Radiation Risk A Realistic View: Impact of Cellular and Molecular Research

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CEMP Meeting July 25, 2006
Mt. Charleston, Nevada
## Acute Effects of Radiation

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>CNS Syndrome</th>
<th>GI Syndrome</th>
<th>Hematopoietic Syndrome</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1.0</td>
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<td></td>
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<tr>
<td>0.1</td>
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</tr>
<tr>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No Detectable Health Effects**

- **Occupational Exposure/Year**
- **Background Dose**

**Population Exposure Limit**

- **Minutes**
- **Hours**
- **Days**
- **Weeks**
- **Months**
- **Years**
Cerebrovascular Syndrome

- Total body dose of 100 Gy or 10,000 rad of gamma rays (or less of neutrons) results in death in a matter of hours.

- All organ systems are also seriously damaged

- Gastrointestinal and hematopoietic systems would fail quickly at this level, but cerebral much faster
Gastrointestinal Syndrome

- Death is caused by more than 10 Gy of gamma rays or neutrons. There is no record of any human surviving over 10 Gy acute dose.

- Symptoms and death are due to depopulation of epithelial lining of the gastrointestinal tract by radiation. Compartments of stem-cells,, differentiating compartment and mature functioning cells.

- 10 Gy doesn’t kill mature cells, but sterilizes dividing cells. As good cells are sloughed off and rubbed away, there are no replacement cells.
Bone Marrow Syndrome

• Death from hematopoietic system failure can occur between 3-8 Gy…

• Mitotically active precursor cells are sterilized, therefore red cells, white cells and platelets are diminished.

• Immune impairment, bleeding and anemia from platelets because of depression of blood elements.

• Red blood cell anemia doesn’t occur.
Summary of High Dose Effects

• No one has survived a dose of 10 Gy or 1,000 Rads without medical intervention
• Doses between 2 and 8 Gy kill dividing cells. If organs cannot replace these cells death occurs. Gut and Bone Marrow and the target organs.
• Doses below 1 Gy, 100 rads, 100,000 mrads produce little life shortening increase in cancer “risk”.
Health Effects of Low Doses of Radiation?

• Cancer primary concern for Low doses of radiation
• Genetic Effects
• Birth Defects
# Calculation of Genetic Risk

<table>
<thead>
<tr>
<th>Disease Class</th>
<th>Baseline Frequency/10^6</th>
<th>Risk/Gy/10^6 progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Generation</td>
<td>2nd Generation</td>
</tr>
<tr>
<td>Mendelian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant and X-linked</td>
<td>16,500</td>
<td>~750-1,500</td>
</tr>
<tr>
<td>• Autosomal recessive</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• Chromosomal</td>
<td>4,000</td>
<td>b</td>
</tr>
<tr>
<td>Milti-factoral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic Multi-factorial</td>
<td>650,000c</td>
<td>~250-1,200</td>
</tr>
<tr>
<td>• Congenital abnormalities</td>
<td>~2,000^d</td>
<td>~2,400-3,000^d</td>
</tr>
<tr>
<td>• Total</td>
<td>738,000</td>
<td>~3,000-4,700</td>
</tr>
<tr>
<td>• Total Risk/Gy expressed as a percent of baseline</td>
<td>~0.41-0.64</td>
<td>~0.53-0.91</td>
</tr>
</tbody>
</table>
Radiation Induced Cytogenetic Damage

- Dose, Dose-rate and LET dependent
- Different types of aberrations and risk
  - Un-Stable Aberrations
  - Stable Aberrations
  - Chromosome type and Chromatid type
- Complex Aberrations
Complex Chromosome Aberrations
Late Non-Cancer Effects of Radiation

- Fetal Malformation
  - Spontaneous abortions
  - Birth defects
  - Developmental abnormalities

- Mental Retardation
  - Change in head size
  - Loss of I.Q.

- Cataracts

- Fibrosis
Embryology of the developmental stages during pregnancy

<table>
<thead>
<tr>
<th>Preimplantation</th>
<th>Embryo</th>
<th>Fetus</th>
<th>Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell proliferation &amp; differentiation</td>
<td>Differentiation &amp; organogenesis</td>
<td>Growth</td>
<td></td>
</tr>
</tbody>
</table>

Time (Days)

0 10 20 30 40 → 270

Endoderm, Mesoderm, Ectoderm
Induction of abnormalities by 200 R (2.0Gy) after acute exposure

Figure 12.1. Incidence of abnormalities and of prenatal and neonatal death in mice given a dose of 200 R at various times after fertilization. The lower scale consists of Rugh’s estimates of the equivalent stages for the human embryo. (Data from Russell LB, Russell WL: An analysis of the changing radiation response of the developing mouse embryo. J Cell Physiol 43[suppl 1]:1030–149, 1954.)
The influence of Time of Exposure on the production of malformation

• There is a window of time when the fetus is in a stage that is sensitive to radiation
• This is related to the organs and tissues being formed at the time.
• High dose radiation exposure during this time window is very effective in producing congenital malformations.
Calculation of Risk using Real World Assumptions.

