Feb 15, 2013

Acute Radiation Syndrome
Radiation Carcinogenesis
Radiation Cataractogensis

Acute Radiation Syndrome

Acute Radiation Syndrome (ARS)

- 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

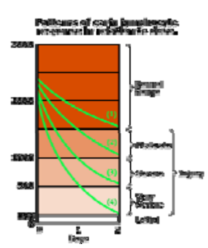
Requirements for ARS

- 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

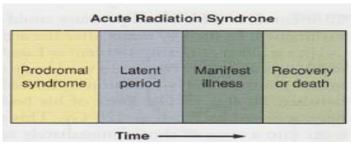
Lab Diagnosis of ARS



Curve 1: 3.1 Gy
Curve 2: 4.4 Gy
Curve 3: 5.6 Gy
Curve 4: 7.1 Gy

- 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

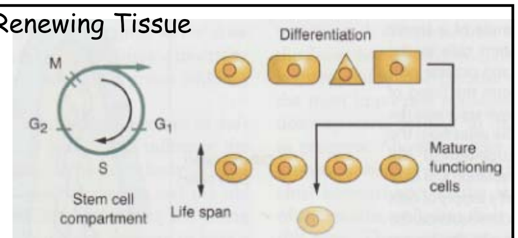
Cerebrovascular Syndrome

- Immediate cause of death is not fully understood
- May be damage to the microvasculature, which results in an increase in the fluid content in the brain
- Results in a build up of pressure within the confines of the skull

Gastrointestinal Syndrome

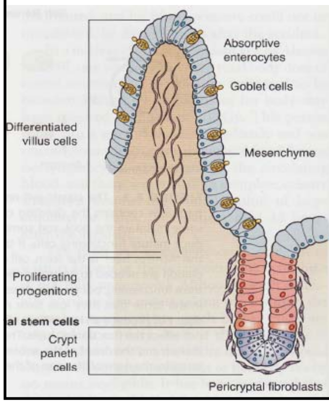
- > 10 Gy radiation dose
- Prodromal stage
  - Symptoms are anorexia, severe nausea, vomiting, cramps and diarrhea
  - Onset a few hours after exposure
  - Lasts about 2 days
- Latent stage
  - Stem cells in bone marrow and GI tract dying
  - Lasts about a week
  - Patient may appear and feel well
- 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 folds 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

Gastrointestinal Syndrome

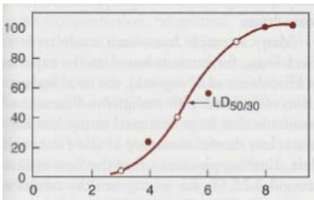
- Systematic effects
  - Maladsorption leading to malnutrition
  - Fluid and electrolyte shifts leading to dehyration, renal failure, cardiovascular collapse
  - GI bleeding to anemia
  - Sepsis
  - Paralytic ileus leading to vomiting and distention

Hematopoietic Syndrome

- 0.7 to 10 Gy dose
- Prodromal phase symptoms, with onset occurring from 2 hours to 2day 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 anorexia, fever
  - Drop in red blood cell counts for several weeks
  - Primary cause of death is infection and hemorrhage
  - Most deaths occur within a few months of exposure
- 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



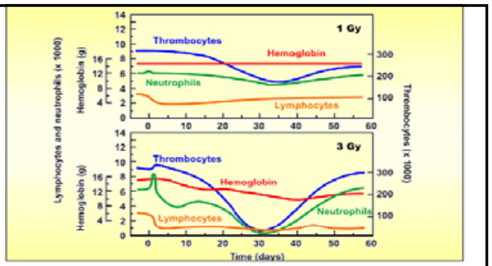
Mortality rate of rhesus monkeys at 30 days after a single dose of total body x-rays

LD50 and Bone Marrow Transplant

TABLE 8.2 The 50% Lethal Doses for Various Species from Mouse to Human and the Relation between Body Weight and the Number of Cells that Need to Be Transplanted for a Bone Marrow "Rescue"

