The Biological Effects of Radiation in Space.

- Early in the Space Age, mission planners realized that the radiation environment in space posed a serious threat to the health and well being of the astronauts.

- Early ballon experiments and satellite flights had defined the radiation types:
  - electromagnetic radiation (x and gamma rays)
  - electrons
  - protons
  - nuclei of elements with $Z > 2$

- Protons and higher Z elements represented an unknown biological risk. The energies varied greatly, and thus the penetration power. Plateau versus Bragg peak doses could generate very different RBEs.

- Limited data from proton therapy indicated a proton RBE of about 1.

- NASA objective: more accurate estimate of biological effects, and thus, shielding requirements.

The USAF/NASA Proton Bioeffects Project

In the early 1960s a major proton bioeffects project was initiated to determine the biological response as a function of proton energy.

Proton energies were chosen to bracket the energies encountered in space:

Proton energy	**Range in tissue**
32 MeV	1 cm
55 MeV	2.5 cm
138 MeV	~ 15 cm
250 MeV	~ 40 cm
400 MeV	~ 80 cm
2300 MeV	~ 1000 cm

Approximately 2000 Rhesus monkeys and 5000 mice were eventually used.

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- Endpoints included clinical findings, physiological changes, hematological changes, histopathology, and mortality.
- About 400 monkeys (survivors of the acute exposures) were kept for lifetime follow-up. (Some are still alive today!)
- There were depth-dose distribution differences between protons and the photon radiations.
- The lower energy protons had limited penetration and caused severe surface damage ("similar to third degree burns") at high doses.

Overall, the RBE for protons was found to be about 1.

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[Leavitt, D.D., Radiation Research, 126, 127-131, 1991]

- Some of the long-term survivors have developed brain tumors.
- This figure shows part of a detailed (retrospective) dose estimation for head irradiations with proton beams.
- The numbers represent percentage of the reference surface dose used, which ranged up to ~ 10 Gy for whole-body exposures (much higher to cause surface burns).
- Lifetime follow-up indicated that the shortening of life was related to dose, not the energy of the protons.

Cataracts

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- One endpoint that did show a difference with the proton irradiations was cartaract formation.

- Cataracts were observed after latent periods of 20-24 years.
  (The median life span of the Rhesus monkey is ~24 years).

- There was a dose response and a difference in the response to similar doses of protons at different energies.

Tumor incidence in the mouse Harderian Gland.

See Alpen, E. L, P. Powers-Risius, S. B. Curtis, R. DeGuzman and R J. M. Fry. "Fluence-Based Relative Biological Effectiveness for Charged Particle Carcinogenesis in Mouse Harderian Gland." Advances in Space Research 14 no. 10 (1994): 573-581.

- Objective: look at the dose-response relationship at *low doses*.
- Obtain initial slope; ratio of initial slopes yields the maximum RBE.
- Novel approach to risk analysis: *base RBE estimates on particle fluence as the dose parameter.*
- Only possible with "track segment" experiments where the LET is constant over the target dimensions.

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TABLE 1

The model system:

- Female mice irradiated in plateau region of Bragg curve.
- Within 72 hours, 2 donor pituitary glands implanted into the spleen.
- Hormone production promotes the expression of Harderian gland tumors.
- Mice sacrificed at 16 months; Harderian glands examined macroscopically and histologically.

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Graph of Dose (Gy) vs. Percent Tumor Prevalence

The primary data:

Dose = fluence x LET

[Estimation of initial slopes can be very subjective]

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Fig. 2.

Cross sections derived from the initial slopes are replotted below.

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Fig. 14.7 in Alpen, E. L. *Radiation Biophysics,* 2nd ed. San Diego, CA: Academic Press, 1998.

Cross sections derived from the slopes of the low dose regions of the fluence vs tumor incidence graph above.

Cross section = the increase in proportion of animals with tumors per unit fluence.

***This graph does not show the decrease in cross section at high LET seen with many other endpoints.

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Fig. 3.

- RBE estimates from the Harderian gland data produced some of the highest values of any experimental system exposed to high LET radiation.
- The RBE values remain large at high LET values.
- The Harderian gland data do not show the dramatic drop to low RBE values at very high LETs seen with other systems (e.g., see below).
- Much attention has been drawn to these results.
- This is very troubling to NASA.

Alpen also examined the statistics of cell traversals by heavy charged particles.

- Fluence/unit area is known as a function of dose.
- Size (average cross sectional area) of the target cell in the Harderian gland is known.
- Calculate the number of traversals as a function of dose.

