McGill Clinical and Molecular Radiobiology Workshop 2015

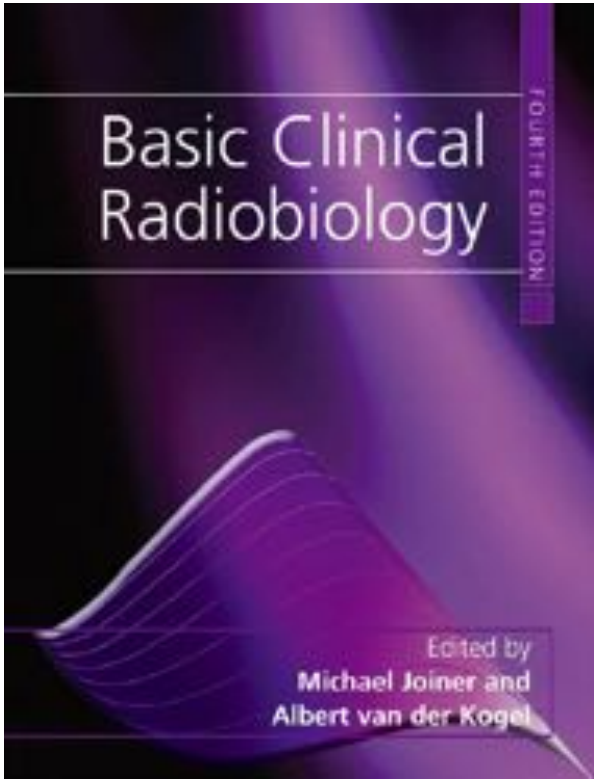
Radiation and normal tissue response

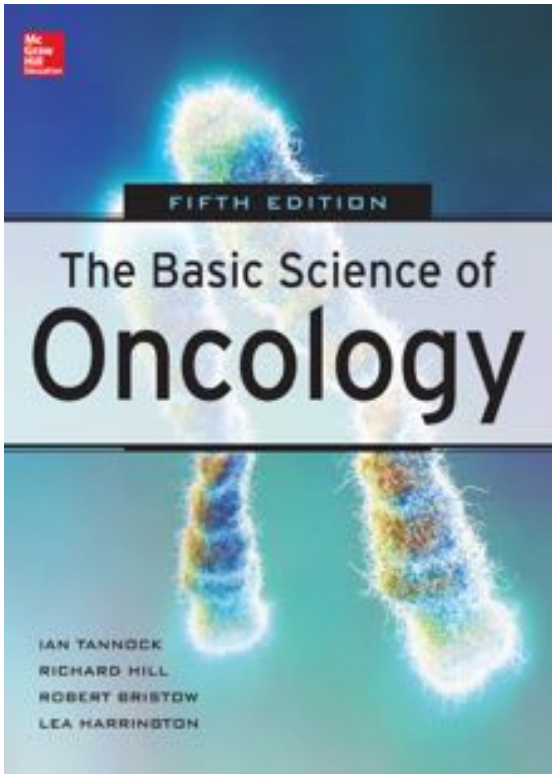
Stanley Liu, PhD, MD
Dept. Radiation Oncology, University of Toronto
Odette Cancer Centre, Sunnybrook Health Sciences Centre

Radiation Oncology
UNIVERSITY OF TORONTO

Sunnybrook
HEALTH SCIENCES CENTRE
when it matters MOST

Recommended textbooks!





Overview

- Acute and late radiation toxicity
- Importance of radiation parameters and tissue type
- Radiation protection

The clinical problem

- Despite improved radiotherapy targeting, normal surrounding tissue will receive dose
- This can result in acute and late normal tissue toxicity
- Some acute toxicities are dose-limiting (e.g., mucositis) and can interrupt treatment
- Late toxicities are irreversible and progressive
- Thus, important to understand the pathogenesis of these events

The time course of toxicity

In the clinic, we observe two types of toxicity:

- **Acute effects** – occurs during or shortly after radiotherapy (within 90 days)