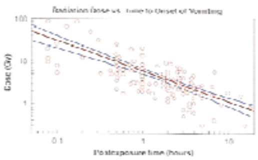
Species	Average Body Weight, kg	50% Lethal Total Body Irradiation, Gy	Rescue Dose per kg $\times 10^{-8}$	Relative Hematopoietic Stem Cell Concentration
Mouse	0.025	7	2	10
Rat	0.2	6.75	3	6.7
Rhesus monkey	2.8	5.25	7.5	7.3
Dog	12	3.7	17.5	1.1
Human	70	4	20	1

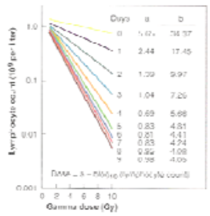
HPS



- 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

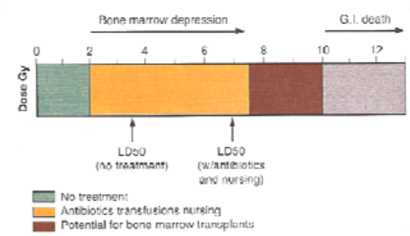
Summary of Latent Effects Based on Dose

	Degree of Acute Radiation Syndrome and Approximate Dose of Acute Whole Body Exposure (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very Severe (6–8 Gy)	Lethal (>8 Gy)
Lymphocytes (G/L) (days 3–6)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0.0–0.1
Granulocytes (G/L)	>2.0	1.5–2.0	1.0–1.5	≤0.5	≤0.1
Diarrhea	None	None	Rare	Appears on days 6–9	Appears on days 4–5
Epilation	None	Moderate, beginning on day 15 or later	Moderate or complete on days 11–21	Complete earlier than day 11	Complete earlier than day 10
Latency period (d)	21–35	18–28	8–18	7 or less	None
Medical response	Hospitalization not necessary	Hospitalization recommended	Hospitalization necessary	Hospitalization urgently necessary	Symptomatic treatment only

Summary of Critical Phase Based on Dose

	Degree of ARS and Approximate Dose of Acute Whole Body Exposure (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very Severe (6–8 Gy)	Lethal (>8 Gy)
Onset of symptoms	>30 days	18–28 days	8–18 days	<7 days	<3 days
Lymphocytes (G/L)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0–0.1
Platelets (G/L)	60–100 10%–25%	30–60 25%–40%	25–35 40%–80%	15–25 60%–80%	<20 80%–100%[a]
Clinical manifestations	Fatigue, weakness	Fever, infections, bleeding, weakness, epilation	High fever, infections, bleeding, epilation	High fever, diarrhea, vomiting, dizziness and disorientation, hypotension	High fever, diarrhea, unconsciousness
Lethality (%)	0	0–50 Onset 6–8 weeks	20–70 Onset 4–8 weeks	50–100 Onset 1–2 weeks	100 1–2 weeks
Medical response	Prophylactic	Special prophylactic treatment from days 14–20; isolation from days 10–20	Special prophylactic treatment from days 7–10; isolation from the beginning	Special treatment from day 1; isolation from the beginning	Symptomatic only

Bone Marrow Transplant



- Beneficial window of dose is small
- Doses of less than 8 Gy likely to survive with supportive care
- At doses of greater than 10 Gy, death from GIS is inevitable

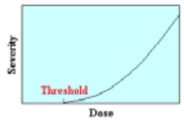
Radiation Carcinogenesis

Before RT | One month after RT | Six months after RT

Radiation Carcinogenesis

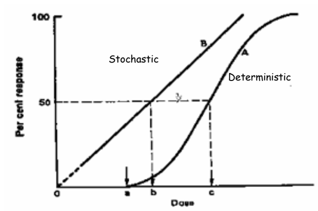
- If cellular damage occurs as the result of radiation that is not adequately repaired
  - It may prevent the cell from surviving or reproducing, or
  - It may result in a viable cell that has been modified (change or mutation)
- These two outcomes have profoundly different implications

