Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer

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Research Approach

• Risk estimates are based on the biological-based hormetic relative risk (HRR) model recently introduced by our research group.
• Dose-response relationships were constructed based on absorbed radiation dose $D$.
• Data from medical, epidemiological, and ecological studies were used.

Scott BR. Dose-Response 3:547-567, 2005
Scott BR. Dose-Response (in press, 2006a)
Scott BR. Chapter In New Research on Genomic Instability (tentative title), Nova Science Publishers, Inc., (accepted, 2006b)
Current Regulatory Risk Assessment Paradigm

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

Cancer Risk vs. Radiation Dose (mGy)

- LNT
- DDREF

BEIR VII discounted hormesis
## BEIR VII vs. French Academies on LNT and Radiation Hormesis

<table>
<thead>
<tr>
<th>BEIR VII</th>
<th>French Academies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectively-chosen A-bomb survivor cancer data was consistent with LNT</td>
<td>LNT may not apply to low-LET doses &lt; 100 mGy</td>
</tr>
<tr>
<td>Even natural background low-LET radiation harms</td>
<td>No evidence of harm from natural background radiation; may 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>
Types of Radiation Hormesis

- Medical Radiation Hormesis
- Therapeutic Radiation Hormesis
- Environmental Radiation Hormesis
- Occupational-Exposure-Associated Radiation Hormesis
Medical Radiation Hormesis

Medical procedure (e.g., chest X-rays, mammograms, CT scans, nuclear medicine diagnosing) induced radiation hormesis is thought to be responsible for the elimination of precancerous and other genomically unstable cells from the body. Medical radiation hormesis likely also suppresses cancer metastasis.

Photo: WHO/TBP/Pierre Virot
Therapeutic Radiation Hormesis

Low-dose radiation induced hormeric effects have been demonstrated to be beneficial in curing existing cancer. Low therapeutic doses can arise from fractionated X-ray or gamma-ray exposure, via low-LET radioimmunotherapy, or via use of radio-labeled pharmaceuticals.
Natural and human-activity-related background radiation induced hormetic effects have been found to be associated with the suppression of spontaneous cancers and other diseases.
Occupational low-LET (or low- plus high-LET) radiation exposure of nuclear workers has been found to induce hormetic effects associated with the suppression of spontaneous cancers and other diseases.

Photo: DOE Nuclear Material Disposition Project web site
Hormetic Relative Risk (HRR) Model for Cancer Induction

- The HRR model is an adaptation of our published NEOTRANS$_3$ model (Scott 2004, 2005a) for low-dose radiation-induced stochastic effects (mutations, neoplastic transformation).

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

- Relative risk for cancer is modeled as being proportion to the relative risk for neoplastic transformation [consistent with observations of Dr. Redpath’s group (BELLE 2006 Conference)].
Cancer Hormetic Relative Risk (HRR) Model: Based on Absorbed Radiation Dose

- **RR***: Cancer incidence at absolute zero background radiation
- **RR**: Relative risk
- **0+ D***: Indicates dose from natural background radiation
- **LNT Zone**: RR = 1
- **Hormetic Zone**: RR = 1 - PROFAC

Graphical representation showing the relationship between absorbed radiation dose and cancer risk.
Cancer Relative Risk in Hormetic Zone: HRR Model

\( RR \approx 1 - \text{PROFAC} \)

- Protection factor (\textit{PROFAC}) gives the proportion of cancer cases avoided due to radiation hormesis; accounts for the PAM process and immunity.
- \textit{PROFAC} depends on the type of radiation, number of dose fractions, dose rate and exposure duration. Appears quite large for protracted exposure of adults over years at very low rates.
- \textit{PROFAC} increases with age.
- \textit{PROFAC} appears to be very small or zero for pure alpha irradiation but not for radon (gamma-ray component).
## Doses from Diagnostic Radiation Sources 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>

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

- High fidelity DNA repair/apoptosis
- * PAM Process
- * Immune function

* Indicates Suppressor Function

Scott 2006a,b
RR < 0.85 cannot be due to healthy worker effect (Sponsler and Cameron, 2005)
PAM Process In Fibroblast: Protective Intercellular Signaling

Transformed Cell

\[ O_2^- \rightarrow \cdot \text{NO} \]

\[ \text{ONOO}^- \rightarrow \text{Induction of Apoptosis} \]

\[ \cdot \text{OH} + O_2 + \text{Cl}^- \rightarrow \text{HOCl} \]

