Acute Radiation Syndrome

- Also known as radiation toxicity or radiation sickness
- Acute illness caused by irradiation of the whole body by a high dose of penetrating radiation over a short period of time
- Major cause of illness is the depletion of immature parenchymal stem cells in specific tissues
- Examples:
  - Survivors of Hiroshima and Nagasaki atom bomb
  - First responders of Chernobyl nuclear power plant explosion

Requirements for ARS

- Radiation dose must be large
  - i.e. greater than 0.7 Gy
- Mild symptoms may be observed at lower doses
- Dose is usually external
- Radiation must be penetrating
  - Gamma rays, X-rays and neutrons
- Entire body or significant portion must have received the dose
- Dose must have been delivered over a short time

Early Deterministic Effects

- Dose of < 0.1 Gy, whole body: no detectable difference between exposed and non-exposed patients
- Dose of 0.1 to 0.2 Gy, whole body: Detectable increase in chromosome aberrations; no clinical signs or symptoms
- Dose of 0.5 Gy, whole body: Detectable bone marrow depression with lymphopenia
- Dose of > 1.2 Gy, whole body: Sperm count decreases to minimum at about 45 days

Lab Diagnosis of ARS

- Circulating lymphocytes are one of the most radiation-sensitive cells
- During early phase of observation, extent of lymphocyte loss is the best and most useful laboratory test to determine level of radiation exposure
- The lowest dose can be detected is about 0.2 Gy
Phases of ARS

- Initial or prodromal phase
  - Classic symptoms: nausea, vomiting
  - Occurs minutes to days following exposure
  - May last (episodically) for minutes to several days
- Latent phase
  - Patient generally feels and looks well
  - Duration is inversely proportional to dose
- Manifest illness phase
  - Symptoms depend on specific syndrome
  - May last from hours to months
- Recovery phase
  - Lasts from several weeks to years

Manifestations of ARS

- Cerebrovascular syndrome (CVS)
- Gastrointestinal syndrome (GIS)
- Hematopoietic syndrome (HPS)

Cerebrovascular Syndrome

- 50-100 Gy dose
- Prodromal phase
  - Symptoms are extreme nervousness and confusion, severe nausea, vomiting, watery diarrhea, loss of consciousness
  - Onset within minutes of exposure
  - Lasts for minutes to hours
- Latent stage
  - Patient may return to partial functionality
  - Lasts for hours but often less
- Manifest illness stage
  - Symptoms are watery diarrhea, convulsions and coma
  - Death occurs within 3 days of exposure

Gastrointestinal Syndrome

- > 10 Gy radiation dose
- Prodromal stage
  - Symptoms are anorexia, severe nausea, vomiting, cramps and diarrhea
  - Onset a few hours after exposure
  - Lasts about 2 days
- Latent stage
  - Stem cells in bone marrow and GI tract dying
  - Lasts about a week
  - Patient may appear and feel well
- Manifest illness stage
  - Symptoms are anorexia, severe diarrhea, fever, dehydration
  - Death due to infection and electrolyte imbalance
  - Occurs within 2 weeks of exposure

Self-Renewing Tissue

- ARS symptoms appear principally due to classic self-renewing tissue
- Stem cell compartment
  - Some maintain the pool
  - Some differentiate and produce mature functioning cells
  - Large doses of radiation are required to kill differentiating cells
  - Modest doses will kill some or all of the stem cells
  - Therefore, radiation does not produce an immediate effect on tissue because it doesn’t affect functioning cells
Gastrointestinal Syndrome
- Dividing cells are confined to the crypts
- Move up the villi, differentiate and become functioning cells
- Cells at top of villi fold are sloughed off slowly but continuously, and continuously replaced
- Single cell barrier separates blood vessels in the villi from contents of the intestine
- Radiation destroys a large portion of the dividing cells in the crypts
  - As surface of villi is sloughed off, there are no replacement cells
  - Villi begin to shorten and shrink

Hematopoietic Syndrome
- 0.7 to 10 Gy dose
- Prodromal phase symptoms, with onset occurring from 2 hours to 2 days after exposure:
  - Nausea
  - Vomiting
  - Anorexia
- Latent stage:
  - Stem cells in bone marrow die; patient may appear and feel well
  - Lasts 1 to 6 weeks
- Manifest illness phase:
  - Symptoms are anemia, fever
  - Drop in red blood cell counts for several weeks
  - Primary cause of death is infection and hemorrhage
  - Mortality rate of rhesus monkeys at 30 days after a single dose of total body x-rays
- Recovery phase:
  - Bone marrow repopulates
  - Full recovery in weeks to years after exposure

