114,127,129,134,135,143,145,154–196</sup>

### **Effects of Irradiation on Cognitive Performance**

Regarding the effects of radiation on cognitive function, it is especially important to distinguish short- and long-term effects on brain function. Brain function can be altered at the time of or shortly after irradiation. Obviously, potential alterations in cognitive function during or shortly after irradiation on the battlefield can be detrimental for executing the aims of a specific operation or effort. In addition to these relatively short effects, there may also be long-term effects that need to be considered. In the extreme, potential effects of irradiation earlier in life might alter one's susceptibility to develop age-related cognitive decline and neurodegenerative diseases like Alzheimer's disease.

In human studies, environmental factors such as diet, sleep cycle, and stress levels are much more difficult to control for. For instance, a few cases of acute retrograde amnesia were reported by individuals who survived the bombing of Hiroshima.<sup>197</sup> Five years after the attack, deficits in memory and intellectual capacity were noted in individuals experiencing radiation sickness.<sup>18</sup> These data are consistent with other human studies reporting memory deficits in patients who had undergone therapeutic irradiations.<sup>198</sup> Radiation-induced brain injury is a limiting factor during therapeutic irradiation of the brain.<sup>199</sup> Overt tissue injury generally occurs only after relatively high doses. However, there is a strong likelihood of developing adverse reactions in terms of cognitive decline after relatively lower doses,<sup>200</sup> but in humans, the memory impairments may have been strongly influenced by other environmental stressors of war or associated with the armed forces.

Cognitive changes following irradiation have a diverse character and, in humans and animals, often include hippocampus-dependent functions involving learning and memory and spatial-information processing.<sup>201–203</sup> The susceptibility to developing selective hippocampus-dependent cognitive impairments remains elusive. One possibility is that these radiation

effects involve alterations in the ability to generate new neurons throughout life and loss of mature neurons in the dentate gyrus,<sup>203–205</sup> alterations in receptor subunits involved in learning and memory,<sup>206</sup> and measures of neuronal signaling as assessed using in-vivo and in-vitro electrophysiology,<sup>207</sup> genetic risk factors,<sup>96</sup> and changes in oxidative stress.<sup>203,208,209</sup>

### *Early Effects*

Early radiation effects are particularly pertinent to the armed forces because its members deal with the potential immediate effects of irradiation on cognitive performance during critical missions. Delayed reaction time was noted in an animal response task fallout study. Delayed reaction times were noted in each study group.<sup>210,211</sup> It is important to consider that fatigue and weakness, more often seen following irradiation above a threshold than as a dose-response effect, will likely affect cognitive performance and contribute to cognitive impairments.

### *Early Transient Incapacitation and Other Early Performance Decrements*

In various animal models, ETI is a strikingly short, intense phenomenon. A less severe variant of ETI is EPD, in which performance is reduced rather than totally suppressed (see Figure 7-5). Initially, it was presumed that ETI and EPD would occur only at supra-lethal radiation doses and that, after behavioral recovery, death would occur in hours or days. However, high doses may not be necessary to produce these effects,<sup>115,118</sup> particularly when performing a more difficult task requiring both visual discrimination and memory.<sup>118</sup> Thus, relatively low doses of radiation may cause rapid, transient disruptions in performance.<sup>210–218</sup>

The issues of task demands and task complexity influencing the effective radiation level are common in the investigation of ETI. For instance, the dose of radiation required to disrupt performance was com-

pared for three tasks: the visual discrimination task (with a 5-second response time), a physical activity task, and an equilibrium-maintenance task.<sup>115,116,219</sup> The data suggest that a range of performance decrements result from radiation exposure, with visual function least affected and physical activity most affected. Recovery time and behavioral effectiveness after radiation exposure have obvious implications for military missions.<sup>115,129</sup>

### *Late Effects*

Retrograde amnesia is a short-term memory loss or an inability to recall recent events following trauma or a novel event.<sup>133</sup> The mechanisms of radiogenic amnesia are unclear but might involve sensory disruption, primarily of the visual system.<sup>220–224</sup> Classical conditioning research data indicate that radiation exposure can alter learning and memory and do not merely reflect nonassociative factors.<sup>225</sup>

It should be emphasized that the effects of irradiation on cognitive function are complex. Decreased, unaltered, and increased performance has been reported. This complexity might depend on the age of animals at the time of irradiation; the cognitive testing paradigm; the genetic makeup and sex of the animals; potential environmental conditions present prior, during, or after the irradiation; the dose of irradiation used; the interval between irradiation and cognitive testing; and the cognitive test and test design used (Figure 7-8).<sup>96,114,145,202,203,209,226–234</sup>

Although some of the behavioral radiobiology literature suggests that learning and performance are relatively radioresistant, most studies have reported postirradiation changes. For instance, maze-learning behavior was reduced after X-ray exposure up to 10 Gy.<sup>158</sup> More challenging tasks might be more radiosensitive than easier ones. Indeed, rats were found to have a temporary reduction in their ability to reorganize previously learned material after exposure to 4 Gy of gamma radiation (Figure 7-9).<sup>159</sup>