Normal Cell

\[ \text{TGF-\( \beta \)} \]

\[ \text{H}_2\text{O}_2 \]

\[ \text{Peroxidase} \]

PAM Process Explains Classical Two-Dose Adaptive Response (Radiation Preconditioning Hormesis)

- Second dose (> 1 mGy) activates high fidelity DNA repair, so DNA repair activation appears not to explain the two-dose adaptive response!
- First dose (> 0.01 mGy low-LET radiation) activates/potentiates the PAM process in addition to DNA repair, based on modeling data from sensitive pKZ1 mouse inversion assay (Pamela Sykes group) [Scott et al., 2006].
- The PAM process explains inverse adaptive response study, since the first dose, when moderate or large, activates high fidelity DNA repair; the second small dose adds the PAM process (radiation postconditioning hormesis).
Medical Radiation Hormesis

• Diagnostic exposures to X-rays (e.g. chest X-rays, CT scans) and gamma and beta rays (used in nuclear medicine) induce adapted protection against cancer and other genomic-instability-associated diseases.

• Maximal horometric protection is expected to occur after protracted or fractionated exposures that over and over induce transient adapted protection.

• For maximal horometric protection, total doses should be restricted to the horometric zone, which appears to be greatly extended with fractionated and protracted exposure.
Suppression of Spontaneous Lung Cancer in Mice: Indirect Evidence for Medical Radiation Hormesis (HRR Model)

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

All doses > 0 are in hormetic zone.
Suppression or Spontaneous Lung Cancer in Canadian TB Patients: Medical Radiation Hormesis

Multiple fluoroscopy examinations

95% Confidence

Males

Females

Proportion of Breast Cancer Cases Avoided Due to Medical Radiation Hormesis

Repeated Rounds of Mammograms

PROFAC = 0.24 for neoplastic transformation, Redpath’s data (Scott et al., 2006)

Based on data from Nyström et al. 2002
Therapeutic Radiation Hormesis

• Cancer cells are resistant to undergoing apoptosis.

• New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., resveratrol).

• Applying low-dose, low-LET radiation (in the hormetic zone) alone or in combination with apoptosis sensitizing agents that target tumor cells can lead to curing cancer.
Therapeutic Radiation Hormesis (continued)

• Fractionated or protracted low doses of low-LET radiation in the hormetic zone are expected to be the most effective forms of therapeutic radiation hormesis.

• Therapeutic radiation hormesis 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.

Low-Dose Total- and Half-Body Irradiation Increases Survival in Non-Hodgkin's Lymphoma Patients: Therapeutic Radiation Hormesis

• 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%.

• Doses given were 100-150 mGy, totaling 300 mGy per week: a total fractionated dose of 1,500 mGy.

Ways To Improve The Therapy Based on Our Research Results

• Use smaller dose fraction sizes, possibly as low as 1 mGy. Extend the period of treatment. \textit{[Same strategy as discussed by Judah Folkman for antiangiogenic therapy for Lewis lung cancer (BELLE 2006 conference).]}

• Use apoptosis-sensitizing agents (e.g., resveratrol) in combination with an antiangiogenic drug and multiple low doses (or chronic low rates) of low-LET radiation.

• Conduct new research to determine the average duration of the activated PAM process and induced immunity. Durations are expected to differ for these processes as was implicated by Ludwig Feinendegen (BELLE 2006 Conference).

• Use the knew knowledge to develop optimal therapeutic schemes.
Resveratrol

- **Trans-3',5,4’-trihydroxystilbene** (resveratrol) is found in grapes, berries, peanuts, and other plants.
- Resveratrol sensitizes cancer cells to undergoing apoptosis and suppresses proliferation of a wide variety of tumor cells (e.g., lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid)

*Aggarwal BB et al. (Anticancer Res. 24, 2004)*
Effect of resveratrol on signaling proteins involved in apoptosis (Aggarwal et al. Anticancer Research 24:3-60, 2004)
Therapeutic Radiation Hormesis Via Radon Exposure

Some Health Conditions Currently Being Treated at a Radon Health Mine in Boulder, Montana, USA Include:

- Ankylosing Spondylitis
- Arthritis (RA)
- Asthma
- Carpal Tunnel
- Fibromyalgia
- Multiple Sclerosis
- Osteoarthritis
- Psoriasis
- Scleroderma
- Ulcerative Colitis