- **Late effects** – occurs months to years after radiotherapy

Potential acute and late effects

TABLE 16–1 Severe acute and chronic side effects of radiotherapy.*

Irradiation Site	Tissues at Risk	Acute Effect	Chronic Effect†
Brain	Brain, neural structures (eye, brainstem)	Drowsiness, hair loss	Cognitive dysfunction and decreased visual acuity
Head and neck	Oral mucosa, salivary glands, skin	Oral inflammation (mucositis), xerostomia (dry mouth), erythema (skin redness)	Permanent xerostomia, decreased ability to open mouth (trismus), dental caries, skin fibrosis
Thorax	Esophageal mucosa, lung, skin	Esophagitis, pneumonitis	Lung fibrosis, esophageal stricture, skin fibrosis
Abdomen	Intestine, pancreas, liver, spleen, kidneys	Nausea, hepatitis, diarrhea	Renal compromise, liver fibrosis, intestinal obstruction
Pelvis	Bladder, rectum, prostate	Increased frequency and dysuria, diarrhea	Bladder or rectal bleeding or rectal ulceration, impotence

*Acute and chronic (late) effects will be idiosyncratic to the patient, the total dose, the dose fractionation, and the irradiation volume.

†Severe chronic effects observed in less than 5% of population at 5 years.

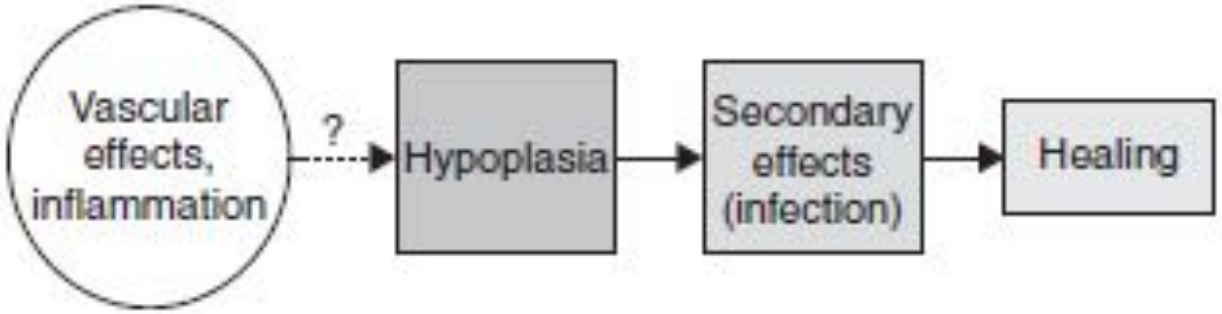
Hill and Bristow (in *Basic Science of Oncology*)

Acute vs Late responding tissues

- **Acute responding tissue** – contain *rapidly proliferating and renewing cells* (e.g., skin, mucosa, intestinal crypt cells, bone marrow)
  - Damage clinically manifests rapidly within days to weeks

- **Late responding tissue** – contain *cells that divide infrequently* (e.g., liver, CNS, kidney, lung)
  - Damage manifests slowly within months to years, well after the initial radiation insult