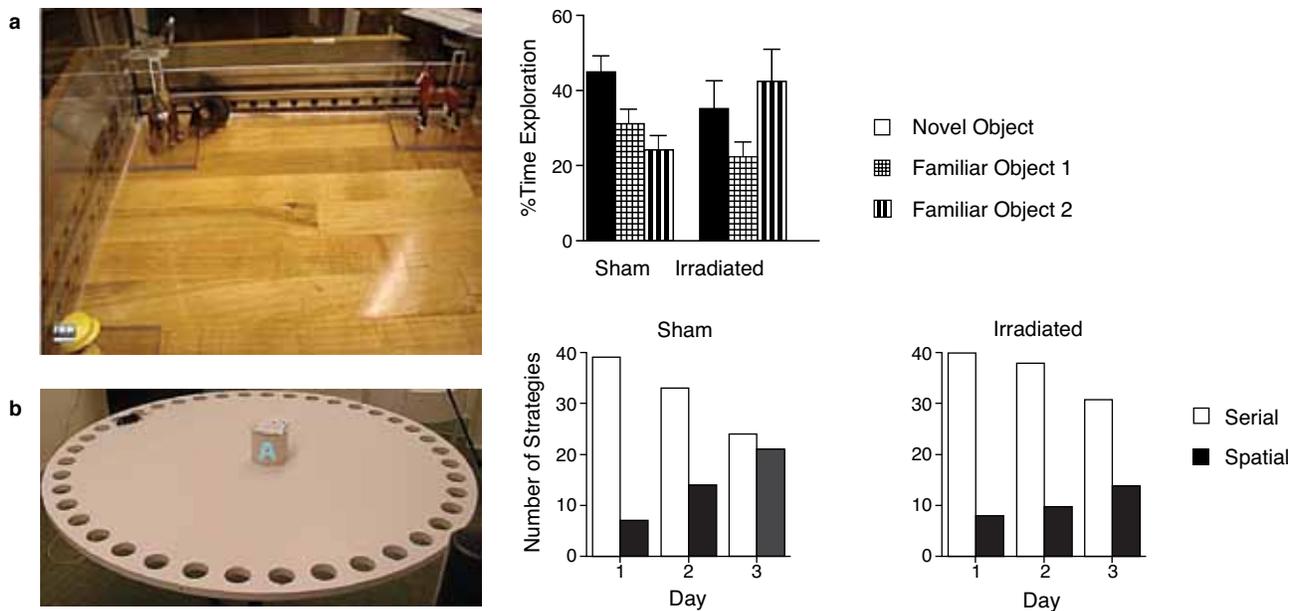
## NEUROPHYSIOLOGICAL CHANGES IN THE HIPPOCAMPUS FOLLOWING RADIATION

There are a number of methods for assessing CNS-induced functional changes within the brains of humans and experimental animals. Some approaches, such as electroencephalography, are truly noninvasive, whereas others—like in-vivo depth electrodes (extracellular recordings)—are not. Electrophysiological recordings from excised tissues are also used. These excised tissues can come from a host of brain regions, but the most common is the hippocampus, an important structure for spatial learning and memory, passive

avoidance, and some forms of object recognition. Human tissues are also available, primarily as neurosurgical resections during the course of amelioration of disease, such as epilepsy or tumors.<sup>59,115,142,143,159,162,229,235–243</sup>

### **Radiation Exposure of the Central Nervous System**

The deleterious effects of radiation are not limited to mitotically active cell types, such as neuronal precursors in the CNS,<sup>203</sup> but also alter nondividing cells,



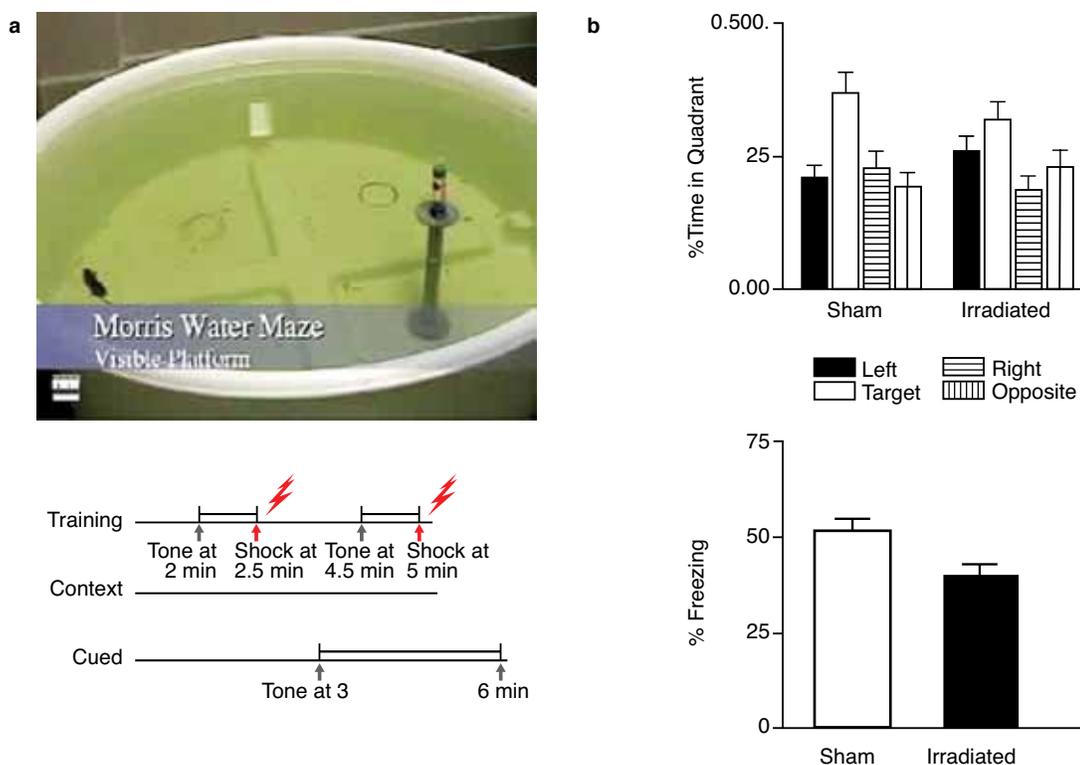
**Figure 7-8.** Effects of cesium-137 irradiation on hippocampus-independent, novel object recognition and hippocampus-dependent search strategies in spatial learning and memory in the Barnes maze. (a) Mice were habituated to an open field without any objects over 3 days. On the fourth day, the mice were trained in three trials containing three objects kept in the same location (left panel). In the novel object recognition trial, one object was replaced with a novel one. While sham-irradiated mice spent significantly more time exploring the novel object than the two familiar ones, mice irradiated with cesium-137 at a dose of 10 Gy and tested 3 months later did not ( $*P < 0.05$  vs both familiar objects; Villasana and Raber, unpublished observations). (b) In the Barnes maze, mice were tested to locate a hidden escape tunnel over 3 days. As the mice learned the task, they switched from using serial searches (searching consecutive holes in either direction until the escape tunnel was located) to spatial searches (directly searching the hole containing the escape tunnel or the adjacent holes). However, with training, the percentage of spatial searches was higher and the percentage of serial searches lower in sham-irradiated mice than mice irradiated with cesium-137 at a dose of 10 Gy and tested 3 months later. Data source: Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments associated with changes in hippocampal neurogenesis. *Radiat Res.* 2004;162:39–47.

such as CNS neurons. Currently, little information is available on the effects of radiation on CNS function using electrophysiological techniques. An array of studies in the last 20 years has examined functional and electrophysiological alterations within the CNS following radiation exposure, but many of these have been surveys. Few electrophysiological studies examine the dose response of CNS injury to radiation.<sup>199</sup>

The hippocampi of humans and experimental animals are often the most studied because this brain region is similar in laminar structure, cellular composition, and function. Excised tissues provide a variety of electrophysiological, extracellular, intracellular, and, more recently, patch clamp recordings, which allow the study of cellular ion channels, each unique in the type of functional data they provide. As noted previously, there are numerous electrophysiological studies examining epileptic and tumor tissues from humans, but no studies involving radiation exposure. In animal studies, electrophysiological field excitatory postsynaptic potential recordings can be evaluated on

the basis of the physiological question posed (Figure 7-10).

