Ionizing and non-ionizing radiation diseases

Damaging irradiation

UV light a “complete carcinogen”

- UV-A: minimal damage – transient immunosuppression
- UV-B: responsible for most UV-induced cancers
- UV-C: potent mutagen - minimal damage due to ozone layer
Radiation injury – why it matters

- Long history of medical misapplication
  - Thorotrast; ankylosing spondylitis; ringworm treatment; "status thymicolympaticus"; pelvic inflammatory disease; "does the shoe fit?"
- Understanding radiation injury as source of short- and long-term tissue damage
  - Early: acute/chronic myelogenous leukemia
  - Lifetime: multiple solid tumors
- Important in natural settings:
  - UV light and cutaneous cancer
  - Natural radiation causes fraction of spontaneous cancer
- Medical treatment:
  - Localized/whole body irradiation and anti-cancer treatment
  - Increased use/higher dosages with CT scans (62 M/annum in US)
- Popular concern

Sources of ionizing radiation

- Radon
- Cosmic
- Terrestrial
- Internal
- Medical
- Nuclear medicine
- Consumer products
  - Man-made: 18%

DNA and radiation-induced damage

- UV-radiation
- Double-strand break
- Cross-link
- Single-strand break
ACUTE effects of UV

- Photodermatoses: sunburn
  - Radiation-damaged epidermis → pro-inflammatory cytokines
  - Direct damage to superficial dermal blood vessels → leakage/edema
- Exacerbation:
  - Phototoxicity = photosensitizing compounds in body:
    - Type 1: Phytotoxicoses and some drugs (specific drugs in large group including sulfonamides, frusemide, tetracycline)
    - Type 2: Metabolic diseases (porphyria)
    - Type 3: Primary hepatic disease + chlorophyll in diet
  - Photoallergy = UV-induced change to topical compounds on skin, converting them to haptens, leading to mischief
  - Selected autoimmune diseases: SLE and DLE; some atopies and forms of seborrhea

Acute sunburn

Chronic actinic dermatitis

“Sunburn cells” (in acute actinic dermatitis) = Apoptotic keratinocytes
Long-term effects of UV

- Chronic actinic dermatitis = chronic sunburn
  - High altitudes
  - Lightly-pigmented, thinly-haired skin of dogs, cats, horses, sheep, pigs and cattle, esp. where epidermis is thin:
    - Eyelids, vulva, penis, ventral skin, ears, nose, lips
  - Light-skinned people – protective role of melanin
  - Characteristic changes in skin: thick and wrinkled due to
    - Fibrosis and degradation of collagen in upper dermis
    - Elastosis
    - Epidermal hyperplasia
  - Accelerated photoaging
  - Immunosuppression:
    - Damaged leukocytes in dermal skin
  - Neoplasia

UV-associated neoplasia in animals

- Dogs:
  - SCC and hemangiommas/hemangiosarcoma
  - Skin (lightly haired) and conjunctiva
- Cats:
  - Esp. SCC of nose and ears
- Cattle:
  - Esp. SCC of conjunctiva, vulva
- Horses:
  - Esp. SCC of conjunctiva, vulva, penis

Chronic actinic dermatitis

Early SCC arising in scalp with multiple foci of actinic dermatitis
Feline squamous cell carcinoma

UV radiation and SCC/basal cell carcinoma

- "Non-melanoma" skin cancer in humans
- Sun-exposed skin
- Higher risk with immunosuppression
- Outdoor workers – ranchers, sailors
- 1.3M human cases/year in US
  - 80% basal cell carcinoma
  - 20% SCC – lifetime risk: 9–14% (men) and 4–9% (women)

UV radiation and melanoma

- Correlated with latitude + pale skin
- Intermittent exposure (indoor workers)
- >5 or more blistering childhood sunburns = x2 risk of melanoma
- Best biological example of tumor progression
  - Common nevus ("mole") → melanocyte dysplasia → radial growth phase melanoma → vertical growth phase melanoma → metastatic disease

Mortality: 5 – 10% 67% 78- 80%
DNA damage vs. mutation

- Damage:
  - Potentially:
    - Single and double strand breaks
    - 8-hydroxydeoxyguanosine residues
    - Polycyclic aromatic hydrocarbon adducts
  - Multiple repair mechanisms
  - DNA damage checkpoints before cells allowed complete cell cycle

- Mutation:
  - Permanent (heritable) change in base sequence of DNA
  - Not subject to repair
  - Most affected cells: lost via apoptosis
    - Germline: transmitted to offspring
    - Somatic: increased probability of dysplastic, senescent, or pre-neoplastic

Repairing DNA

- Direct chemical reversal:
  - Photolyase:
    - Breaks covalent dimer bonds
  - Methyl guanine methyl transferase
    - Corrects methylation of guanine bases

- Single strand breaks:
  - Multiple repair mechanisms
    - Base excision repair
    - Mismatch (of two DNA strands) repair
  - Nucleotide excision repair
    - Low error rate

- Double strand breaks:
  - Homologous recombination
  - Nonhomologous end joining
  - High error rate = Deletions and translocations