Acute effects

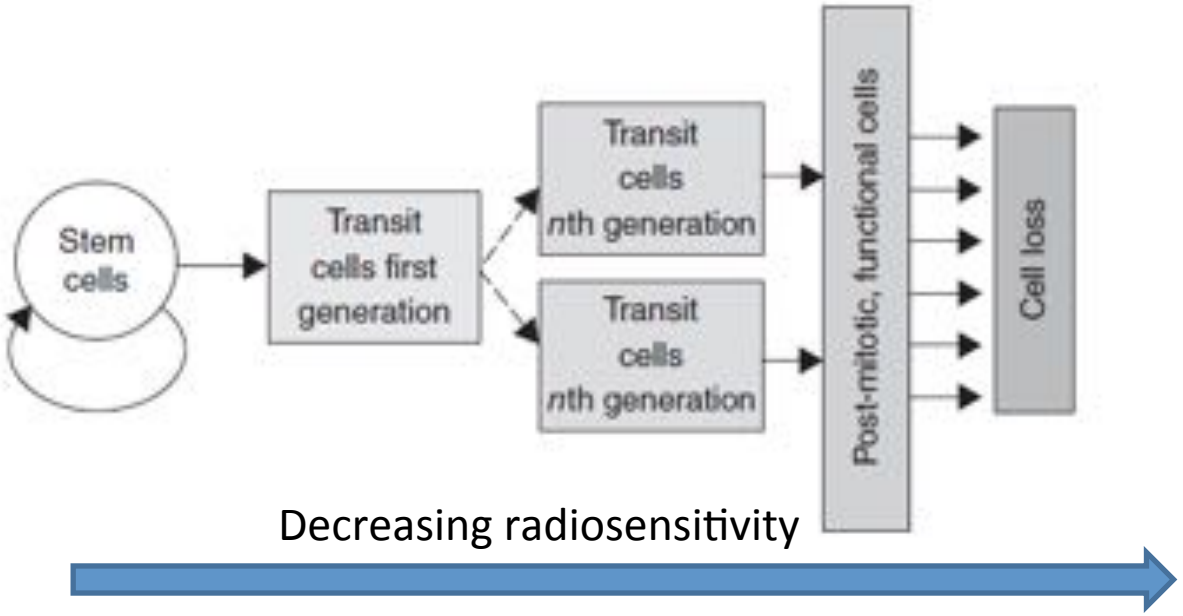


- Inflammatory and vascular changes predominate initially
- Followed by loss of functional cells in organ (hypoplasia)
- Healing occurs by stem cells

W. Dorr in Basic Clinical Radiobiology

Importance of stem cells

- Organization of 'renewal' tissue (e.g., skin, gut)

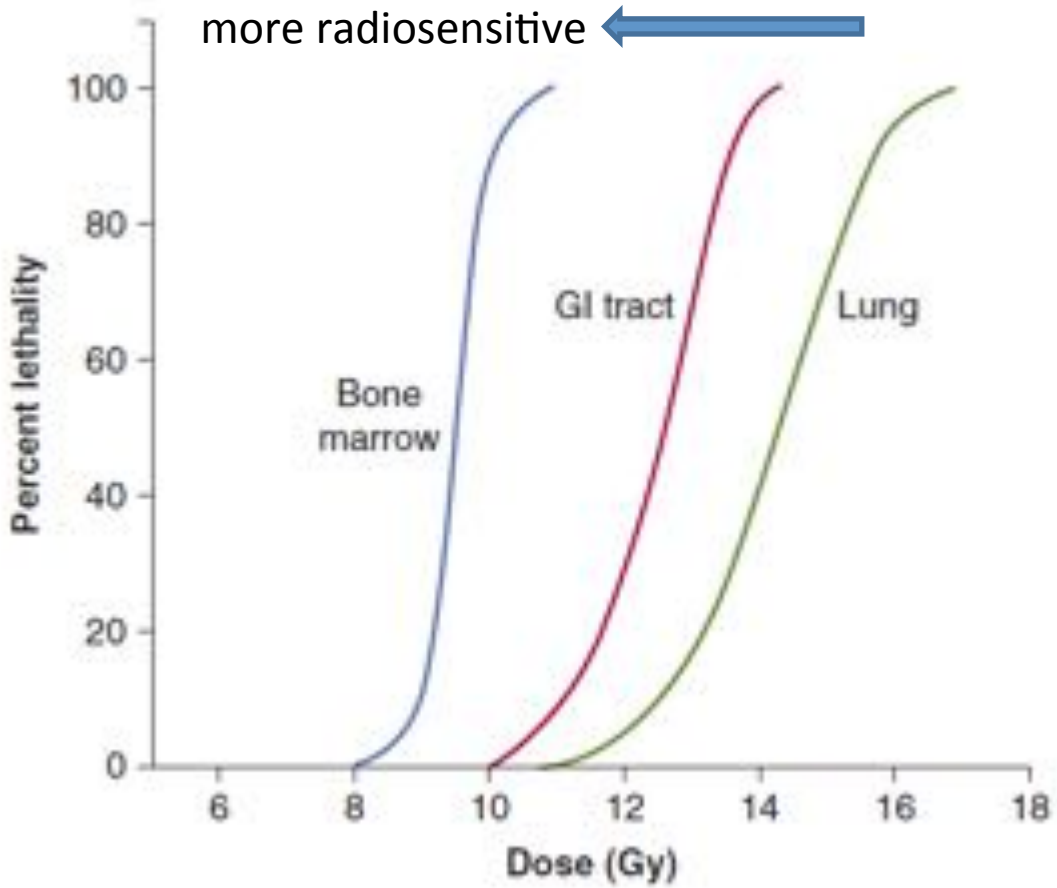


- Stem cells are radiosensitive compared to transit cells.
- Radiation tolerance of normal tissue partly determined by abundance of stem cells