Table 7-1 briefly summarizes some of the types of information that can be gleaned from electrophysiological recordings. Synaptic excitability can be evaluated by constructing input-output curves at incrementally increasing stimulation intensities. Paired-pulse facilitation (PPF) is often used to test changes in presynaptic glutamate release. PPF is evoked by paired-pulse stimulation, in which a second electrophysiological response is elicited at interpulse intervals ranging from 20 to 200 milliseconds using 30% to 50% of maximal response derived from the input-output tests. Typically, the second response is facilitated and PPF is calculated as a ratio of the second/first electrophysiological response. The function of feedback-inhibitory interneurons can be assessed by paired-pulse inhibition. Similar to PPF, two stimuli are applied at 10- to 200-millisecond interpulse intervals and the second response is typically reduced because of feedback inhibition of the primary hippocampal neurons. Long-



**Figure 7-9.** Effects of cesium-137 irradiation on hippocampus-dependent spatial memory retention in the water maze probe trial and hippocampus-dependent contextual fear conditioning. **(a)** In the water maze, 2-month-old C57Bl6/J male mice were trained to locate a visible platform in 12 trials over 2 days (left panel shows the water maze with the clearly visible platform). The mice were trained to locate visible platforms in four different locations. Subsequently, they were trained to locate a hidden platform in 12 trials over 2 days. One day after the last hidden-training trial, the mice were tested in a probe trial (no platform). While sham-irradiated mice spent more time searching the quadrant of the pool where the hidden platform was previously located, mice irradiated with cesium-137 at a dose of 10 Gy and cognitively tested 3 months later did not ( $P < 0.05$  vs any other quadrant).<sup>1</sup> **(b)** Two-month-old C57Bl6/J male mice were trained in a fear conditioning paradigm. As indicated in the left panel, mice received two tone-shock pairings. The next day, hippocampus-dependent fear conditioning was assessed in the same environment in which the mice were trained. No tone or shock was administered. Sham-irradiated mice showed significantly more freezing (immobility measure) than mice irradiated with cesium-137 at a dose of 10 Gy ( $P < 0.05$  vs sham-irradiated mice).

(1) Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal

term potentiation (see Figure 7-10) is used to test cellular plasticity and can be evoked by high-frequency stimulation of hippocampal pathways, which leads to potentiated responses (> 200% increases). Intracellular and patch clamp recordings are used to assess the fundamental characteristics of neurons under investigation, including action potential amplitudes and duration and the ability of the cell to maintain its resting membrane potential. While numerous other cellular electrophysiological tests exist, the few cited here demonstrate the wealth of neurophysiological function that can be obtained in these studies.

Pellmar and colleagues have reported the most comprehensive data using in-vitro hippocampal slices to model acute radiation-induced injury. Two

models were developed, one employing peroxide application<sup>244</sup> and another that exposes slices directly to gamma irradiation.<sup>245</sup> Direct exposure of hippocampal slices to gamma rays resulted in a dose- and dose-rate-dependent decrease of evoked activity. While lower doses resulted in synaptic impairment, high doses resulted in postsynaptic efficacy decrements, and decreased action potential generation (ie, decreased neuronal output). The observed postsynaptic damage was not sensitive to dose rate. In conclusion, these studies demonstrate that radiation can alter the integrated functional activity of hippocampal neurons.<sup>245</sup> Depleted uranium exposure is also thought to result in neurotoxicity.<sup>246</sup> Further study is required to determine the effects of depleted uranium on CNS

TABLE 7-1

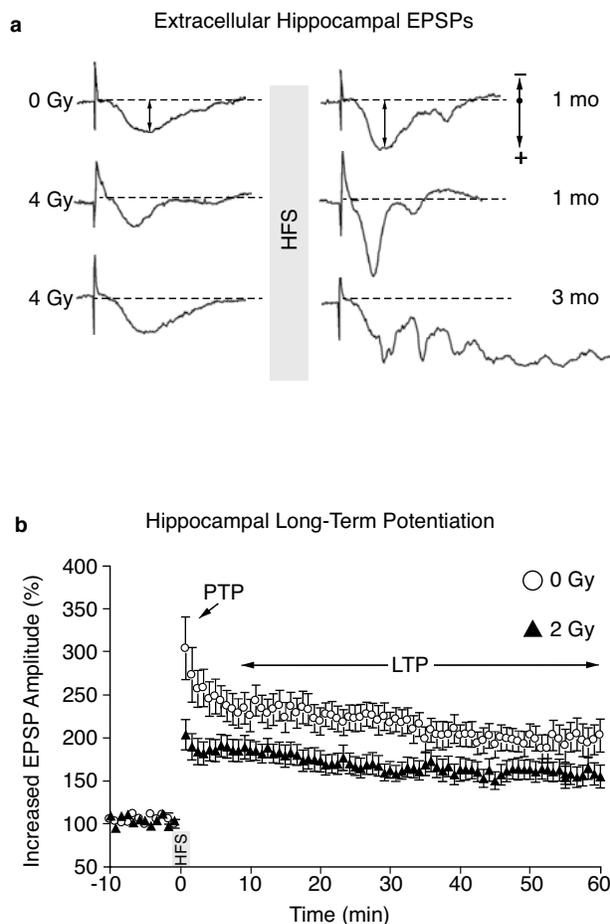
**MAJOR NEUROPHYSIOLOGICAL OUTPUTS FROM ELECTROPHYSIOLOGY**

Parameter	Definition
<i>Extracellular</i>	
Input-output relationship	Presynaptic vs postsynaptic excitability, synaptic efficacy
Paired-pulse facilitation	Short-term plasticity, presynaptic glutamate release
Long-term potentiation	Long-term plasticity and cellular model of learning and memory
Paired-pulse inhibition	Assess feedback inhibitory neurons (GABAergic)
<i>Intracellular</i>	
Resting membrane potential	Resting membrane potential of the cell
Input resistance	Input resistance of the cell
Action potential amplitude	Size of the action potential
Action potential duration	Duration of the action potential

function. Radiotherapy treatment reports can yield some insight into altered physiology, but most are not directly applicable.<sup>245,247-252</sup>

**Space Radiation Exposure of the Central Nervous System**

More recently, the effects of heavy ion radiation on the CNS, specifically the CA1 region of the hippocampus, have been described. Extracellular in-vitro recordings were obtained following brain-only exposure to iron-56, a component of space radiation, which demonstrated a number of changes that were dose and time sensitive. First, synaptic efficacy was increased after radiation exposure but appears to be more prominent earlier (1 month) after irradiation rather than later (12 months). No enhancement was found within the CA1 using PPF at any of the time points investigated. Long-term potentiation, an established model of learning and memory in hippocampal slices, is altered after radiation exposure at 1 month after radiation exposure. These decrements in long-term potentiation become more pronounced over the 12-month observation period, consistent with and suggesting progressive deterioration of the synaptic circuitry within the hippocampus. These findings were



**Figure 7-10.** Neurophysiological alterations following radiation exposure within the CA1 region of the hippocampus. (a) Cranial radiation (iron-56, 600 MeV) resulted in hyperexcitability within the CA1 of the hippocampus. High-frequency stimulation was used to simulate learning and memory (long-term potentiation), as evidenced by increased amplitude of the extracellular excitatory postsynaptic potentials (double-headed arrows). Evidence for altered hippocampal circuitry, in the form of increased excitability, was observed at 3 months following a single radiation exposure, which then returned to “normal” at later time points (> 6 months). (b) Decrements in learning and memory using a model system (long-term potentiation) have been observed following iron-56 irradiation. These decrements were also observed immediately after high-frequency stimulation and were manifested as an immediate decrease in the extracellular excitatory postsynaptic potential amplitude in the posttetanic potentiation phase and was followed by a sustained decrease in the output of the hippocampus (ie, decreased learning and memory). EPSP: excitatory postsynaptic potential HFS: high-frequency stimulation LTP: long-term potentiation PTP: posttetanic potentiation Data source: Obenaus A, Vlkolinsky R, Loma Linda University, Loma Linda, CA.

not dose dependent. However, at every time point, the 2-Gy dose appeared to be more deleterious, a finding that has been previously reported.<sup>251</sup> One of the more interesting observations was that at early time points (1 and 3 months), there was increased hyperexcitability within the CA1 region of the hippocampus after radiation exposure. Multiple population spikes appeared to be more pronounced at higher doses, particularly in the 4-Gy animals (see Figure 7-10). These findings are in agreement with the earlier studies by Pellmar et al<sup>253,254</sup> that demonstrate altered excitability following radiation exposure. In addition, while many of the studies use different radiation types and qualities, the fact that similar decrements in neurophysiological function have been reported suggests the possibility that common cellular pathways are altered.