Photo: Lewis & Anderson’s Free Enterprise Radon Health Mine, Boulder, Montana, USA

http://www.radonmine.com/area.html
# Environmental Radiation Hormesis: Radon-Spa Areas in Japan (Misasa)

<table>
<thead>
<tr>
<th>Cancer Site or Type</th>
<th>100*PROFAC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Leukemia</td>
<td>47 ± 1.6</td>
</tr>
<tr>
<td>Stomach</td>
<td>55 ± 1.6</td>
</tr>
<tr>
<td>Breast</td>
<td>74 ± 1.4</td>
</tr>
<tr>
<td>Lung</td>
<td>81 ± 1.2</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>86 ± 1.1</td>
</tr>
</tbody>
</table>

Radon exposure involves a gamma radiation component, which is considered responsible for activating the PAM process and inducing immunity. *Data from Mifune et al. 1992*
Conclusions

• Many cancer cases (and other diseases) are likely being prevented worldwide via medical and environmental radiation hormesis.

• Less costly, more tolerable, and possible more successful cancer therapy could be achieved via use of multiple low doses of low-LET radiation (or chronic low rates) in combination with agents (e.g. resveratrol) that selectively sensitize cancer cells to undergoing apoptosis and with antiangeogenic therapy.

• Current high-dose radiation and chemotherapy may be promoting cancer metastasis. Medical radiation hormesis likely suppresses cancer metastasis.

• Radon in the home is likely suppressing cancer occurrence and other diseases. Removing radon therefore may be more harmful than beneficial.
Acknowledgments

This research was supported by the Office of Science (BER), U.S. Department of Energy (DOE) Grants DE-FG02-03ER63671 and DE-FG02-03ER63657.
Backup Slides
**Doses from Diagnostic X-Rays Fall in the Hormetic Zone**

<table>
<thead>
<tr>
<th>Number of X-Rays</th>
<th>Dose Range(^a)</th>
<th>Hormesis Likely?</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>

**Routine nuclear medicine diagnostic procedures involve low-LET doses < 30 mGy.**

\(^a\) Boice JD, Jr. et al. JAMA 265(10):1290-1294, 1991
Hormetic Effect in Chernobyl Workers

Hormetic effect observed for the solid cancer incidence among nuclear workers who participated in recovery operations following the accident at the Chernobyl plant and for cancer mortality among the Chernobyl emergency workers.

Ivanov et al. NPP. J Radiat Res. 45:41–4, 2004
Expected Lives Saved From Diseases Other Than Cancer Due to Radiation Hormesis in Nuclear Shipyard Workers

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>100*PROFAC (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous and sensory organs</td>
<td>52</td>
<td>&lt; 10^{-7}</td>
</tr>
<tr>
<td>Cirrhosis of liver</td>
<td>37</td>
<td>1.3 x 10^{-3}</td>
</tr>
<tr>
<td>Digestive system diseases</td>
<td>29</td>
<td>&lt; 10^{-7}</td>
</tr>
<tr>
<td>Vascular lesions of CNS</td>
<td>27</td>
<td>5.9 x 10^{-5}</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24</td>
<td>1.1 x 10^{-5}</td>
</tr>
<tr>
<td>Total mortality</td>
<td>22</td>
<td>1.1 x 10^{-7}</td>
</tr>
<tr>
<td>All circulatory diseases</td>
<td>20</td>
<td>&lt; 10^{-7}</td>
</tr>
<tr>
<td>Arteriosclerotic heart disease</td>
<td>17</td>
<td>5.8 x 10^{-6}</td>
</tr>
</tbody>
</table>

Expected Lives Saved From Cancer Due to Radiation Hormesis in Oak Ridge Nuclear Workers

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>$100\times\text{PROFAC}$ (%)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer of buccal cavity &amp; pharynx</td>
<td>79</td>
<td>$p &lt; 10^{-4}$</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>46</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Leukemia and aleukemia</td>
<td>40</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>36</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>28</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>All lymphopoietic cancer</td>
<td>17</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Cancer of digestive organs and peritoneum</td>
<td>15</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

Expected Lives Saved From Diseases Other Than Cancer Due to Radiation Hormesis in Oak Ridge Nuclear Workers