From W. Dorr – Basic Clinical Radiobiology

Tissue-specific radiosensitivity

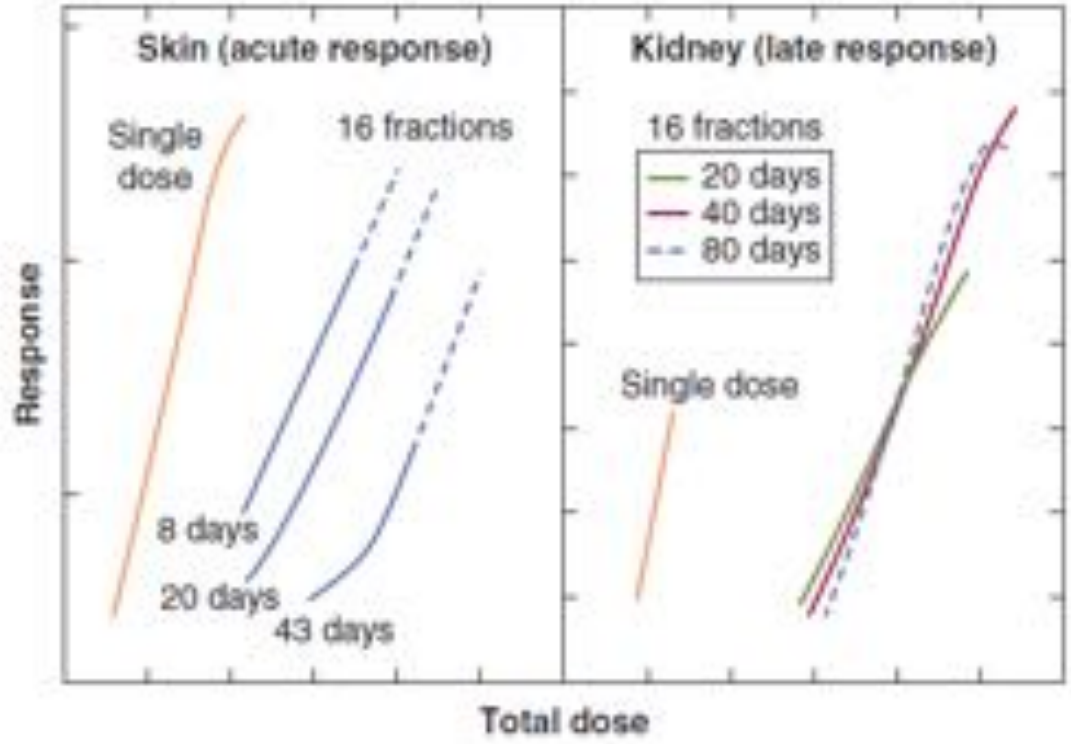
- There is a steep dose-response portion to the curve, especially pronounced for bone marrow



Hill and Bristow (in *Basic Science of Oncology*)