To investigate the underlying physiological mechanisms responsible for these observed changes, a series of experiments using patch clamp recordings were used to determine if the intrinsic properties of the pyramidal cell neurons were altered. No changes were found in the input resistance, resting membrane potential, action potential amplitude, or duration of the evoked pyramidal cells at any of the postirradiation time points that were investigated (3, 6, and 12 months). This would suggest that many of the electrophysiological changes in the hippocampus after iron-56 irradiation are likely due to synaptic and cellular reorganization with no changes in the intrinsic neuronal properties. Pharmacological isolation methods to remove the excitatory drive within the hippocampus allow investigation of the miniature inhibitory postsynaptic potentials that are GABAergic ( $\gamma$ -aminobutyric-acid-producing). A dose-dependent decrease in the miniature inhibitory postsynaptic potentials consistent with decreased inhibitory tone 18 months after radiation was observed. This decrease in inhibitory tone, particularly its dose dependence, is consistent and mechanistically plausible to account for the increased hyperexcitability after radiation exposure.

Recent work was reported that evaluated the functional effects of radiation on neuroinflammation. Using a peripheral immunological stressor, lipopolysaccharide, the response of the immune system was evaluated in animals that received brain-only radiation.<sup>251,252</sup> These results suggested altered processing of peripheral immune signals by the irradiated CNS. While the exact cellular and molecular radiation targets remain unknown, it has been hypothesized that space radiation may impact the functional properties of neurons and thus lead to an imbalance in neuronal network activity. Such an imbalance could potentially lead to neurological manifestations that may impact

intellectual performance and behavioral patterns (ie, learning and memory) during long-term space missions.

There is a dearth of in-vivo, adult radiation exposure research using electrophysiological methods, but several studies have used brainstem recordings to demonstrate an increased latency and length of auditory waves after 2-Gy whole-body irradiation. Follow-up microscopy revealed changes only in the cells within the brainstem auditory nuclei.<sup>255</sup> Reder et al<sup>250</sup> reported time- and dose-dependant changes in the receptive field of the lateral geniculate nucleus following proton radiation, but found no cellular necrosis or vascular damage; however, the afferents to the nucleus were disrupted.

Other model systems have been used to study the effects of radiation exposures.<sup>248</sup> Electrophysiological assessment of cerebellar neurons in culture following laser radiation detected damage to mitochondria and cellular membranes and increased membrane conductance to some ion species.<sup>256</sup>

Long-term changes within the CNS following irradiation are reminiscent of those associated with senescence. For example, Carlson et al suggested that the increased metabolic rate in irradiated animals may accelerate aging.<sup>257</sup> Later, using brain-only irradiation with argon and iron particles at a dose of 0.5 Gy, Philpott et al observed a progressive decline in motor performance and morphological changes in synaptic density in the hippocampus of C57Bl/6 mice.<sup>131,258</sup> Iron-56 radiation was also shown to impair spatial learning and reference memory where the deficits were related to synaptic neurotransmitter release.<sup>259</sup> Many of these functional changes have also been reported during normal aging.<sup>260</sup>

To further investigate if radiation mimics or alters the temporal evolution of aging, experiments were conducted using mice that exhibited accelerated aging and age-related behavioral abnormalities.<sup>207,251</sup> Amyloid precursor protein transgenic mice (APP23) showed significant deficits in synaptic transmission and electrophysiological correlates of learning and memory. A 2-year temporal study evaluating the CA1 region of the hippocampus found that radiation accelerated the onset of age-related electrophysiological decrements. In APP mice without radiation exposure, decrements in learning and memory were observed at greater than 14 months of age, but in radiation-exposed mice these same deficits were observed as early as 9 months of age. At 6 months of age, the radiation-treated animals also showed a transient reduction in inhibition that then later appeared to recover. Radiation did not significantly affect overall survival of APP23 mice. It was concluded that irradiation of

the brain may accelerate Alzheimer’s-disease–related neurological deficits.<sup>251</sup>

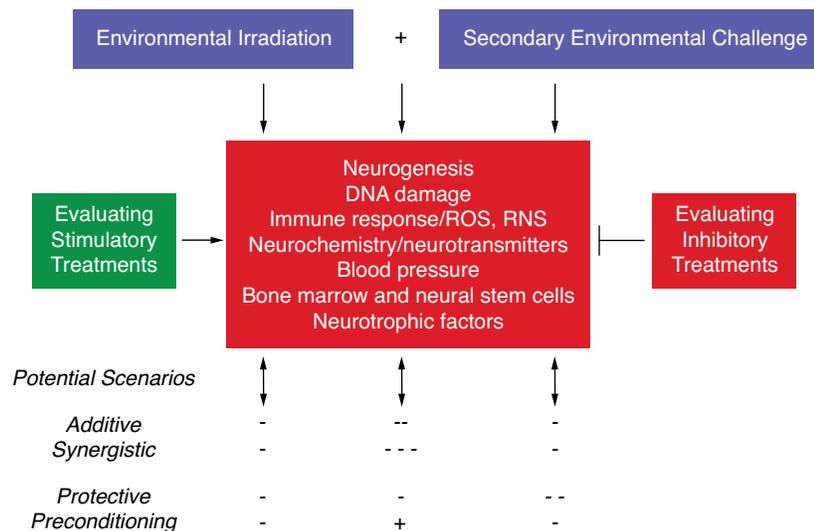
**Radiation-Induced Hyperexcitability**

Increased evoked hippocampal synaptic activity at 1 month after 0- to 4-Gy iron-56 ions,<sup>252</sup> and increased evoked and spontaneous hyperexcitability after either proton or iron-56 radiation exposure have been found (see Figure 7-10). These alterations are reminiscent of seizure disorders.<sup>261</sup> Intracellular (patch clamp) recordings evaluating functional changes within individual neurons in the face of altered networks were used to show that intrinsic neuronal membrane properties, such as input resistance, membrane time constant, action potential thresholds and duration, and spike frequency adaptation were not significantly altered at 1 to 3 months after brain-only radiation exposure.<sup>262</sup> These data suggest that the increased excitability observed in the extracellular recordings was likely the result of increased excitatory or decreased inhibitory neurotransmission, mediated in part by alterations in inhibitory neurotransmitter receptors.<sup>263,264</sup> More

recently, an interesting report demonstrated that high radiosurgical doses of photon radiation decreased the frequency of observed and electroencephalography-defined seizures in a rat model of epilepsy.<sup>265</sup> There were no changes in brain tissue at 20, 40, or 60 Gy and only moderate changes at 100 Gy, and the report further suggests that radiosurgical approaches to epilepsy treatment are warranted. Finally, age-related changes in a variety of measures also showed that older rats have increased inflammatory responses compared to younger rats after whole-body irradiation.<sup>266</sup> Younger rats have a sustained decrease in neurogenesis compared to older rats.

