Low-Level Radiation and Health

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http://www.radiation-scott.org
Contents

• Ionizing radiation and its sources
• Spontaneous and radiation-induced damage
• Radiation activated natural protection (radiation hormesis)
• Biological basis for radiation hormesis
• Hormetic cancer relative risk model
Contents (continued)

- Abundant evidence for radiation hormesis
- Hormesis implications for low-dose cancer therapy
- Utopian-world LNT vs. real-world hormesis: Implications for radiation disaster preparedness
- Conclusions
Radiation Has Existed Since the Beginning of the Universe

Universe created 10 - 20 billion years ago from a cosmic explosion
Radiation Sources are Everywhere

- The Sun
- Indoor Radon
- Plants
- Our Bodies
- Radioactive Soil and Rocks
Man-made Radiation Sources

- X-ray machines
- Medical isotopes
- Televisions
- Smoke detectors
- Weapons fallout
- Radioactive waste
Low- and High-LET Forms of Radiation

- LET (linear energy transfer) is the average energy lost by radiation when traversing a small thickness of material.
- Examples of low-LET radiation are X-rays, gamma-rays, and beta particles.
- Examples of high-LET radiation are alpha particles, neutrons.
Adverse Consequences of Exposure of Humans to Radiation

• Low and high radiation doses can cause stochastic effects such as cancer and genetic effects.

• High doses and dose rates can cause life-threatening effects such as severe damage to organs as well as serious morbidity.

• Damage to DNA above the spontaneous level is largely responsible for most detrimental radiobiological effects.
Radiation Bystander Effects


Deleterious Signals

• Activated by low and high doses of high-LET radiation and by high doses of low-LET radiation.
• Can lead to stochastic bystander effects, including genomic instability.
• Elevated genomic instability elevates cancer risk.
Protective Signals

- Form of natural defense.
- Induced by low-dose low-LET radiation and other stressors.
- Reactive oxygen (ROS) and nitrogen (RNS) species and specific cytokines (e.g., TGF-β1) participate.
- Enhances DNA repair capacity in bystander cells.
- Stimulates selective removal of aberrant bystander cells.

Radiation Hormesis

- Survival of all organisms on Earth depends upon their ability to adapt to environmental and other stresses.
- Numerous genes evolved over time to mediate adaptive responses to both internal and external genotoxic stresses.
- Protective signaling regulates ANP (Scott 2007; in press and submitted papers).
Radiation Activated Natural Protection Is Evolutionary Conserved

Occurs in:
- Single cell organisms
- Insects
- Plants
- Lower vertebrates
- Mammalian, cells
- Mammals including humans

Mitchel, REJ (2006 IHS Meeting presentation)
Low-Level, Low-LET Radiation Protects Us

- Protects against chromosomal damage (Ed Azzam’s group)!
- Protects against mutation induction (Pam Sykes’ group), even when the low dose follows a large dose (Tanya Day’s work)!
- Protects against neoplastic transformation (Les Redpath’s group)!
- Protects against high dose chemical- and radiation-induced cancer (Kazou Sakai’s group)!
- Enhances immune system defense (Shu-Zheng Liu’s group)!
Low-LET Radiation Protects Us (continued)

- Suppresses cancer induction by alpha radiation (Chuck Sanders group)!
- Suppresses metastasis of existing cancer (Kiyohiko Sakamoto’s group)!
- Extends tumor latent period (Ron Mitchel’s group)!
- Protects against diseases other than cancer (Kazuo Sakai’s group)!
Hormetic Risk (J-Shaped) Curve

Cancer Incidence vs. Absorbed Radiation Dose (mGy)

- Hormetic Zone
- Spontaneous Cancer Frequency
- Increased Cancers
- Hormetic Effect
Biological Basis for Hormetic Zone for Low-LET Radiation

Spontaneously Occurring Genomic Instability

DNA Damage Accumulation

Neoplastic Transformation

Proliferation of Malignant Cells

Cancer

Low Dose/Dose Rate Low-LET Radiation

Protective Intercellular Signaling

Adapted Protection (ANP)

* Contributed to PROFAC

Indicates Suppressor Function

Scott 2007

ROS scavenging contributes to protection
PROFAC, A Measure of ANP Efficiency

- **PROFAC** stands for protection factor.
- Cancer suppression **PROFAC**: Expected fraction of cancer cases that do not occur that would have occurred in the absence of radiation ANP.
- ANP is regulated via protective intercellular signaling and the **PAM process** component is a protective bystander effect.