- 3.5 Radiation induced Cases in the population of 100,000 people followed over 10 years (Worst Case)
- $3.5 \times 0.018$ fraction of time in sensitive stage = 0.063
- $0.063 \times 0.01$ fraction of population receiving Maximal Dose = 0.0063
- $0.0063 \times 0.5$ for dose rate effectiveness = 0.0032
- $0.0032 \times$ the LNTH assumption = ???
- Relate 0.0032 radiation induced malformations to the 2,800 “normal” cases.
- At what dose do you recommend an abortion???
Radiation induced Mental Retardation

Hall
“Dose and time Response” for induction of cataracts
Overview of Radiation Exposure of Tissues and Organs

403 accidents worldwide from 1944-1999
120 Acute deaths from these accidents

- 19 reactors
- 303 involved radiation devices, sealed sources or x-ray machines
- 81 radioisotopes
Effects of Atomic Bomb

- Killed outright by the bomb or acute radiation effects.  
  About 200,000 people

- Survived for lifespan study  
  86,572 people
A-BOMB SURVIVOR STUDIES

5% less cancer than total controls

10,159 "Controls"

46,249 "Exposed"

2.45 Km (5 mSv)

3 Km (2 mSv)

5 Km

Pierce and Preston 2000
A-BOMB SURVIVOR STUDIES

Excess Cancers

572 Total
Excess Cancers

479 Total

Preston et al. 2004

Leukemias

CONTROL AREA

Excess Solid Tumors

28.2

27.7

18.9

10.4

4.7

4.0

0.1

93 Total

2

113

116

99

41

44

3 Km

2. Km

1 Km
Atomic Bomb Survivor
Excess Cancer

Population of Survivors Studied 86,572

40% of these people are still alive 60 years after the bomb

Cancer Mortality observed after the Bomb 10,127
Cancers Mortality Expected without Bomb 9,555

Total Cancer Mortality Excess 572

Excess Tumor + Excess Leukemia = 572

479 + 94 = 572
Problems with Detection of Cancer following Low Doses

- Background radiation
- Background cancer
- High signal to noise ratio

Radiation is a poor mutagen/carcinogen, but a very good cell killer
Background Radiation
Radiation is everywhere
We live in a sea of radiation…

Cosmic
Inhaled Radon
Rocks
Radioactive Elements
Bodies
Plants
Normal annual exposure from natural radiation

About 300 mrem/yr

- Radon gas: 200 mrem
- Human body: 40 mrem
- Rocks, soil: 28 mrem
- Cosmic rays: 27 mrem

Normal annual exposure from man-made radiation

About 70 mrem/yr

- Medical procedures: 53 mrem
- Consumer products: 10 mrem
- One coast to coast airplane flight: 2 mrem
- Watching color TV: 1 mrem
- Sleeping with another person: 1 mrem
- Weapons test fallout: less than 1 mrem
- Nuclear industry: less than 1 mrem
Medical Radiation Exposures

- 300 million medical x-rays/year
  - X-ray 0.1 mGy
- 100 million dental x-rays/year
  - Dental 0.06 mGy
- 10 million doses of radiopharmaceuticals/yr
- 37 million CT scans/year
  - Head scan 4-6 mGy/scan
  - Body scan 40-100 mGy/scan
- Large doses from radiation therapy
Background Cancer
U.S Dose Rates from Natural Background

Terrestrial Gamma-Ray Exposure at 1m above ground

Source of data: U.S. Geological Survey Digital Data Series DDS-9, 1993
Nevada Test Fallout

Figure 7. Cesium-137 deposition density resulting from the cumulative effect of the Nevada tests generally decreases with distance from the test site in the direction of the prevailing wind across North America, although isolated locations received significant deposition as a result of rainfall.

Simon et al. 2006
What Causes Cancer?

- Cigarette smoke
- Diet & nutrition
- Chronic infection
- Occupational exposure
- Genetic
- Alcohol drinking
- Environmental factors including radiation
How Much Radiation?

- It is very difficult to understand units

- Huge range of every day exposures

- How much radiation does it take to significantly increase cancer frequency?
It takes a lot of radiation to produce cancer!!