Repopulation

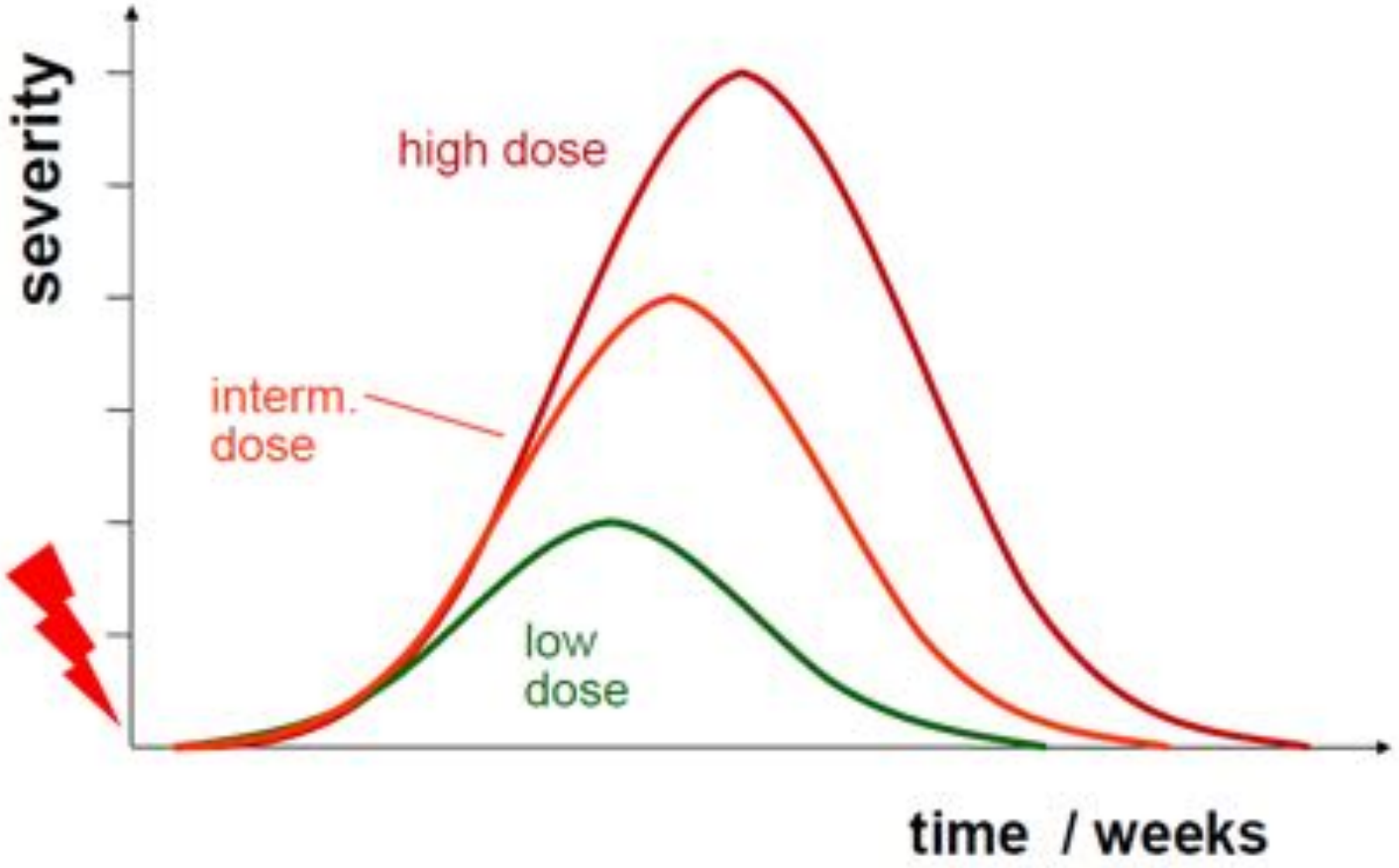
- Increased proliferation of surviving cells during radiation.
- Relevant to acute responding tissue (e.g., skin, mucosa); not relevant to late responding tissue.



- Prolonging ***treatment time*** (e.g., from 8 to 43 days) allows for repopulation of tissue, and thus higher dose can be delivered. Not the case for late responding tissue.

Hill and Bristow (in *Basic Science of Oncology*)

Acute effects – severity and resolution is <u>dose</u> dependent



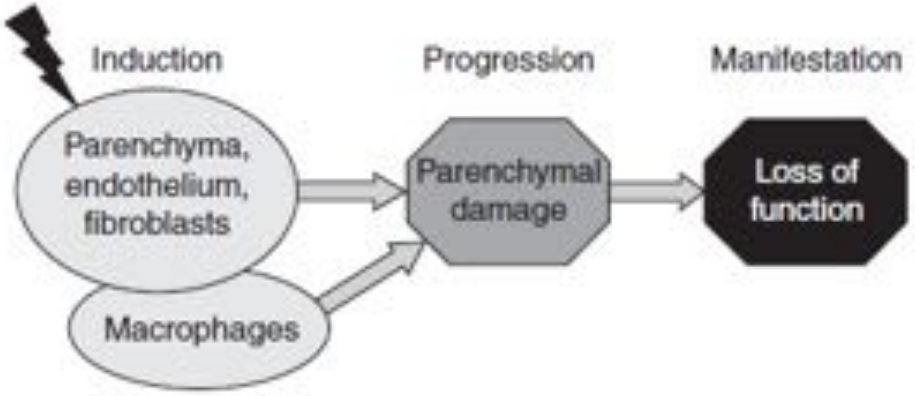
From W. Dorr – Basic Clinical Radiobiology

Acute effects - resolution

- Surviving stem cells or stem cells from adjacent healthy tissue, can ***repopulate*** the irradiated tissue.
- As treatment time increases, repopulation effect increases.
- Severity and healing time is proportional to dose delivered.
- Damage is almost always reversible and healing is complete.