*Explained on next slide.*
Protective Apoptosis Medicated (PAM) Process in Fibroblast: Protective Intercellular Signaling

Induction of Apoptosis

PAM Process Signaling

• Can eliminate precancerous and other genomically-unstable cells caused by different agents.
• May vary for different stressing agents (e.g., ionizing radiation, UV radiation, chemical, etc.).
• May differ for different organs/tissue.
• Appears independent of p53.
• TGF-β appears to play an important role in fibroblast.
NEOTRANS$_3$ Model for Radiation-Induced Stochastic Effects in Cells

- Models the induction of genomically unstable cells by low dose radiation.
- DNA repair errors leads to mutations and neoplastic transformations.
- Normal apoptosis (presumably p53-dependent) when activated, removes moderately- and seriously-damaged cells.
- Auxiliary apoptosis (presumably p53-independent) when activated, removes some of the remaining aberrant cells including already existing precancerous cells (PAM Process).
NEOTRANS\textsubscript{3} Model Modes of Death after Low Doses of Low-LET Radiation

- **Moderately damaged cell**: p53-related death sentence
- **Mildly damaged cell**: p53-related DNA repair
- **Bystander precancerous cell**: p53-independent death sentence: PAM process
Cancer Hormetic Relative Risk (HRR) Model

- **Key Assumption:** Cancer arises from cells with persistent genomic instability through a series of stochastic changes, independent of how the instability originates, but dependent on the number of cells with this instability in an organ.

- Cancer relative risk (*RR*) proportional to neoplastic transformation *RR*.

- Neoplastic transformation *RR* based on NEOTRANS$_3$ model developed at LRRI.

- Protective and deleterious stochastic dose thresholds cause hormetic dose-response curve shape.
Hormetic Relative Risk (HRR) Model

\[ RR^* = \frac{1}{1 - PROFAC} \]

- **cancer incidence at absolute zero background radiation**
- **Transition Zone A**
- **LNT Zone**
- **Phantom Risk**
- **Zone of Maximal ANP**
- **Transition Zone B**
- **Absorbed Radiation Dose \( D \)**

\( b \) indicates dose from natural background radiation.
Radiation ANP from Some Diagnostic Procedures is Likely

<table>
<thead>
<tr>
<th>Number of X Rays</th>
<th>Dose Range</th>
<th>Hormesis Induced?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>0.01 mGy - 30 mGy</td>
<td>&gt; 0.01 mGy Yes</td>
</tr>
<tr>
<td>5 – 14</td>
<td>0.1 mGy – 50 mGy</td>
<td>Yes</td>
</tr>
<tr>
<td>≥ 14</td>
<td>1 mGy – 230 mGy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Doses from Diagnostic X Rays Fall in the Hormetic Zone*

<table>
<thead>
<tr>
<th>Source</th>
<th>mGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental, full-mouth (X ray)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chest X ray</td>
<td>0.25</td>
</tr>
<tr>
<td>Mammograms (X ray)</td>
<td>4</td>
</tr>
<tr>
<td>CT scan, head (X ray)</td>
<td>20</td>
</tr>
<tr>
<td>CT scan, body (X ray)</td>
<td>60</td>
</tr>
<tr>
<td>Thyroid scans:</td>
<td></td>
</tr>
<tr>
<td>Iodine-131 (β + γ radiation)</td>
<td>50-100</td>
</tr>
<tr>
<td>Iodine-123 (γ radiation)</td>
<td>30-50</td>
</tr>
<tr>
<td>Technetium-99 (β radiation)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Doses from Other Diagnostic Sources*


Cancer Relative Risk as a Function of the ANP-Related $PROFAC$ for the Hormetic Zone
### Protection Factors Against Cancer in Humans

<table>
<thead>
<tr>
<th>Region or Group</th>
<th>Effect</th>
<th>PROFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>High radon levels, USA</td>
<td>all cancers</td>
<td>0.35</td>
</tr>
<tr>
<td>Canada, nuclear industry workers</td>
<td>Leukemia</td>
<td>0.68</td>
</tr>
<tr>
<td>US DOE labs workers</td>
<td>Leukemia</td>
<td>0.78</td>
</tr>
<tr>
<td>Mayak Plutonium facility workers</td>
<td>lung cancer</td>
<td>0.86²</td>
</tr>
</tbody>
</table>

Proportion of spontaneous and other cancers prevented!