Inherited DNA repair disorders

- Homozygous recessive traits
- Defective nucleotide excision repair
  - 9 major proteins involved and named after associated diseases
    - Xeroderma pigmentosum: XPA, XPC, XPD, etc
    - Cockayne syndrome: CSA and CSB
- The disease:
  - Prone to severe sunburn dermatoses
  - Photosensitivity and ocular injury
  - Pigmentation changes
  - Multiple skin tumors in childhood:
    - Es. SCC, BCC and MM
Factors affecting severity of radiation injury

- Dose and rate of delivery
- Field size
- Tissue type (fraction of actively dividing cells)
- Type: Densely ionizing: heavy particles vs. sparsely ionizing: x- and gamma rays
- Oxygen effect
- Vascular damage
- Ability to repair DNA damage
- Chronological age

Effects of irradiation

- Short term: inhibition of proliferation in cells with high turnover: esp. intestinal and bone marrow:
  - Esp. small intestine
  - Also large bowel, stomach and esophagus
  - Ulceration and secondary bacterial infections
    - Compounded by immunosuppression due to white blood cells
- Long term:
  - Failure of organs to develop fully (when exposed in utero)
  - Sterility
  - Scar tissue and vascular injury
  - Neoplasia:
    - Esp. when exposed as children
Risk of post-irradiation neoplasia for two tumors: younger at exposure = higher risk

Consequences of whole-body irradiation over time

Tissues have susceptibility hierarchy
Absorbed dose is major determinant of tissue injury

Table 2. Skin Changes After a Single Acute, Localized Exposure.*

<table>
<thead>
<tr>
<th>Absorbed Dose</th>
<th>Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–4 Gy</td>
<td>Erythema is 2–3 wk.</td>
</tr>
<tr>
<td>10–35 Gy</td>
<td>Threshold for erythema; appears 1–8–20 days after exposure at lower doses, may appear within a few hours at higher doses.</td>
</tr>
<tr>
<td>25 Gy</td>
<td>Moist desquamation, possible ulceration.</td>
</tr>
<tr>
<td>35 Gy</td>
<td>Ulceration with slow healing.</td>
</tr>
<tr>
<td>50–58 Gy</td>
<td>Blistering, necrosis at 3–wk.</td>
</tr>
<tr>
<td>100 Gy</td>
<td>Blistering, necrosis at 1–2 wk.</td>
</tr>
</tbody>
</table>

*Data are from Guer et al.

Erythema progressing to ulceration

Estimated dose 22 Gy

<table>
<thead>
<tr>
<th>Effect</th>
<th>Threshold (Gy)</th>
<th>Single-dose Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early transient erythema</td>
<td>2</td>
<td>Hours</td>
</tr>
<tr>
<td>Main erythema</td>
<td>6</td>
<td>6–10 d</td>
</tr>
<tr>
<td>Temporary hair loss</td>
<td>3</td>
<td>3 wk</td>
</tr>
<tr>
<td>Permanent hair loss</td>
<td>7</td>
<td>3 wk</td>
</tr>
<tr>
<td>Dry desquamation</td>
<td>14</td>
<td>4 wk</td>
</tr>
<tr>
<td>Moist desquamation</td>
<td>18</td>
<td>4 wk</td>
</tr>
<tr>
<td>Secondary ulceration</td>
<td>24</td>
<td>6 wk</td>
</tr>
<tr>
<td>Late erythema</td>
<td>15</td>
<td>6–10 wk</td>
</tr>
<tr>
<td>Ischemic dermal necrosis</td>
<td>18</td>
<td>&gt;10 wk</td>
</tr>
<tr>
<td>Dermal atrophy (1st phase)</td>
<td>10</td>
<td>&gt;14 wk</td>
</tr>
<tr>
<td>Dermal atrophy (2nd phase)</td>
<td>10</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Induration (excessive fibrosis)</td>
<td>10</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>10</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Late dermal necrosis</td>
<td>&gt;127</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>not known</td>
<td>&gt;5 yr</td>
</tr>
</tbody>
</table>
Gestational age affects outcome of radiation injury

- Pre-implantation:
  - Death
    - Exquisitely sensitive to low doses of radiation
    - 60% of embryos died after exposure to 1 Gy 3 hours post-conception
    - Even lower doses (0.2 Gy) can cause x10 increase in chromosomal abnormalities
- Major organogenesis:
  - Organ malformations
- Fetal development:
  - Disturbances of growth, esp. brain (+IQ) and eye
- Early post-natal:
  - Esp. in developing tissues (brain; bones; gonads; pituitary)
  - Cancer

Phases of acute radiation sickness

1. Prodromal:
   - Nausea, vomiting, diarrhoea (minutes - days post-exposure)
   - Duration: <24 hours
2. Latent:
   - Patient looks and feels OK for hours – weeks
   - At high doses (>10 Gy), may be short or absent
3. Principal:
   - Hemopoietic; gastrointestinal; acute incapacitation syndrome
   - Duration: hours – months