Late effects

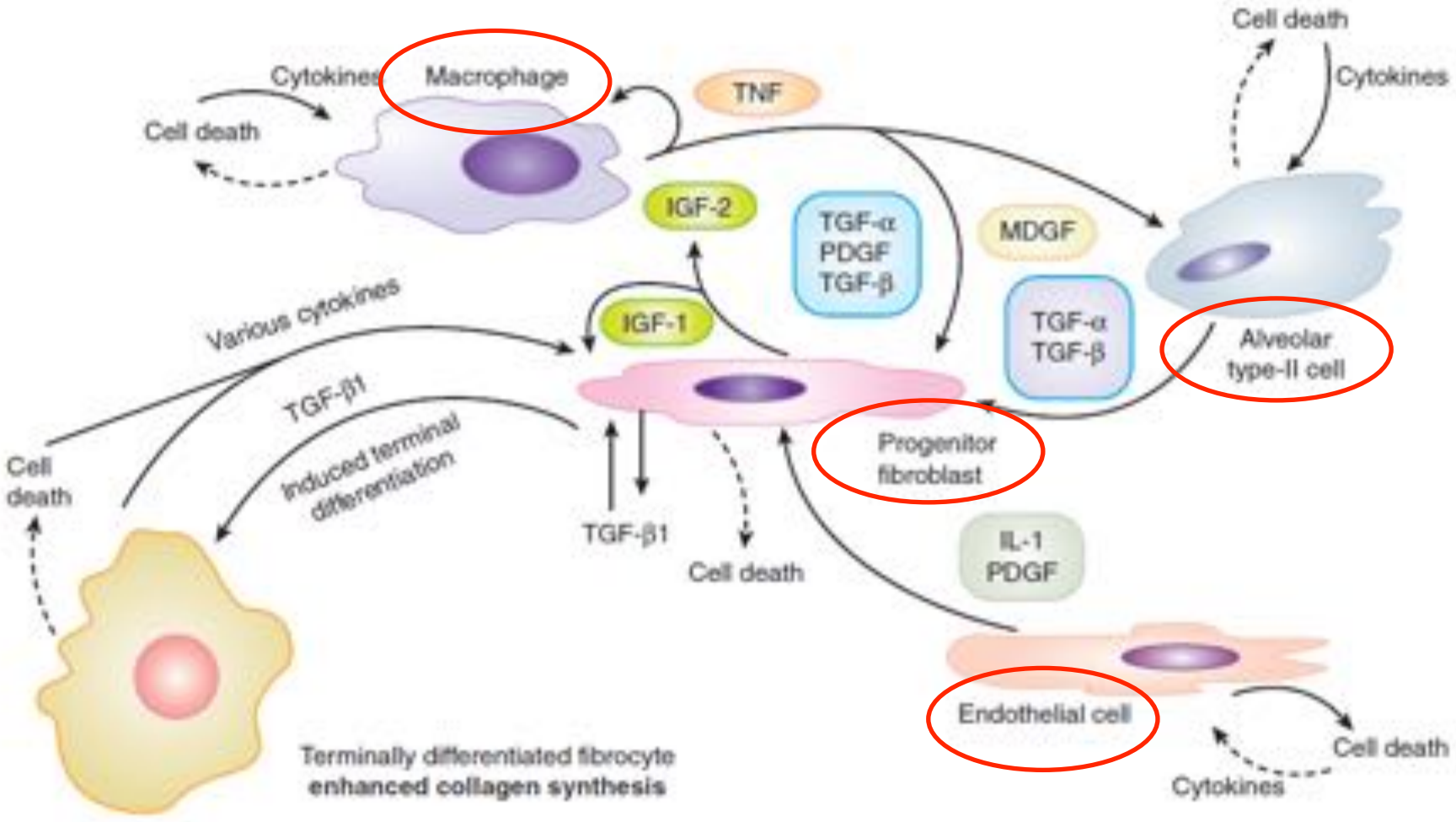
- Complex interactions and processes determine these effects



- Vascular changes (impaired perfusion), fibroblast differentiation (scarring), macrophages & mast cells (inflammatory mediators)
- Radiosensitivity of any one cell type cannot predict radiosensitivity of whole organ