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>100*PROFAC (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infective &amp; parasitic diseases</td>
<td>62</td>
<td>(p &lt; 10^{-3})</td>
</tr>
<tr>
<td>Diseases of nervous system &amp; sense organs</td>
<td>45</td>
<td>(p &lt; 10^{-2})</td>
</tr>
<tr>
<td>Allergic, endocrine, metabolic, nutritional diseases</td>
<td>44</td>
<td>(p &lt; 10^{-2})</td>
</tr>
<tr>
<td>All diseases of genitourinary system</td>
<td>41</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>All diseases of digestive system</td>
<td>40</td>
<td>(p &lt; 10^{-5})</td>
</tr>
<tr>
<td>All diseases of circulatory system</td>
<td>17</td>
<td>(p &lt; 10^{-8})</td>
</tr>
<tr>
<td>All respiratory diseases</td>
<td>15</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

HRR Model: Based on Normalized Dose $S$

$S = \frac{D}{D^*}$

$cancer incidence at absolute zero background radiation$

$RR^*$

$RR$

Increased Cancers

$LNT$ Zone

$RR = 1$

Hormetic Zone

$RR = 1 - PROFAC$

$0^+ indicates dose from natural background radiation$

$Normalized Dose S = \frac{D}{D^*}$
Suppression of Spontaneous Lung Cancer in Mayak Plutonium Facility Workers

Data corrected for influence of alpha radiation (Scott, 2006a).

Additional indirect evidence for medical radiation hormesis
How Hormesis is Inappropriately Discounted by Regulatory Agencies

• All radiation assumed harmful including doses from diagnostic low-LET radiation (e.g., routine chest X-rays, CT scans, nuclear medicine diagnostic procedures).
• Persons receiving low doses included with controls when evaluating the shape of the dose-response curve.
• Low-dose data are excluded, ignored, or assigned low statistical weight.
• Evidence for nonlinearity is ignored.
• Ecological data showing hormesis are discounted based on poor dosimetry.
• DNA repair, protective apoptosis, and induced immunity are ignored.
• Lifespan prolongation is not considered.
• Hormetic effects missed due to assuming a healthy worker effect.
• Years of radiation dose accumulation are simply thrown away (called dose lagging) changing threshold-like dose responses into what appears to not have a threshold.
Relative Risk at Reduced Natural Background Radiation

• *RR* at reduced natural background radiation level can be evaluated based on the normalized dose \( S = \frac{D}{b} \) relative to \( b \), where \( b \) is a reference natural background low-LET dose evaluated over the period of interest and \( D \) is the corresponding reduced background low-LET dose.

• *RR* increases linearly from 1 at current natural background to a value > 1 at zero natural background radiation. Only the low-LET component to the dose is considered important for this dose region since it is responsible for inducing the adapted protection that is lost when dose is reduced (Scott, 2006b).
Expected Effects of Reducing Natural Background Radiation on Cancer Mortality

Normalized Dose $S$ relative to 450 mSv

Subjective Upper Estimate

Subjective Lower Estimate

Central Estimate

Solid Cancer Mortality for Yangjiang, China 1979-1998

0 represents absolute zero radiation dose

Expected Impact of Reducing Natural Background Radiation on Relative Risk for All Cancers

Data are based on various cities and states of India. Only gamma-ray exposures were evaluated. \( RR = 1 \) at \( 0+ = 850 \, \mu\text{Sv y}^{-1} \).

Data from Nambi KSV and Soman SD. Health Physics 53(5):653-657, 1987
Environmental Radiation Hormesis: Cosmic and Terrestrial Radiation

Annual Cancer Mortality/100,000 for US States (1950 to 1967)

Frigerio and Stowe. IAEA Publication (1976)
Environmental Radiation Hormesis

Solid Cancer Mortality for Yangjiang, China 1979-1998

HRR Model
PROFAC = 0.34
Mean
Slope of the line = -6.33E-04/mSv

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

Effective doses are used

Conclusions

• Routine diagnostics (e.g., nuclear medicine procedures, chest X-rays, CT scans) protect us from cancer and other diseases (*medical radiation hormesis*). Likely suppresses metastasis.

• Low-LET radiation sources have been used to successfully treat cancers without any serious side effects. (*Therapeutic radiation hormesis*).

• Repeated exposures (or chronic low rate exposure) over a prolonged period to small doses of low-LET radiation in combination with antiangiogenic therapy and tumor sensization therapy (e.g., application of resveratrol) might greatly increase the frequency of cancer cures.

• Benefits of radon therapy can be explained based on radiation hormesis.

• Reducing radon exposure in the home may cause more harm than benefit through loss of adapted protection.