Age-Dependent Protection Factors Against Breast Cancer for Diagnostic X-Rays

Repeated Rounds of Mammograms

Based on data from Nyström et al. 2002
### PROFACs for Nuclear Shipyard Workers Chronically Exposed to $\gamma$ Rays

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>SMR</th>
<th>$p$ value</th>
<th>PROFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic, endocrine, metabolic</td>
<td>0.69</td>
<td>4.3 x $10^{-3}$</td>
<td>0.31</td>
</tr>
<tr>
<td>All respiratory disease</td>
<td>0.62 ± 0.08</td>
<td>1.4 x $10^{-6}$</td>
<td>0.38</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.68 ± 0.04</td>
<td>2.4 x $10^{-14}$</td>
<td>0.32</td>
</tr>
<tr>
<td>Emphysema</td>
<td>0.63 ± 0.26</td>
<td>7.2 x $10^{-2}$</td>
<td>0.37</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.30 ± 0.43</td>
<td>5.1 x $10^{-2}$</td>
<td>0.70</td>
</tr>
<tr>
<td>All infectious &amp; parasitic</td>
<td>0.86 ± 0.72</td>
<td>4.2 x $10^{-1}$</td>
<td>0.14</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.78 ± 0.04</td>
<td></td>
<td>0.22</td>
</tr>
</tbody>
</table>

Based on combining SMR data from Sponsler and Cameron (2005).
Benefits of Natural Background Radiation

Solid Cancer Mortality for Yangjiang, China 1979-1998

Effective doses are used

Slope of the line = -6.33E-04/mSv

D* where blue curve bottoms out implicated to be at least hundreds of mSv

Epidemiological Studies with Appropriate Internal Controls that Negate the Healthy Worker Effect (C. L. Sanders, 2007)

<table>
<thead>
<tr>
<th>Worker Comparison</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Cancer</td>
</tr>
<tr>
<td>Badged/Unbadged DOE Female Workers</td>
<td>0.83</td>
</tr>
<tr>
<td>UK Radiologists/Physicians</td>
<td>0.71</td>
</tr>
<tr>
<td>High-Dose/Control Shipyard Workers</td>
<td>0.84</td>
</tr>
<tr>
<td>Monitored/Unmonitored UK Nuclear Utility Workers</td>
<td>0.73</td>
</tr>
<tr>
<td>Radiation/Non-Radiation UKAEA Workers</td>
<td>As low as 0.30</td>
</tr>
</tbody>
</table>
Cancer Relative Risk In Hormetic Zone: Irradiated Human Populations

RR< 0.85 cannot be due to healthy worker effect (Sponsler and Cameron, 2005)
Gamma-Ray ANP Against Spontaneous Lung Cancer in Mice

Study involved more than 15,000 mice (R. Ulrich et al., 1976)

All doses > 0 are in hormetic zone, and zone extends to at least 1000 mGy
Gamma-Ray ANP Against Spontaneous Lung Cancer in Humans

Multiple fluoroscopy examinations

95% Confidence

Low-Dose-Rate, Gamma-Ray ANP Against Alpha-Radiation-Induced Lung Cancer

C. L. Sanders, International Hormesis Conference, 2006
Expected and Observed $RR$ for Lung Cancer in Wistar Rats Exposed to Pu-239 + Yb-169

<table>
<thead>
<tr>
<th>Average Alpha Dose (mGy)</th>
<th>Average Gamma Dose (mGy)</th>
<th>Expected $RR$</th>
<th>Observed $RR$</th>
<th>PROFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>0.9</td>
<td>21</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>190</td>
<td>1.8</td>
<td>67</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>620</td>
<td>1.3</td>
<td>218</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Gamma-ray dose from Yb-169 protracted over several months.
Gamma-Ray ANP Against Alpha-Radiation-Induced Lung Cancer

Dashed curve: unprotected $\alpha$-irradiated humans

Smooth curve: gamma-ray protected $\alpha$-irradiated humans
Low-Rate Gamma-Ray ANP Against MC-Induced Skin Tumors in Mice