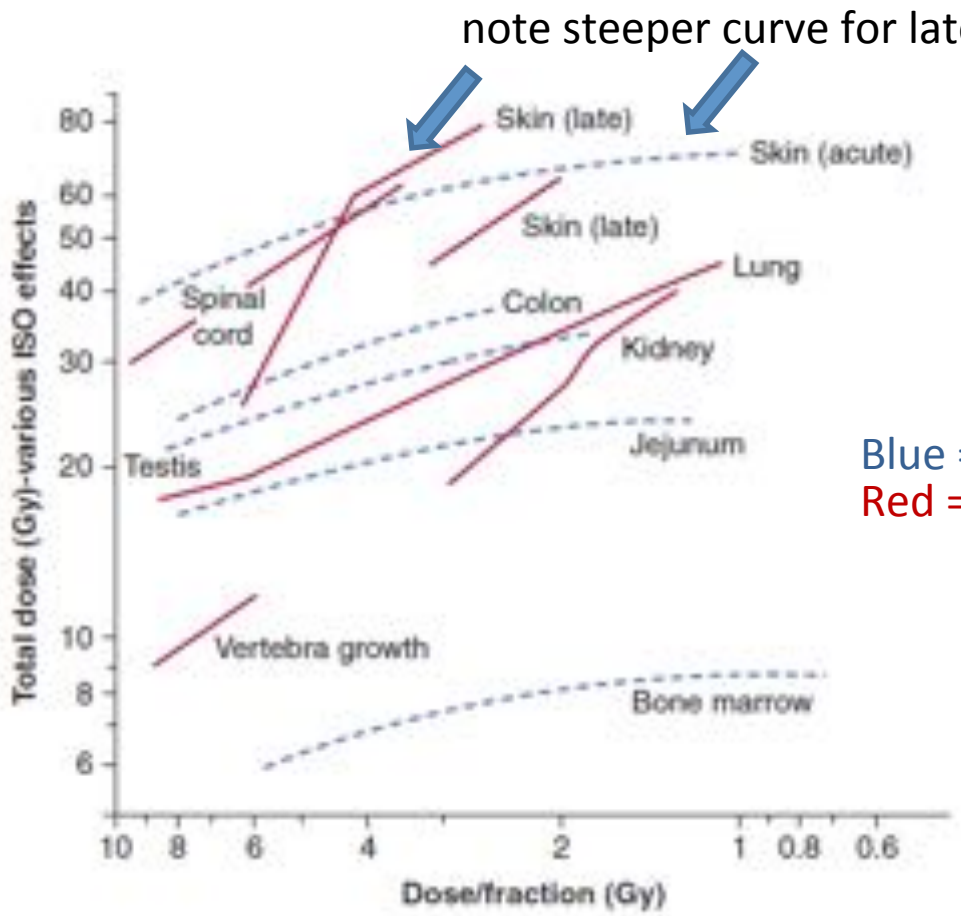
From W. Dorr – Basic Clinical Radiobiology

Complex interactions for late effects



Hill and Bristow (in *Basic Science of Oncology*)