**Interaction of Irradiation With Other Environmental Factors**

Nuclear war would produce few “pure” radiation injuries. It is more likely that victims will experience burns, wounds, and perhaps trauma from chemical agents and environmental stresses combined with the damage from ionizing radiation (Figure 7-11). The physiological effects and treatment of irradiation



**Figure 7-11.** Schema of potential effects of combined injury on brain function. When the brain is challenged not only with irradiation but with a secondary environmental insult as well, the resulting effects on brain function are complex and hard to predict without experimental evidence. For example, the two insults might have additive or synergistic effects on brain function. However, it is also possible that the first insult serves as a preconditioning challenge and actually relatively protects the brain against the second challenge or even reverses the direction of the effects of the irradiation on brain function. Along the same lines, individuals with higher levels of antioxidant mechanisms prior to cranial irradiation might react differently to radiation effects on cognition than individuals with lower levels of antioxidant mechanisms. Based on these complex interactions, treatments targeting mechanisms potentially contributing to altered cognitive function following irradiation should also be evaluated following combined injuries.

-: detrimental effect on brain function

+: beneficial effect on brain function

DNA: deoxyribonucleic acid; RNS: reactive nitrogen species; ROS: reactive oxygen species

tion with other environmental factors has received significant attention.<sup>267,268</sup> Less clear are the behavioral and cognitive consequences from combined traumas that include irradiation. In one study, mice were exposed to 3 Gy of neutron-gamma radiation, and some were then exposed to sublethal trauma (wound or burn).<sup>269</sup> Radiation exposure alone caused reduced measures of locomotion. While the wound injury increased the harmful effects of radiation, the burn injury did not.

In a study of the combined effects of radiation (7 Gy) and an anticholinesterase agent (physostigmine, 0.1 mg/kg, which was used in recent military missions and was postulated to have contributed to Gulf War Syndrome), rats were evaluated on a behavioral test battery that included measuring their balance on a rotating rod and recording several components of their locomotor activity.<sup>270,271</sup> Forty-five minutes after irradiation, a radiation-only group had a 30% deficit in performance, while a physostigmine-only group had

a 40% deficit. A combined-treatment group showed a 60% performance deficit on the rotating rod task. All measures of performance indicated that the effect of combined ionizing radiation and physostigmine was much greater than the effect of either insult alone.<sup>272</sup> Environmental and combat stresses may also combine with radiation injuries to increase behavioral decrements.<sup>165,273-276</sup>

Other environmental stresses can alter the effectiveness of radiation on behavior or lethality. For instance, daily exhaustive exercise, continuous exposure to cold (6°C), or continuous exposure to high altitude (15,000 feet) considerably reduced the time to death and the incidence of death after irradiation.<sup>114,277</sup>

These data suggest that the behavioral effects of radiation may interact with other environmental stresses. Therefore, any estimates of battlefield performance decrements that do not include these factors might under- or overestimate the behavioral and cognitive changes actually observed in a military conflict.

## MECHANISMS AND POSSIBLE INTERVENTIONS

Although various organ systems may contribute to radiation-induced lethargy and reduced responsiveness, the nervous system's central role in behavior makes it the presumed primary mediator of radiation-induced behavioral changes (see Figure 7-11).<sup>278-280</sup> Although radiation-induced behavioral changes are well established, it is unclear which specific changes in the brain mediate these changes. Sufficiently large radiation doses cause permanent brain lesions, demyelination, and necrosis, which in turn produce chronic behavioral deficits. In addition, short-lived behavioral changes may be mediated by transient vascular changes that induce edema or ischemia in the brain. Alternatively, behavioral changes might be mediated by significant alterations in brain function due to changes in neurochemistry and neurophysiology.

### Radiogenic Pathology of the Nervous System

The anatomical specificity of radiation-induced brain injury may in part explain the ability of a particular dose of ionizing radiation to disrupt one type of behavior but not another.<sup>116</sup> Classically conditioned reflexes seem more radioresistant than motor coordination, and ionizing radiation might mainly affect the functions of the subcortical brainstem.<sup>68,281-284</sup>

Evidence for the direct action of radiation on the parenchymal cells of the nervous system (rather than the indirect effects through the vascular bed) was first provided when brain tissue in irradiated human pa-

tients was examined.<sup>285</sup> None of the brain lesions could be attributed to vascular damage because they were (a) predominantly in white matter and not codistributed with blood vessels, (b) not morphologically typical of ischemic necrosis, and (c) often found in the absence of any vascular effects.<sup>286-290</sup> Thus, direct neuronal and/or glial mechanisms caused at least some of the observed brain injury in the irradiated subjects.

In the brain, hypertension accelerates the onset of radiation-induced vascular damage but not white-matter lesions.<sup>87</sup> Thus, vascular damage is distinct from pathogenesis of white-matter lesions, and ischemia and edema are likely not important in white-matter pathogenesis. Selective necrosis of white matter might be due to slow reproductive loss of glia or their precursors. Certain types of glial cells are particularly sensitive to radiation effects.<sup>291,292</sup> The earliest sign of white-matter damage is widening of the nodes of Ranvier and segmental demyelination as early as 2 weeks after an irradiation dose of 5 to 60 Gy.<sup>293</sup> Clinical evidence also supports radiation-induced demyelination. After radiotherapy for head and neck cancers, several patients experienced sensations like electric shock (referenced to sensory levels below the neck).<sup>294</sup> These symptoms gradually abated and disappeared after 2 to 36 weeks. This transient radiation myelopathy could be a result of temporary demyelination of sensory neurons. Mitotic activity in the subependymal plate (important in glial production) did not recover after radiation doses capable of producing necrosis, but did recover after doses that

did not produce necrosis, supporting the concept that glial cells are primary targets for radiation-induced brain injury.<sup>295</sup>

Both vascular and glial changes may be important in the development of late radiation-induced brain damage.<sup>54</sup> The preponderance of one type of cell damage over another depends on the radiation dose used. Vascular effects occur at lower doses of irradiation but after a longer latent period than effects mediated through damage to glia.<sup>54</sup> Thus, while radiation-induced brain injury is well accepted after high doses (greater than 15 Gy), increasing evidence supports radiation-induced brain injury at lower doses. The mechanisms underlying this brain injury have not been adequately explored.