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

Radiation Carcinogenesis
Deterministic vs. Stochastic Effects

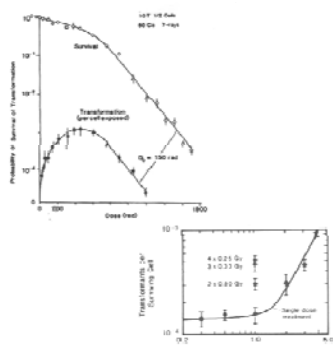


- **Stochastic effect:**
  - Is independent of dose (i.e. severity is independent)
  - Has no threshold
  - Probability is proportional to dose (i.e. probability increases with dose)
  - Main effects are carcinogenesis and genetic mutations

Radiation Carcinogenesis

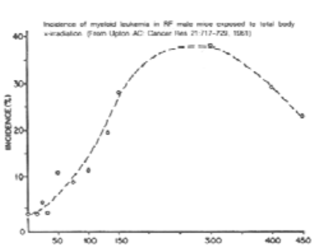
- Radiation-induced damage can produce changes that lead to:
  - Cell death
  - Neoplasia (in somatic tissue)
  - Heritable genetic damage (in reproductive tissue)
- Experiments *in vitro* and *in vivo* with radiation identify 3 distinct steps in carcinogenesis:
  - Initiation: chromosome/DNA damage 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

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

Radiation Carcinogenesis
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

Relative risk of thyroid cancer after exposure to radiation

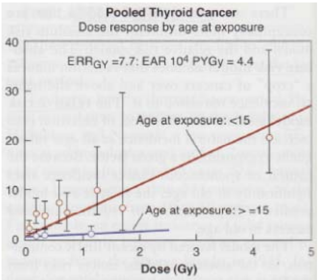
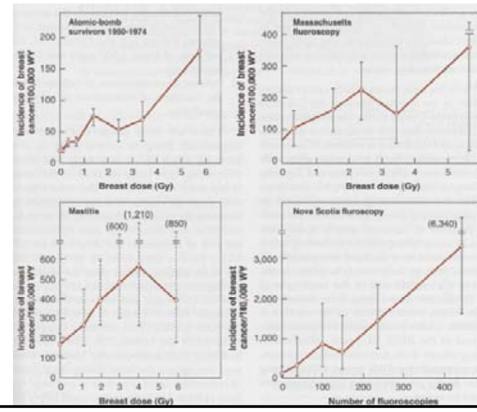


FIGURE 10.3 Relative risk of thyroid cancer after exposure to external radiation, taken from a pooled analysis of seven studies. The data clearly show the importance of age at exposure. (Figure prepared by

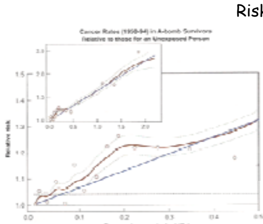
Incidence of breast cancer as a function of dose

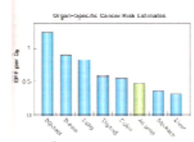


Radiation Carcinogenesis
Risk Models

- **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

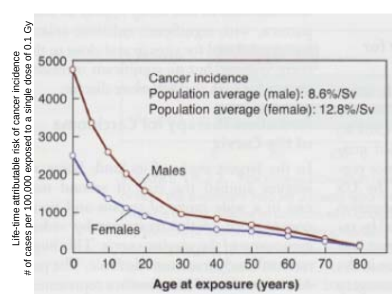
TABLE 10.2 Population Average Cancer Risk Percent per Sievert

	Incidence	Mortality
Male	8.6	4.6
Female	12.8	6.2
Combined	10.8	5.4

Source: Calculated from the Biologic Effects of Ionizing Radiation (BEIR) VII report.