K. Sakai, International Hormesis Conference 2005
Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation

Diebetic mice, Sakai K
IHS 2006

Survival (%)

Non Irradiated

0.70mGy/hr

Gamma rays

Age (Weeks)
Appearance of \( db/db \) Mice at 90 Weeks of Age

Irradiated

Non-Irradiated

Sakai K, IHS 2006
Low-Dose vs. High-Dose Cancer Therapy
Radiation Hormesis and Low-Dose Cancer Therapy

• Cancer cells are resistant to undergoing apoptosis.
• New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., resveratrol, gene therapy).
• Applying low-dose, low-LET radiation (in the hormetic zone) alone or in combination with apoptosis sensitizing agents that target tumor cells could lead to curing cancer.
• Adding multiple small doses of antiangiogenic drugs may enhance efficacy some treatments.
High-Radiation-Dose Therapy

- Severely harms the patient via massive killing of normal cells!
- Suppresses the immune system, thereby promoting cancer metastasis!
- Inhibits signaling associated with the PAM process!
- Is unnecessary because multiple-low-dose radiation therapy or chronic low-rate radiation therapy could cure cancer without harming the patient!
Low-Dose Radiation Therapy

• Low-dose radiation therapy has been used to successfully treat ovarian, colon, and hematologic cancers without any symptomatic side effects.
• Low-dose, low-dose-rate immunotherapy (using beta radiation) has been used to successfully treat follicular lymphoma.

Utopian-World LNT vs. Real-World Hormesis: Implications for Radiation Disaster Preparedness
Current Radiation Risk Assessment
Paradigm: Utopian-World LNT

BEIR VII Low-Dose, Low-Dose-Rate Extrapolation

Cancer Risk vs. Utopian-World Radiation Dose (mSv)

LNT
DDREF

BEIR VII discounted hormesis
LNT and Radiation Phobia

• The notion that any amount of radiation harms us is false and drives radiation phobia.

• LNT-related radiation phobia was responsible for the loss of more than 100,000 lives (via abortions) following the Chernobyl accident!
<table>
<thead>
<tr>
<th>BEIR VII</th>
<th>French Academies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectively chosen A-bomb cancer data was</td>
<td>LNT should not be applied to low-LET doses &lt; 100 mGy</td>
</tr>
<tr>
<td>consistent with LNT</td>
<td></td>
</tr>
<tr>
<td>Even natural background low-LET radiation</td>
<td>No evidence of harm from natural background radiation; may</td>
</tr>
<tr>
<td>harms</td>
<td>be beneficial</td>
</tr>
<tr>
<td>Radiation hormesis dismissed</td>
<td>Radiation hormesis not dismissed</td>
</tr>
<tr>
<td>Looked at basic research results and ignored</td>
<td>Considered implications of basic research results</td>
</tr>
</tbody>
</table>
LNT-Associated Radiation Phobia Following a Dirty Bomb Incident

Radiation-Phobia-Associated Impacts:

- **Loss of lives** associated with frantic evacuations.
- **Severe injuries** during evacuations.
- **Increased suicides** and abortions.
- **Increased psychosomatic disorders**.
- **Increased drug/alcohol/cigarette abuse**.
- **Permanent abandonment of properties with low-level contamination**.
Things the U.S. Government Should Do Now to Reduce Casualties in the Event of a Future Dirty-Bomb Incident

Institute a well-funded program to educate the public, medical community, news media, and governmental agencies about:

- The many radiation-phobia-related casualties LNT could cause: e.g., death by LNT slope factor!
- The abundant evidence for health benefits of low-level radiation exposure!
- How cancer and some other diseases could be prevented in high-risk groups by harmless low radiation doses!
- How cancers could be cured with low harmless doses of radiation in combination with other agents!
Conclusions

- The LNT risk model is invalid and promotes radiation phobia.
- Radiation-phobia-related casualties after a dirty bomb incident in a populated area are likely to be more prevalent than those related to actual radiation-induced damage.
- The public and others need to be better informed about low-dose radiation ANP against diseases.
- Persons receiving radiation doses in the hormetic zone would not likely be harmed and may be protected from developing some diseases that would otherwise occur.
Conclusions (continued)

- The public, news media, medical community, and others need to be informed about the powerful cancer preventative aspects of low-dose radiation ANP.
- They also need to be informed about the great potential for curing cancer using essentially harmless multiple low doses of radiation plus other agents that sensitize cancer cells to apoptosis.
Conclusions (concluded)