LD_{50}
The dose of radiation causes a mortality of 50% in an experimental group within a specified period

LD_{50} and Bone Marrow Transplant

HPS
- Death, if it occurs is a result of radiation damage to the hematopoietic system
- Mitotically active precursor cells are sterilized by radiation
- Subsequent supply of mature red blood cells, white blood cells and platelets is diminished
- When mature circulating cells die off and precursor population is inadequate, the full effect of radiation becomes apparent
Measurement of Severity

- Prodromal stage
  - Time of onset
  - Degree of symptoms
- Hematological changes
  - Lymphocyte counts
  - Biological dosimetry

Summary of Latent Effects Based on Dose

<table>
<thead>
<tr>
<th>Degree of Acute Radiation Syndrome and Approximate Dose of Acute Whole Body Radiation Exposure (Gy)</th>
<th>Mild (1-2 Gy)</th>
<th>Moderate (2-4 Gy)</th>
<th>Severe (4-6 Gy)</th>
<th>Very Severe (6-8 Gy)</th>
<th>Lethal (&gt;8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (G/L) (days 3-7)</td>
<td>0.8-1.5</td>
<td>0.5-0.8</td>
<td>0.3-0.5</td>
<td>0.1-0.3</td>
<td>0.0-0.1</td>
</tr>
<tr>
<td>Granulocytes (G/L)</td>
<td>&gt;2.0</td>
<td>1.0-2.0</td>
<td>1.0-1.5</td>
<td>0.5-1</td>
<td>0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>None</td>
<td>Rare</td>
<td>Appears on days 6-9</td>
<td>Appears on days 4-5</td>
</tr>
<tr>
<td>Epilation</td>
<td>None</td>
<td>None</td>
<td>Moderate, beginning on day 13 or later</td>
<td>Complete or more complete on days 14-21</td>
<td>Complete earlier than day 11</td>
</tr>
<tr>
<td>Latency period (d)</td>
<td>21-35</td>
<td>10-18</td>
<td>8-10</td>
<td>7 or less</td>
<td>None</td>
</tr>
<tr>
<td>Late Effects</td>
<td>Hospitalization not necessary</td>
<td>Hospitalization recommended</td>
<td>Hospitalization necessary</td>
<td>Hospitalization urgently necessary</td>
<td>Hospitalization treatment only</td>
</tr>
</tbody>
</table>

Summary of Critical Phase Based on Dose

<table>
<thead>
<tr>
<th>Degree of illness and approximate dose of acute whole body radiation exposure (Gy)</th>
<th>Mild (1-2 Gy)</th>
<th>Moderate (2-4 Gy)</th>
<th>Severe (4-6 Gy)</th>
<th>Very Severe (6-8 Gy)</th>
<th>Lethal (&gt;8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
</tr>
<tr>
<td>Hematological changes</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>Fatigue, weakness</td>
<td>Fatigue, weakness, bleeding, weakness, edema</td>
<td>Fatigue, weakness, bleeding, edema</td>
<td>Fatigue, weakness, bleeding, weakness, edema</td>
<td>Fatigue, weakness, bleeding, weakness, edema</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Medical response</td>
<td>Psychiatric</td>
<td>Psychiatric</td>
<td>Psychiatric</td>
<td>Psychiatric</td>
<td>Psychiatric</td>
</tr>
</tbody>
</table>

Bone Marrow Transplant

- Beneficial window of dose is small
- Doses of less than 6 Gy likely to survive with supportive care
- At doses of greater than 10 Gy, death from GIS is inevitable

Radiation Carcinogenesis

- If cellular damage occurs as the result of radiation that is not adequately repaired
  - It may prevent the cell from surviving or reproducing, or
  - It may result in a viable cell that has been modified (change or mutation)
- These two outcomes have profoundly different implications
Radiation Carcinogenesis

Deterministic vs. Stochastic Effects

• Most organs or tissues are unaffected by the loss of a few cells
• However, loss of tissue function can result if cell loss is too large
• Loss of tissue function is minimal at low radiation doses, but above some level of dose, called the threshold dose, the probability increases rapidly with dose

• Deterministic effects characterized by:
  - A threshold in dose
  - Dose-related severity
• Examples are radiation-induced cataracts and late tissue fibrosis

Stochastic effect:

- Is independent of dose (i.e. severity is independent)
- Has no threshold
- Probability is proportional to dose (i.e. probability increases with dose)
- Main effects are carcinogenesis and genetic mutations