In addition to axonal demyelination, other direct neuronal damage may occur in irradiated adult animals. Although mitotic neurons of the prenatal and neonatal brain are extremely sensitive to radiation, the neurons of more mature animals are relatively resistant and less likely to result in cell death.<sup>114,150,296</sup> However, as early as 1962, neurogenesis was proposed to take place in the adult brain as well.<sup>297</sup> Adult and juvenile neurogenesis was found to be especially prominent in the granule cell populations of the hippocampus and the olfactory bulb. Neurogenesis in other brain regions has been reported but is still controversial. This might be partially due to a detection limit at low levels of neurogenesis. The newly formed cells have the ultrastructural characteristics of neurons,<sup>298</sup> and the number of granule cells in the hippocampus increases in adult rodents.<sup>299,300</sup> In mice, neurogenesis quickly reduces after birth and levels of neurogenesis are relatively low at 6 months of age. Neurogenesis was also reported in the hippocampal subgranular cell layer of adult rabbits and shown to be quite radiosensitive (4.0–4.5 Gy).<sup>301,302</sup> Thus, certain populations of proliferating neurons in the adult brain can be damaged or destroyed by relatively low doses of ionizing radiation. These findings have been confirmed in nonhuman primates and humans and collectively suggest that certain neuronal populations in the adult brain are radiosensitive due to their mitotic state.<sup>303</sup> It should be pointed out, however, that there is no simple relationship between neurogenesis and cognitive function, and the exact role of reduced neurogenesis in radiation-induced cognitive changes is still unclear.

In addition to alterations in neurogenesis, there are subtle dendritic alterations following X-irradiation in the cerebral cortex of the monkey. They include decreased dendritic intersections, branchings, and length, as well as reduced packing density of neuronal elements.<sup>304</sup> Consistent with these findings, altered levels of the dendritic marker microtubule-associated

protein 2 were reported in the mouse hippocampus and cortex.

## Cellular Models

In addition to animal models, cellular models are also being used to assess the potential effects of irradiation on brain function. Cellular models are particularly useful for mechanistic questions and to determine the direct and indirect effects of irradiation on a particular cell type (see Figures 7-3 and 7-11). In general, irradiation produces DNA (deoxyribonucleic acid) and other cellular lesions that cause a severe stress response.<sup>305</sup> The cellular response includes activation of injury pathways, such as those involved in DNA repair, cell-cycle checkpoints, and apoptosis.<sup>305</sup> In turn, these pathways might involve reactive oxygen species (ROS) or reactive nitrogen species, impaired mitochondrial function, cell survival, and cell death pathways.<sup>306</sup> The effects of irradiation can be studied in homogeneous cultures (for example, those consisting of cells such as progenitor cells, which are particularly sensitive to irradiation or in mixed cultures). Mixed cultures can contain different sources of cell lines. Alternatively, these effects can be studied in primary 2- or 3-dimensional cultures, or “brain balls.” For example, the role of ROS irradiation effects is being studied in cellular models. ROS affects the basal redox state of cells<sup>307</sup> and proliferation and differentiation of glial precursors, and may also contribute to the enhanced susceptibility of neural precursors to effects of irradiation.<sup>308</sup> In addition to ROS, reactive nitrogen species might be involved as well. While nitric oxide (NO) can inhibit the apoptotic pathway through cyclic-guanosine-monophosphate-dependent mechanisms and caspase inhibition, NO can have proapoptotic effects via mitochondria, DNA damage, and inhibition of proteasome.<sup>305</sup> In the developing brain, ionizing radiation induces an early increase of neuronal NO synthase activity and a further augmentation in the NO steady-state concentration.<sup>309</sup> Consistent with in-vivo data supporting the involvement of apoptosis in radiation-induced cell death in the developing brain,<sup>310</sup> radiation-induced cell death of neural precursor cells in vitro was shown to be caspase-3-dependent.<sup>311</sup> The advantage of in-vitro systems is that relatively simple, more mechanistic questions can be addressed. For example, a cellular model system showed more apoptosis in irradiated cells after inhibition of NO synthase, indicating NO was protective in the early irradiation response.

A combination of cellular models and whole-animal models are particularly useful when studying the effects of brain irradiation and in developing potential therapeutic strategies. For example, in a 2007 study,

it was shown that brain irradiation enhances the survival of implanted neural progenitor cells in normal and tumor-bearing brains.<sup>312</sup> Recently, it was shown that implanting cells in nonirradiated brains has detrimental effects on hippocampus-dependent object recognition, while implanting cells in an irradiated brain enhances object recognition.<sup>313</sup> Together, these data emphasize that the microenvironment in irradiated and nonirradiated brains might be such that opposite therapeutic effects are encountered. Similar paradoxical effects are seen with inhibitors of oxidative stress.<sup>314</sup>

### Alterations in Nervous System Function and Potential Therapeutic Targets

With the exception of immature neurons, the adult brain is relatively resistant to radiation-induced cell death; however, the mature brain is quite sensitive to functional changes in neurophysiology and neurochemistry. These functional changes, following low or intermediate doses of ionizing radiation (less than 15 Gy), might contribute to the radiation-induced behavioral changes.<sup>315,316</sup>

#### Neurochemistry

**Sodium.** One of the best-studied neurochemical changes following irradiation is ionic flow across the semipermeable neuronal membrane. The flow of sodium ions is believed to be involved in the control of neuronal excitability<sup>317</sup> and can be disrupted after either a very high or very low dose of radiation. A study using the radioactive isotope sodium-24 compared the sodium intake across the membrane of the squid giant axon before and after exposure to X-rays.<sup>318</sup> There was a significant increase in sodium intake during the initial hyperactive period following a dose of 500 Gy. Similar results were reported using frog sciatic nerves irradiated with 1,500 to 2,000 Gy of alpha particles, although a simultaneous decrease in the rate of sodium extrusion also occurred.<sup>319</sup> Peripheral nerves may be less radiosensitive than neurons in the CNS. The artificially stimulated uptake of sodium into brain synaptosomes was significantly reduced by an ionizing radiation exposure (high-energy electrons) of 0.1 to 1,000 Gy.<sup>320</sup> This effect was later confirmed using 1 to 100 Gy of gamma radiation.<sup>321</sup>

**Dopamine and norepinephrine.** The brain has been described as a radiosensitive biochemical system<sup>315</sup> and many changes in brain neurochemistry have been observed after irradiation. One to two days after an exposure to 3 Gy of X-radiation, neurosecretory granules in the hypophysial-hypothalamic system

showed a transient increase in number over the controls.<sup>322</sup> Brain monoamines have been reported to leak from the neuronal terminals of rats irradiated with 40 Gy of X-rays, as well.<sup>323</sup> These changes may correlate with alterations of neurotransmitter systems following irradiation.