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TABLE 3

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TABLE 4.

At the same low doses, the number of traversals by protons is very large.

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Fig. 4.

- The probability of one or more traversals by the HZE iron particles mirrors the tumor induction probability.

- Alpen used the cell area for the calculation of traversal probabilities shown above.

- If the cell nucleus area is used instead, the observed incidence of tumors would match the probability of one or more traversal line even better.

These data suggest that only a single hit by a high LET iron particle is sufficient to cause transformation and tumor induction.

Skin cancers induced by high LET radiation in rats

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Fig. 6.

- At low doses, some of the damage from low-LET radiation can be repaired by skin cells.
- The high-LET radiation shows a linear response for tumor induction per unit dose.

Radiation-Induced Cataracts

Cataracts are a late-appearing deterministic endpoint.

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Fig. 7.

- The time of onset is earlier at the highest doses for both x rays (left) and for 600 MeV/amu iron particles.
- The iron particles are equally effective at doses ~ 5 times lower than the x-rays.

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Fig. 8.

- Iron ions appear much more effective than x-rays for cataract induction.
- In humans a grade 2 cataract is the threshold for surgical removal.

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Fig. 9.

- Higher dose rates produce a higher incidence of cataracts in mice.
- Higher dose rates would be produced during SPEs.

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Fig. 10.

Data from humans undergoing radiation therapy.

Whole body irradiation with photons for bone marrow transplant.

Low dose (651 cGy) versus high dose (1150 cGy) delivered in a single fraction or multiple fractions.

Fractionation spares the lens.

Refer to: Shukitt-Hale, Barbara, Gemma Casadeusus, John J. McEwen, Bernard M. Rabin and James A. Joseph. “Spatial Learning and Memory Deficits Induced by Exposure to Iron-56-Particle Radiation.” Radiation Research 154 (2000): 28-33.

Previous studies:

- Exposure of rats to low (0.1 Gy) whole-body doses of ^{56}Fe HZE ions alters neurotransmitter biochemistry and function as well as the associated behaviors: motor performance, conditioned taste aversion.
- At 12 hrs, 3, 8, and 14 days post-irradiation, motor performance on a wire suspension test was reduced.
- Levels of dopamine receptors were affected.

Conditioned Taste Aversion Test

- A novel, good taste (like sucrose) is paired with a toxic stimulus.
- Rats develop an aversion to the taste and will avoid it at a subsequent presentation.
- ^{56}Fe particles interfered with the development of this aversion at a lower dose than other types of radiation.

Conclusions:

- Exposure to ^{56}Fe particles disrupts behavior mediated by the dopamine system.
- The changes are similar to those seen in aged rats.

Current study looks at cognitive function: spatial memory and learning; areas known to be affected in aging.

Rats were tested at 1 month after 1.5 Gy whole-body exposure.

Morris water maze

- Requires rats to use spatial learning to find a hidden platform just below the surface of a pool and remember the location from the previous trial.
- Testing on 4 consecutive days/6 trials per day.
    - Day 1: Trials 1-6; put rat into pool, measure time to find the platform and escape.
    - Days 2 and 3: Trial 6; remove platform, measure time spent in quadrant where platform was previously located. **Measures memory**.
    - Day 4
        - Change location of platform
        - Trials 1-5; measure time to find platform and escape.
        - Trial 6; remove platform, measure time spent searching in the correct quadrant. **Measures learning.**

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FIG. 1.

Difference on Day 4, the "reversal day":

- Trial 1: Control rats, **using a spatial strategy**, spend more time searching the old location.
- Trials 2-5: Control rats learn new strategy faster.

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FIG. 2.

- The escape platform has been removed.

- Measure the time spent searching in the correct location (where the platform used to be).

- Control rats are using a spatial strategy

- Irradiated rats are using non-spatial strategy.

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FIG. 4.

- Time it took for rat to first cross the previous location of the platform.
- Control rats have better memory and are using spatial cues for orientation.

Conclusions:

- Whole-body irradiation with 1.5 Gy of ^{56}Fe 1000 MeV/amu disrupted spatial memory and learning.
- Irradiated rats took longer to learn a new task, and forget the old one, during reversal training.
- Irradiated group did not use spatial strategies to find the submerged platform. Random circular swimming.
- Both of these are deficits similar to those seen in aged rats.

X-rays can produce similar effects, but at doses of 20-30 Gy and not until 200-280 days post irradiation.