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

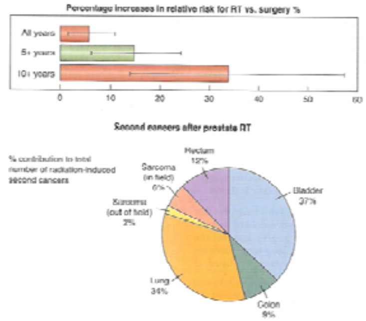
Prostate cancer RT – cancer of bladder, rectum, lung and sarcoma

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%)

Radiation Carcinogenesis
Secondary Malignancies Following Radiation

Incidence of Second Malignancy in Hodgkin's Disease Within 10 Years After Treatment Involving Radiation and/or Chemotherapy

Treatment Modality	Type of Malignancy	Incidence of Second Malignancy within 10 Years (% of Survivors)
Radiation therapy[a]	Solid tumor	12
Radiation therapy	Leukemia	0
Chemotherapy	Solid tumor	0
Chemotherapy	Leukemia	3.5
Radiation therapy	Solid tumor	0
Chemotherapy (MOPP)[b]	Leukemia	5.4
Radiation therapy	Solid tumor	2.1
Chemotherapy (MABOP)[c]	Leukemia	3.8
Radiation therapy	Solid tumor	0
Chemotherapy (ABVD)[d]	Leukemia	0
Radiation therapy	Solid tumor	12
Chemotherapy (other)	Leukemia	2.9

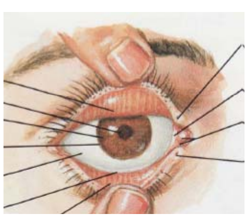
[a] Radiation therapy = 3000–5000 rads.
[b] MOPP = mustine, vincristine, procarbazine, and prednisone.
[c] MABOP = MOPP with adriamycin and bleomycin substituted for procarbazine.
[d] ABVD = adriamycin, bleomycin, vinblastine, and dacarbazine.

Data from Valagussa, P., Santoro, A., Kenda, R., Fossati-Bellani, F., Franchi, F., Banfi, A., Rilke, F., and Bonadonna, G., *Br. Med. J.*, 280, 216, 1980.

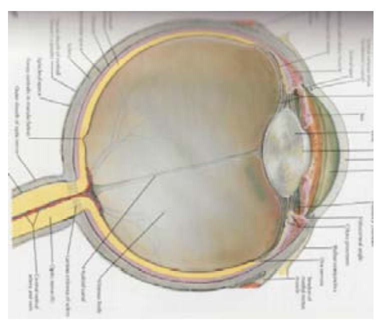
Hodgkin Disease
- Second cancer is the leading cause of death in long-term survivors
- High risk of breast cancer among women treated at a young age

Radiation Cataractogensis

Where is the lens ?



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

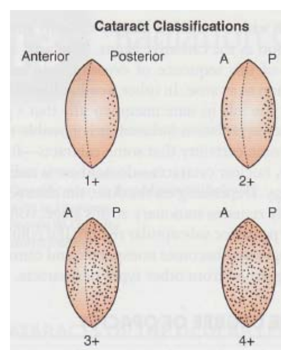
° Neutrons and other densely ionizing radiation are more effective in inducing cataracts, due to higher RBE

Cataracts in humans

FIGURE 13.2 Cataract in the posterior subcapsular region 4 years after a dose of 24 Gy of x-rays to a patient on radiotherapy. (From Merriam GR, Worgul BV. Experimental radiation cataract: its clinical relevance. *Bull NY Acad Med.* 1983;59:372–392, with permission.)

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

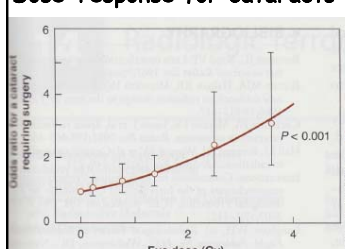


FIGURE 13.5 Odds ratio as a function of dose for the induction of a cataract requiring surgical lens removal in Japanese A-bomb survivors. (Adapted from Neriishi K, Nakashima E, Minamoto A, et al. Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat Res.* 2007;168:404–408, with permission.)

- 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