<table>
<thead>
<tr>
<th>Number of people</th>
<th>Dose/Person (Gy)</th>
<th>Amount/Person (J)</th>
<th>Amount (J)</th>
<th>Background Cancer</th>
<th>Excess Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>*700</td>
<td>700</td>
<td>0.42</td>
<td>0.0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>70</td>
<td>700</td>
<td>4.2</td>
<td>1.0</td>
</tr>
<tr>
<td>100</td>
<td>0.1</td>
<td>7</td>
<td>700</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>1,000</td>
<td>0.01</td>
<td>0.7</td>
<td>700</td>
<td>420</td>
<td>1.0</td>
</tr>
<tr>
<td>10,000</td>
<td><strong>0.001</strong></td>
<td>0.07</td>
<td>700</td>
<td>4,200</td>
<td>1.0</td>
</tr>
<tr>
<td>100,000</td>
<td>0.0001</td>
<td>0.007</td>
<td>700</td>
<td>42,000</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*This is a large lethal amount of radiation given to one person. Cancer can never be detected with this quantity of radiation regardless of population size!!!

**Background low LET dose/person
It takes a lot of radiation to produce Cancer!!!

<table>
<thead>
<tr>
<th>Number of people</th>
<th>Dose / Person (Gy)</th>
<th>Quantity/ Person (J)</th>
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<td>0.42</td>
<td>0.01</td>
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<td>7.0</td>
<td>70</td>
<td>4.2</td>
<td>0.1</td>
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<td>7000</td>
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<td>10</td>
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<td>0.1</td>
<td>7.0</td>
<td>70,000</td>
<td>4,200</td>
<td>100</td>
</tr>
<tr>
<td>100,000</td>
<td>0.1</td>
<td>7.0</td>
<td>700,000</td>
<td>42,000</td>
<td>1000</td>
</tr>
<tr>
<td>86,611</td>
<td>0.14</td>
<td>10.3</td>
<td>894,557</td>
<td>10,127</td>
<td><strong>572</strong></td>
</tr>
</tbody>
</table>

Amount per person and the population size is below the level to detect cancer
Cancer is detectable in this range of population, dose, exposure.

*BEIR VII
** A-bomb observed response.
Mechanisms for Cancer Induction

**High Doses**

- Changes in gene expression
- Mutations
- Chromosome aberrations
- Genomic instability
- Cell killing
- Stimulate cell proliferation
- Tissue and matrix disruption
- Inflammation

**Low Doses**

- Changes in gene expression
- Mutations
- Chromosome aberrations
- Adaptive response

Cancer?
LNTH Assumption with Dose

High dose x small number of subjects

Low dose x large number of subjects

Energy to system
DOE Low-Dose Radiation Research Program

- A 10 year program, running for 7 years.
- Focused on biological mechanisms of low-dose (< 0.1 Gy) and low dose-rate (< 0.1 Gy / Yr) radiation
- International in scope (currently 80 projects)
- To develop a scientific basis for radiation standards

http://lowdose.tricity.wsu.edu
Key Research Areas

- Technological Advances
- Biological Advances
Alpha-Particle Radiation System

- Video Camera
- Microscope Objective Lens
- Mylar Bottom Petri Dish
- Viewing Light
- Scintillation Detector
- Newport Positioning Stage
- Scintillation Plastic
- Manually Adjustable Collimeter
- Piezoelectric Shutter
- Beam Control Slits
- Faraday Cup
- Beam from Accelerator
- Vertical Bending Magnet

Texas A&M
Microbeams recent findings

- Localised DNA damage observed after both focussed soft X-ray production and charged particle induction using γH2AX

5 mm Helium ion

Single 3 MeV Helium ion

Focused $\text{C}_\text{K}$ X-rays
Cellular Changes

• **Bystander Effects**
  — Cells respond without energy deposition
  — Cell-cell communication
  — Materials into the media

• **Adaptive Response**
  — Small dose alters response to large dose
  — Small dose decreases spontaneous damage

• **Genomic Instability**
  — Loss of genetic control many cell generations after the radiation exposure
Relationship between biological responses to radiation

- Adaptive Response
- Genomic Instability
- Bystander Effects
Bystander Effects *in vitro*
Micronuclei in non-Exposed Cells

Geard
Each cell hit by one particle

10% of cells hit with 1 alpha particles

Sawant et al. 2000
Cell Transformation

Every nucleus hit
One in ten nucleus hit

Sawant et al. 2000
Low Dose Rate exposures: No Bystander Effects in unexposed Tissues or Organs

- Cancer from internal emitters are at the site of radionuclide deposition
- Secondary cancers from radio-therapy located at the exposure site
- At low dose rates there is little evidence for cancer in non-exposed tissues
Relationship between biological responses to radiation

- Adaptive Response
- Genomic Instability
- Bystander Effects
What Genes are Responsible for the Adaptive Response?