Catecholamine functioning appears to be damaged following exposure to intermediate or high doses of ionizing radiation. After 100 Gy, there is a transient disruption in dopamine functioning (similar in some ways to dopamine-receptor blockade).<sup>324</sup> Similarly, a 30-Gy radiation exposure increases the ability of the dopamine receptor blocker haloperidol to produce cataleptic behavior.<sup>325</sup> Radiation-induced effects on dopamine have been correlated in time with ETI, suggesting that changes in this neurotransmitter system may play a role in behavioral disruptions. However, other neuromodulators (such as prostaglandins) also seem to influence dopaminergic systems and might contribute to radiation-induced behavioral changes.<sup>325</sup> On the day of exposure to 6.6 Gy of gamma radiation, there was a transient reduction in the norepinephrine content within the monkey hypothalamus; the norepinephrine levels returned to normal 3 days later.<sup>326</sup> Although similar effects have been reported in one study,<sup>327</sup> another study found no change in noradrenaline content after 8.5 Gy of X-rays.<sup>328</sup> Monoamine oxidase, an enzyme that breaks down catecholamines, was significantly reduced by a supralethal, 200-Gy dose of mixed neutron-gamma radiation. This enzymatic change occurred within 4 minutes of exposure and lasted for at least 3 hours. In contrast, a very marked increase in monoamine oxidase activity was observed when animals received the same dose of radiation rich in gamma rays.<sup>329</sup>

**5-hydroxytryptamine.** Similar to norepinephrine, there is contradiction about the effects of irradiation on 5 hydroxytryptamine (5 HT). While a radiogenic stimulation of 5 HT release following approximately 10 Gy was reported in one study, other studies observed a decrease or no change in 5-HT levels.<sup>328,330,331</sup>

**Acetylcholine.** A variety of measures involving the neurotransmitter acetylcholine (ACH) are altered by exposure to ionizing radiation. ACH synthesis rapidly increases in the hypothalamus of the rat after less than 0.02 Gy of beta radiation, but is inhibited at only slightly higher radiation doses.<sup>315</sup> A dose of 4 Gy of cobalt-60 gamma radiation produces a long-term increase in the rate of ACH synthesis in dogs.<sup>332</sup> Also, high-affinity choline uptake (a correlate of ACH turnover and release) slowly increases to 24% above control levels 15 minutes after irradiation with 100 Gy.<sup>324</sup> Choline uptake is back to normal by 30 minutes after exposure. Massive doses of gamma or X-rays (up to

600 Gy) are required to alter brain acetylcholinesterase activity,<sup>333</sup> whereas much smaller doses depress plasma acetylcholinesterase by 30%.<sup>334</sup>

**Cyclic adenosine monophosphate.** Cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP), act as second messengers in synaptic transmission. After irradiation at a dose of 50 Gy, concentrations of cAMP are reduced in rats<sup>335</sup> and monkeys.<sup>336</sup> The transient nature of these changes also suggests their possible role in EPDs.

**Histamine.** The massive release of histamine after exposure to a large dose of ionizing radiation has been proposed as a mediator of radiogenic hypotension and EPDs.<sup>337</sup> Exposure to large doses of ionizing radiation results in postirradiation hypotension in monkeys,<sup>118,338,339</sup> with arterial blood pressure decreasing to less than 50% of normal.<sup>340</sup> Postirradiation hypotension also produces a decrease in cerebral blood flow immediately after a single dose of either 25 or 100 Gy of cobalt-60 gamma radiation.<sup>118,123,341–343</sup> This hypotension may be responsible for ETI after a supralethal dose of ionizing radiation.<sup>118,341,343</sup> In support of this hypothesis, the antihistamine chlorpheniramine maleate is effective in reducing performance decrements and postirradiation hypotension in monkeys.<sup>340,344,345</sup> However, other studies do not support a close association between blood pressure and behavioral changes.<sup>118,346,347</sup> Thus, changes in blood pressure may not be sufficient to explain behavioral and cognitive changes. Changes in blood pressure might also be pertinent to the potential therapeutic effects of antiinflammatory compounds that have antihypertensive effects as well (see “Inflammation” below).

Histamine is a very active biogenic amine and putative neurotransmitter located in neurons and mast cells throughout the body, especially around blood vessels.<sup>348</sup> Attempts to alter the development of behavioral deficits by treating animals with antihistamines before exposure have been encouraging.<sup>95,96,340,349,350</sup> Diphenhydramine (a histamine H1 receptor antagonist) inhibits radiation-induced cardiovascular dysfunction.<sup>351</sup> Because these histamine blockers produce only partial relief from radiation effects, the histamine hypothesis explains only a portion of the behavioral and physiological deficits observed after radiation exposure.<sup>352</sup>

**Opioids.** Cross-tolerance between endorphins and morphine has been demonstrated for a variety of behavioral and physiological measures.<sup>71,114,193,353–361</sup> Given the similarity of radiation and opiate-induced symptoms, endorphins might be involved in some aspects of radiogenic behavioral changes. For example, ionizing radiation produces dose-dependent analgesia in mice, and this can be reversed by the opiate antagonist naloxone.<sup>151</sup> Morphine-induced analgesia

in rats was enhanced 24 hours after neutron (but not gamma) irradiation, so combined delayed effects of endogenous and exogenous analgesics may be radiation specific.<sup>152</sup> Ionizing radiation exposure can also attenuate naloxone-precipitated abstinence syndrome in morphine-dependent rats.<sup>362</sup>

Further supporting a role for endorphins in radiation-induced behavioral changes, mice exhibit a similar stereotypic locomotor hyperactivity following morphine injection and after receiving 10 to 15 Gy of cobalt-60 gamma radiation.<sup>106</sup> This effect of irradiation is reversed by administering naloxone or by pre-exposing the mice to chronically stressful situations (a procedure that produces endorphin tolerance).<sup>363–368</sup> In addition, naloxone given immediately before exposure to 100 Gy of high-energy electrons attenuates ETI in rats.<sup>366</sup> Conversely, rats either undergo no change<sup>187</sup> or are more sensitive to radiation effects after chronic treatment with naloxone on a schedule that increases the number of endorphin receptors.<sup>369</sup> Similar to histamine, the manipulation of opioid systems cannot fully account for postirradiation performance deficits. Thus, multiple neurotransmitter systems might be involved in radiation-induced brain injury.

### Inflammation

Following irradiation, neurogenesis is inversely correlated with the activation of microglia, and the antiinflammatory drug indomethacin partially restores radiation-induced decreases in neurogenesis.<sup>370</sup> Antiinflammatory drugs might antagonize radiation-induced cognitive injury as well. For example, the angiotensin-converting enzyme inhibitor ramipril<sup>371</sup> and angiotensin II type I receptor blocker L-158809<sup>372</sup> prevent or ameliorate fractionated, whole-brain, irradiation-induced cognitive impairments in rats. Angiotensin-converting enzyme converts angiotensin I to angiotensin II, a vasopressor that binds to the angiotensin II type 1 and type 2 receptors. While binding to type I receptors causes vasoconstrictive effects, binding to type II receptors produces vasodilating effects. Angiotensin II is proinflammatory, but angiotensin-converting enzyme inhibitors are used to reduce blood pressure as well. Because hypotension following irradiation might relate to early cognitive radiation-induced injury, as described earlier, different therapeutic approaches might be required to treat early radiation-induced cognitive injury.

