

## 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 balloon 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:

<u>Proton energy</u>	<u>Range in tissue</u>
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 cataract 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*, 2<sup>nd</sup> 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.

Image removed.  
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  $\sim 5$  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 Casadeus, 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 <sup>56</sup>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.
- <sup>56</sup>Fe particles interfered with the development of this aversion at a lower dose than other types of radiation.

**Conclusions:**

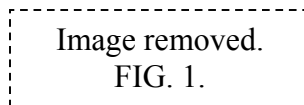
- Exposure to <sup>56</sup>Fe particles disrupts behavior mediated by the dopamine system.
- The changes are similar to those seen in aged rats.

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.

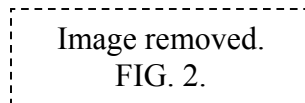
## Morris water maze

- 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.**



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.



- 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  $^{56}\text{Fe}$  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.