At high doses (>50 Gy), death occurs in hours due to acute incapacitation syndrome
### Basis for acute irradiation syndrome

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Form</th>
<th>Cellular event</th>
<th>Time of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 - 10</td>
<td>Hematopoietic</td>
<td>Necrosis of bone marrow</td>
<td>2 – 3 weeks</td>
</tr>
<tr>
<td>10 - 50</td>
<td>Gastrointestinal</td>
<td>Necrosis of stem cells in GIT mucosa</td>
<td>5 – 12 days</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Acute incapacitation</td>
<td>Death of neurons; vascularitis; cerebral edema</td>
<td>10 – 36 hours</td>
</tr>
</tbody>
</table>

Grey (Gy) = dose of any form of radiation resulting in absorption of 1 joule of energy per 1 kg of absorbing material

1 Gy = 100 rad

### Hematologic response following exposure to 2 Gy

![Graph showing hematologic response](image)

### Blood cell components and radiation

<table>
<thead>
<tr>
<th>Lineage</th>
<th>Time to maturation</th>
<th>Life span*</th>
<th>Consequences when lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>4 – 6 days</td>
<td>120 days</td>
<td>Anemia</td>
</tr>
<tr>
<td>Platelet</td>
<td>4 – 6 days</td>
<td>8 – 11 days</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Monocyte</td>
<td>50 – 60 hours</td>
<td>16 – 20 hours</td>
<td>Infection</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>14 – 20 days</td>
<td>6 – 24 hours</td>
<td>Infection</td>
</tr>
</tbody>
</table>

*: in peripheral blood
Effect of acute high dose whole body irradiation on blood components varies in timeline

Predicting the likely medical outcome within 48 hours

<table>
<thead>
<tr>
<th>Fractional Lymphocytes Count</th>
<th>Acute Injury</th>
<th>Event of Injury</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-300 Gy (cordal range)</td>
<td>0-4.4</td>
<td>No clinical significance</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>105-199 Gy</td>
<td>4.5-7.4</td>
<td>Clinically significant</td>
<td>Good</td>
</tr>
<tr>
<td>50-99 Gy</td>
<td>7.5-13.5</td>
<td>Severe</td>
<td>Fair</td>
</tr>
<tr>
<td>&lt;50 Gy</td>
<td>&gt;13.5</td>
<td>Very severe</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Chronic irradiation

- Delayed lesions:
  - Atrophy in glandular tissues:
    - Alimentary, respiratory and reproductive tracts
    - E.g. sebaceous glands in skin and salivary glands
  - Necrosis:
    - E.g. white matter of brain
  - Atypia/dysplasia:
    - "Radiation fibroblasts" and other cells
  - Fibrosis
  - Blood vessels:
    - Pruning of microvascular network → susceptibility to ischemia
    - Veno-occlusive disease
Neoplasia and radiation

- Carcinogenesis:
  - Can be seen after relatively low dose exposures
  - Probability of malignancy increases proportionate to dose
- Latent period between initiation and effect:
  - 8 years for some forms of leukemia (human)
  - Balancing translocations
  - 2-3x longer for solid tumors (e.g., lung and breast cancers)
- Chromosomal deletions
- Influenced by:
  - Dose rate
  - Nature and location of radiation source

Localized, high energy radiation

<table>
<thead>
<tr>
<th>Source</th>
<th>Exposure</th>
<th>Localization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium</td>
<td>Radium dial</td>
<td>Mouth</td>
<td>Oral and nasal sinus cancer</td>
</tr>
<tr>
<td></td>
<td>Uranium mining</td>
<td>Lung</td>
<td>Pulmonary carcinoma</td>
</tr>
<tr>
<td>Radium</td>
<td>Radium implants</td>
<td>Cervix</td>
<td>Tumors of bladder, cervix, gut</td>
</tr>
<tr>
<td>Iodine</td>
<td>Radiotherapy</td>
<td>Thyroid</td>
<td>Tumors of thyroid</td>
</tr>
<tr>
<td>Thorium</td>
<td>Thorotrast</td>
<td>RE system</td>
<td>Hepatic and other solid neoplasia</td>
</tr>
</tbody>
</table>
Radiomimetic viruses

- Paroviruses:
  - Rat parovirus
  - Feline panleukopenia virus
- BVD
- Bluetongue

Risk of various cancers after exposure to 1 Gy

<table>
<thead>
<tr>
<th>Cancer (diagnosis or treatment exposure)</th>
<th>Grade 1-4</th>
<th>Grade 3 or 4</th>
<th>2a Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Brain irradiation</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Choroid inlution</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Alveolar inlution</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

42.4% of people surviving successfully treated childhood cancers later developed severe, disabling, or life-threatening conditions.

Oeffinger et al: Chronic health conditions among cancer survivors, according to the type of tumor and treatment, as compared with siblings.

<table>
<thead>
<tr>
<th>The classical radiomimetic injury</th>
<th>canine and feline parvovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="WSVL_08F8327" alt="Image" /></td>
<td></td>
</tr>
</tbody>
</table>

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