ROS inhibitors are also tested for their ability to antagonize radiation-induced cognitive injury. However, the complex dual role of ROS in learning and memory—from being required for memory and long-term potentiation, but detrimental following chronically

highly elevated levels—should be kept in mind. The beneficial effects of high ROS levels preirradiation in regard to cognitive changes following irradiation (as seen in mice lacking EC-SOD [extracellular superoxide dismutase]) underlines the need to consider ROS levels prior to irradiation as well. It could be argued that in most instances, ROS levels will be elevated in military personnel during combat missions.

### *Bone Marrow and Neural Stem Cells*

Bone-marrow transplants have been used to challenge radiation-induced damage to the blood-forming systems (see Figure 7-3). This treatment might provide some behavioral benefits as well.<sup>373</sup> Measures of activity and lethality were recorded in rats that were irradiated with 6.5 Gy of X-rays. Twenty percent of the nontreated rats died, whereas 86% of the marrow-treated group survived. The initial decreases in spontaneous locomotor activity were less severe in the marrow-treated rats. Instead of showing a second drop in activity 10 days after irradiation, the treated rats showed near-normal activity for the entire 35 days of testing.<sup>155</sup> A similar outcome for behavior was observed in rats exposed to 7.5 Gy of whole-body X-rays, except for shielded, marrow-containing bones.<sup>373</sup> Consistent with these findings, implantation of bone-marrow stromal cells in the brains of neonatal mice enhanced object recognition 6 months later.<sup>374</sup> Similar beneficial effects might be seen when bone-marrow stromal cells or neural stem cells are given following irradiation. Although bone marrow or neural stem cell transplantation may be impractical in military situations, shielding may enable stem cells to survive. In addition, there is evidence that these cells serve as vehicles of neurotrophic factors, such as brain-derived neurotrophic factor. If this turns out to be the case, administration of one or a mixture of these neurotrophic factors might be sufficient to produce similar effects with regard to regenerating the injured brain and enhancing cognitive performance.

### *Antiemetics*

The prodromal phase of radiation sickness, occurring hours to days after radiation exposure, includes nausea, vomiting, diarrhea, and abdominal cramp-

ing.<sup>187</sup> The prodromal phase is distinct from acute radiation sickness in that the absorptive, secretory, and anatomic changes associated with radiation damage are not easily identifiable.<sup>375</sup> It is during the prodromal phase of radiation sickness that gastrointestinal motility changes<sup>376,377</sup> and motor activity in the gut contributes to some of the effects of radiation.<sup>378,379</sup> Although considerable research on antiemetics has been done, its focus has been mainly limited to drugs effective in radiation therapy.<sup>181,380,381</sup> In this regard, various antiinflammatory drugs (such as dexamethasone and steroids) have been useful in managing patients' emesis.<sup>382,383</sup> However, therapy makes few task demands on the recipients; in the military, antiemetics that are effective against radiation-induced vomiting must also not disrupt behavioral performance. That requirement significantly reduces the number of potentially useful antiemetics. For example, metoclopramide, dazopride, and zacopride (5-HT<sub>3</sub> receptor blockers) were tested for antiemetic effects in monkeys exposed to 8 Gy of gamma radiation.<sup>380</sup> While all three drugs are effective antiemetics, only zacopride has no readily observable behavioral effects; metoclopramide disrupts motor performance and dazopride produces drowsiness.<sup>180,311,384-388</sup>

### *Shielding*

In addition to pharmacological radioprotection, the immediate effects of radiation may be mitigated by shielding (placing material between the radiation source and the subject). Studies have focused on either head shielding (body exposed) or body shielding (head exposed). Head shielding offered significant protection from ETI. However, equivocal study results raise questions about the exclusive role of the brain in the production of radiation-induced performance deficits. As with radiation-induced taste aversion, postirradiation behaviors may be influenced by peripheral mechanisms that have not been fully explored.<sup>179,389-393</sup> These peripheral mechanisms might involve neuroimmune interactions as well. Together, these results suggest the need to determine the effects of therapeutics on various organs and outcome measures following whole-body irradiation. This will require a multidisciplinary approach and specific funding opportunities, like center grants, to engage such a broad approach.

## SUMMARY

The success or failure of military operations is often measured in terms of missions completed or tasks performed. Exposure to ionizing radiation can significantly impede this success. In the case of

low-to-intermediate doses of radiation (up to 10 Gy), performance changes may be slow to develop, may be relatively long lasting, and will usually abate before the onset of chronic radiation effects, such as cancers.

After large doses, the behavioral effects are often rapid (within minutes), and they usually abate before the onset of the debilitating chronic radiation sickness. These rapid effects can also occur after intermediate doses. But all tasks are not equally radiosensitive; tasks involving complex, demanding requirements are more easily disrupted than simple tasks, with the exception of certain naturalistic behaviors that are also radiosensitive. Radiation parameters such as dose, dose rate, fractionation, and quality can all influence the observed degree of performance changes. For example, electron radiation can produce more behavioral deficits than other radiation types, such as neutron radiation. In addition, combined injuries will probably be prevalent in future nuclear conflicts. Trauma interacts with radiation exposure in a complex fashion to modulate the direction and magnitude of the cognitive changes. The time interval and sequence of the two insults might be critical in how cognitive function is affected.

Possible sensory and neurophysiological mediators of radiation-induced behavioral changes have been identified. Long changes in performance may be mediated in part by radiogenic brain damage from ischemia, edema, direct damage to the parenchymal tissues themselves (such as dendrites and glia), or more subtle changes, such as alterations in a specific neurotransmitter or second messenger system. Various levels of neurotransmitters (such as acetylcholine, dopamine, and histamine), putative neurotransmitters (such as endorphins), and other neurochemicals (such as ROS) undergo significant changes after radiation exposure. Like the modifications of morphology and electrophysiology, many of these neurochemical changes may also be capable of mediating the performance decrements observed after ionizing radiation exposure.

More transient cerebrovascular changes after radiation exposure may also produce short-lived behavioral deficits. Postirradiation alterations in brain metabolism and the disruption of the normal electrophysiology of the axon and synapse may have important roles in certain performance changes. A wide range of neurochemical alterations following irradiation, such as the reduced ability of synaptic sodium channels to respond to stimulation, have been characterized. The radiosensitivity of the brain is revealed by the fact that alterations in the basic substrate of neural excitation are observed at doses of less than 1 Gy.

The literature on radiation-induced cognitive injury in animals is extensive. Limited human data are derived from radiation accidents or therapeutic studies, and correlate with the animal studies' findings. Based on all data now available, the Human Response Program of the DTRA has estimated the expected performance changes in irradiated soldiers. These projections depend on factors such as radiation dose, time after exposure, and task difficulty. Although complex, human and laboratory animal data should permit the description, prediction, and (eventually) amelioration of the behavioral effects of ionizing radiation exposure. However, many of the pharmacological compounds that protect animals from the lethality of ionizing radiation are associated with adverse behavioral changes. Increased efforts are warranted to further explore the potential for using behaviorally compatible antiemetics that have beneficial effects on multiple organ systems and outcome measures. Further research investigating selective physical shielding and cognitive injury following irradiation will facilitate development of post-radiation guidelines for preservation of physical and behavioral performance.

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