Radiation Carcinogenesis

Tissue Culture Studies

• Survival parallels transformation at doses greater than 600 rads
• Above 100 rads: Transformation frequency may exhibit a quadratic dependence on doses
• Between 30 and 100 rads: Transformation frequency may not vary with dose
• Below 30 rads: Transformation frequency may be directly proportional to dose

Radiation Carcinogenesis

Animal Studies

• Radiation-induced tumors in mice:
  - Lung
  - Bone
  - Breast
  - Ovarian
  - Uterine
  - Skin
  - Alimentary tract
  - Thyroid
  - Pituitary
  - Adrenal

Human Studies

• Leukemia, thyroid cancer, breast cancer, lung cancer, bone cancer and skin cancer
• Japanese survivors of the atomic bomb
  - Most important group because of their large number, care with which they have been followed, and people of all ages and both sexes were exposed
• Patients suffering from ankylosing spondylitis in Britain from 1935-1944: increased risk of leukemia
• Leukemia in radiologists before 1922
• Thyroid cancer in children receiving radiation for an enlarged thyroid
• Treatment of children for ringworm of the scalp: increased risk of brain tumors, salivary gland tumors, skin cancer and leukemia
• Patients with tuberculosis: increased risk of breast cancer

Experiments in vitro and in vivo with radiation identify 3 distinct steps in carcinogenesis:

- Initiation: chromosome/DNA damage events
- Promotion: Low doses of tumor initiators are necessary to convert initiated cells to cancer cells
- Examples include estrogen, excessive fat
- Progression: Increased genetic instability resulting in aggressive growth phenotype

Evidence for radiation as a carcinogen comes from tissue culture, animal and human models.
Relative risk of thyroid cancer after exposure to radiation

Incidence of breast cancer as a function of dose

Radiation Carcinogenesis
Risk Models

- **Absolute risk model**
  - Radiation induces cancers over and above the natural incidence.

- **Relative risk model**
  - Assumes the effect of radiation is to increase the natural incidence at all ages subsequent to exposure.
  - Because the natural or spontaneous incidence of cancer rises significantly in old age, the relative risk model predicts more radiation-induced cancers in old age.

- **Time dependent relative risk model**
  - Excess incidence of cancer is a function of dose, the square of the dose, age at exposure and time since exposure.

Radiation Carcinogenesis
Risk Estimates

- Estimated relative risks of A-bomb survivors suggest low dose risks are above the relative risk over the whole dose range.
- Bladder, breast, lung, thyroid and colon are more radiation-sensitive, whereas stomach and liver are less sensitive.

Radiation Carcinogenesis
Summary of Risk Estimates

- Radiation-induced cancer incidence at 10.8% per Sv is about double the cancer mortality at 5.4%.
- Female cancer risks are higher than male cancer risks.

Radiation Carcinogenesis
Age at Exposure

- Children and young adults are much more susceptible to radiation-induced cancer.
- Higher risk for young age groups is not expressed until late in life.
Radiation-induced second malignancy

Prostate cancer RT - cancer of bladder, rectum, lung and sarcoma
Cervical cancer RT - cancer of bladder, rectum, vagina, bone, uterus, cecum and non-Hodgkin's lymphoma
RT for Hodgkin's lymphoma - breast cancer
RT to the brain - meningioma and glioma

Radiation Carcinogenesis
Secondary Malignancies Following Radiotherapy

Prostate cancer RT
- No increase in leukemia, overall increased relative risk
- Increased risk in bladder (77%) and rectum (105%)

Hodgkin Disease
- Second cancer is the leading cause of death in long-term survivors
- High risk of breast cancer among women treated at a young age

Radiation Cataractogenesis

Where is the lens?
Cataracts of the ocular lens

Opacification of the transparent lens

Causes of cataracts

Age
Metabolic disorders
Chronic infection
Trauma
Radiation

Radiation-induced cataracts in experimental animals

° Elderly mice develop cataracts

° Mice are very sensitive to radiation, <1 mGy can induce cataracts

° Neutrons and other densely ionizing radiation are more effective in inducing cataracts, due to higher RBE

Cataracts in humans

The degree of opacity

Merriam and Focht classifications

The latent period

• Time from radiation exposure to onset of clinically relevant disabling opacity

• Latency gets shorter with increasing exposure dose

• 8 years after exposing to 2.5 – 6.5 Gy, 4 years after a dose of 6.51 – 11.5 Gy

Dose-response for cataracts in humans

• Deterministic effect

• Threshold: 2 Gy in a single exposure, 5-8 Gy for a prolonged or fractionated exposure

• The severity increases with dose above the threshold