• Governmental agencies (e.g., NIH, DOE, NSF, DOD, NASA, DHS, FDA, others) need to support radiation adaptive response/hormesis research because of the enormous homeland-security, cancer-prevention, lifespan-prolongation, and cancer-therapy benefits that would be expected.
Radiation Hormesis Presentations on our Website (www.radiation-scott.org)

- *Hormesis Implications for Managing Radiological Terrorism Events.*
- *Low-Dose/Dose Rate Low-LET Radiation Protects Us from Cancer.*
- *Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer.*
- *Biological Basis for Horimetic Relative Risk Model and Implications*
Collaborators and Student Participants

- **Scientists:** Pam Sykes, Tanya Day, Les Redpath, Chuck Sanders, Zoya Tokarskaya, Galina Zhuntova, Ed Calabrese, Noy Rithidech and others
- **Students:** Jenni Di Palma, Munima Haque
Acknowledgement

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Backup Slides
Annual Cancer Mortality/100,000 for U.S. States (1950-1967)

Natural Background Radiation

- Atlantic and Gulf Costal Plain: 1.05 mSv/y
- Middle America: 1.25 mSv/y
- Rocky Mountain Plateau: 1.45 mSv/y
- Denver, Colorado: 1.65 mSv/y
- Ramsar, Iran: 200 mSv/y

Green indicates values that appear to be in the hormetic zone.
Stochastic Thresholds

• Each of us has a different radiation threshold (organ specific) for activating protective natural processes (i.e., ANP).
• Each also has a different higher threshold for inhibiting some of the protection (e.g., p53-independent PAM process).
Low-Dose Radiation Therapy for Non-Hodgkin’s Lymphoma

• Total-body irradiation (TBI) (repeated doses of 100-150 mGy) increased the four-year survival to 70-74% compared to 40% of untreated controls and 52% of patients treated with localized high doses.

• Upper half-body irradiation (HBI) (repeated doses of 100-150 mGy) increased the four-year survival to 84% compared to 65% of patients treated with localized high doses.

• All patients treated with low-dose HBI or TBI survived to 10 years, compared to localized-high-dose-treatment controls, who survived to nine years at a rate of 50%.

Hormetic Relative Risk (HRR) Model for Cancer Induction

Low-LET irradiation (dose-independent zone):

\[ RR = 1, \text{Dose} = 0 \]

\[ RR = 1 - \text{PROFAC}, \text{otherwise} \]

PROFAC depends on dose rate pattern and exposure time; accounts for PAM and immune system stimulation. Dose-independent zone increases importance of highly-criticized ecological studies!
HRR Model Continued:
\( \alpha + \gamma \) Irradiation, Low Doses

\[ RR = (1 - \text{PROFAC})[1 + F(B)KD], \quad D \geq 0 \]

Low-LET radiation suppresses cancer via protection factor (PROFAC) (Scott 2005a,b).

\[ F(B) = (1 - B)/B, \quad \text{for baseline incidence } B. \]

\( \text{PROFAC} = 0, \quad \text{for alpha radiation.} \)

\( D \) is the alpha radiation dose.
Markov Chain Monte Carlo Implementation HRR Model

• Why? To address stochastic threshold for ANP induction and inhibition.
• Number of chains = 1 or 2.
• WinBUGS software used.
• Uniform prior distributions assigned for model parameters.
• Predictions made for fixed baseline incidence.
## WinBUGS Sampling Hierarchies

<table>
<thead>
<tr>
<th>Sampling Type</th>
<th>Method of Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Conjugate</td>
<td>Direct, using standard algorithms</td>
</tr>
<tr>
<td>2. Log-concave</td>
<td>Derivative-free adaptive rejection</td>
</tr>
<tr>
<td>3. Restrictive range</td>
<td>Slice</td>
</tr>
<tr>
<td>4. Unrestricted range</td>
<td>Current-point Metropolis</td>
</tr>
<tr>
<td>1. Finite upper bound</td>
<td>Inversion</td>
</tr>
<tr>
<td>2. Shifted Poisson</td>
<td>Direct, using standard algorithm</td>
</tr>
</tbody>
</table>

Green: continuous target dist.; red: discrete distribution