![Graph showing aberrations vs. dose (cGy)]

Aberrations

<table>
<thead>
<tr>
<th>Dose cGy</th>
<th>0</th>
<th>0.5</th>
<th>150</th>
<th>0.5 + 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>0</td>
<td>5</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>Expected</td>
<td>0</td>
<td>10</td>
<td>80</td>
<td>45</td>
</tr>
</tbody>
</table>

Shadley and Wolff 1987
Adaptive Response
Sub-linear dose response

Redpath et al. 2001
Relationship between biological responses to radiation

Adaptive Response

Genomic Instability

Bystander Effects
Radiation-induced Genetic Damage

Old Paradigm

After a cell is mutated by radiation, all of its progeny are mutated

Mutation is a rare event
After a cell is exposed to radiation, different things can happen …sometimes after many cell divisions. This is a frequent event.
Genomic Instability can be demonstrated in some strains of mice

Mechanisms involved in new phenomena

- Altered gene expression
- Impact of oxidative status of the cell
- Radiation-induced changes in differentiation pathways
- Cell/cell, cell/matrix interactions
- Nutrition and radioprotectants
Radiation-related Gene Induction

It has been shown that certain genes are inappropriately induced, or “turned on” or “turned off” by radiation. The genes involved depend on the radiation dose delivered.
DIFFERENCES IN TRANSCRIPTION PROFILES BETWEEN LOW AND HIGH DOSE IRRADIATION IN MURINE BRAIN CELLS

703 Genes with Significant F-ratio

Total gene set contains nearly 10,000 genes

Numbers of Genes Differentially Regulated in HLB Cells 4 hr after IR

- Up-regulated at 2Gy: 245
- Down-regulated at 2Gy: 135
- Up-regulated at 0.1Gy: 182
- Down-regulated at 0.1Gy: 187

Yin 2003
Radiation-induced changes in gene expression

Dose (cGy)

Low Dose Genes

High Dose Genes

Wyrobek
Protective Response

It was found that low-dose IR exposures modulated genes involved in stress response, synaptic signaling, cell-cycle control and DNA synthesis/repair, suggesting that low-dose IR may activate protective and reparative mechanisms as well as depressing signaling activity.

Yin 2003
DNA damage and signaling

- Alterations in gene expression
- Changing redox status of the cells
- Modifying signaling pathways
- Modification of cell cycle
- Alterations in differentiation
Dynamic Interactions with Microenvironment

- Organized epithelial cells
- Integrin-mediated signaling
- Fibroblasts
- Immune cells
- Vasculature

Park et al. 2000
It takes a tissue to make a tumor...

Normal mammary epithelial cells (milk production)

Normal matrix

Artificial substrate

Mammary epithelial cells

Irradiated matrix

CANCER

CANCER

Barcellos-Hoff et al. 2000
Dietary Intervention
Supplements reduce Oxidative Stress Levels after Radiation

Guan, et al 2004
Summary of New Paradigms

- **Hit theory shift to bystander paradigm**
  A cell does not have to be hit in order to be biologically altered

- **Mutation theory shifts to gene expression paradigm**
  Radiation induces changes in gene expression that may alter subsequent responses in a large fraction of the cell population

- **Single mutation cancer theory shifts to tissue paradigm**
  Tissues respond as whole and not as individual cell

- **LNTH challenged by adaptive response & genomic instability**
  - Adaptive response may result in protective, nonlinear dose-responses
  - Genomic instability or bystander effects could result in either super-linear or sub-linear dose-responses
Radiation is a rather poor mutagen and Carcinogen

• It is a very good cell killer
  – Induction of apoptosis
  – Chromosome cell death
  – Necrosis
  – Wide use in radiation therapy
Summary:
“My View on Low Dose Cancer Risk”

• Radiation is not a major environmental carcinogen. It takes a large amount of radiation to produce an increase in cancer frequency.

• Both non-linear and linear models must be considered in determining dose-response relationships for radiation-related human cancer.

• Single hit, single DNA damage/mutation, single cancer biophysical model must be modified to accommodate modern molecular biology.

• Additional research is needed to define mechanisms of action for observed low dose biological responses before they can be used in cancer risk estimates.

• Scientific basis for radiation standards is needed to help define the shape of the dose-response relationships in the low dose regions.
• Good review of the literature, summaries and conclusions, “The risk from radiation is small.”

• Failure to acknowledge the differences between real data and extrapolated risks using the LNT-H.

• Dismissal of new mechanistic biological data that demonstrate non-linear biology.

• Failure to include the caveats in conclusions and public summaries.

• Since the risk is small it takes a lot of radiation to produce excess cancers.
Solid Cancer Risk and Radiation Exposure

Radiation Dose (Sv)

Cancer Risk

Extrapolated Risk

Excess Risk

Background Cancer risk

Modified from BEIR VII, McClellan and Brooks

A-bomb data
Linear fit
Linear-quadratic

Background dose/yr
Background dose/40 years