Dose fraction size: late vs acute effects

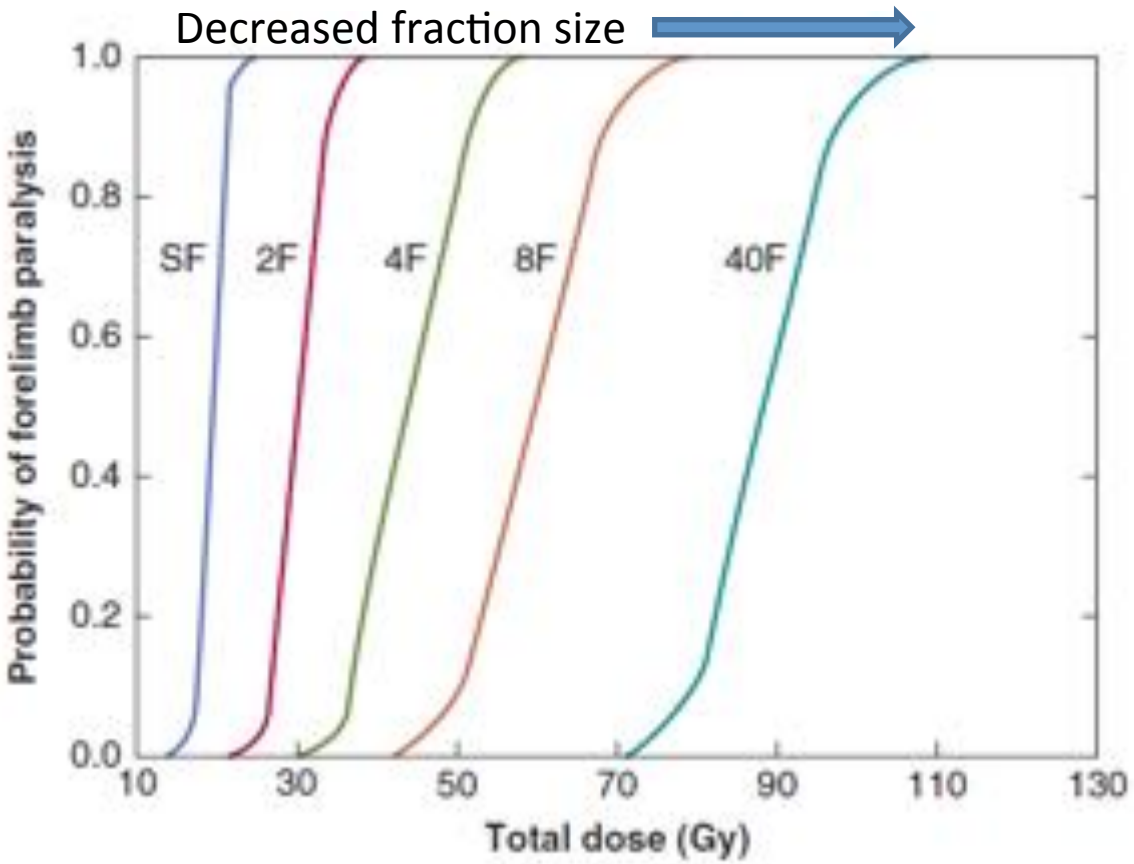


Blue = acute effects
Red = late effects

- Dose ***fraction size*** has greater influence on late effects than acute effects *for above experiments, total treatment times were approximately the same

Hill and Bristow (in *Basic Science of Oncology*)

Dose *fraction size* effects on late tissue toxicity

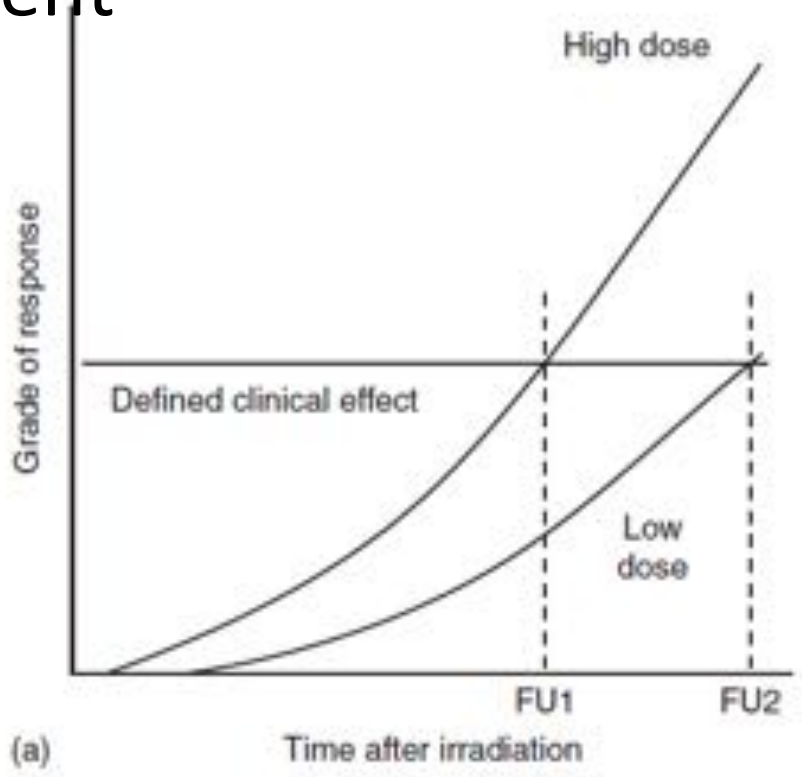


- Larger fraction size increases probability of late tissue toxicity

Hill and Bristow (in *Basic Science of Oncology*)

Late effects

- **Clinical onset** and **severity** of late effects is dose-dependent



- Important to consider follow-up time

From W. Dorr – Basic Clinical Radiobiology

Late effects – importance of follow up

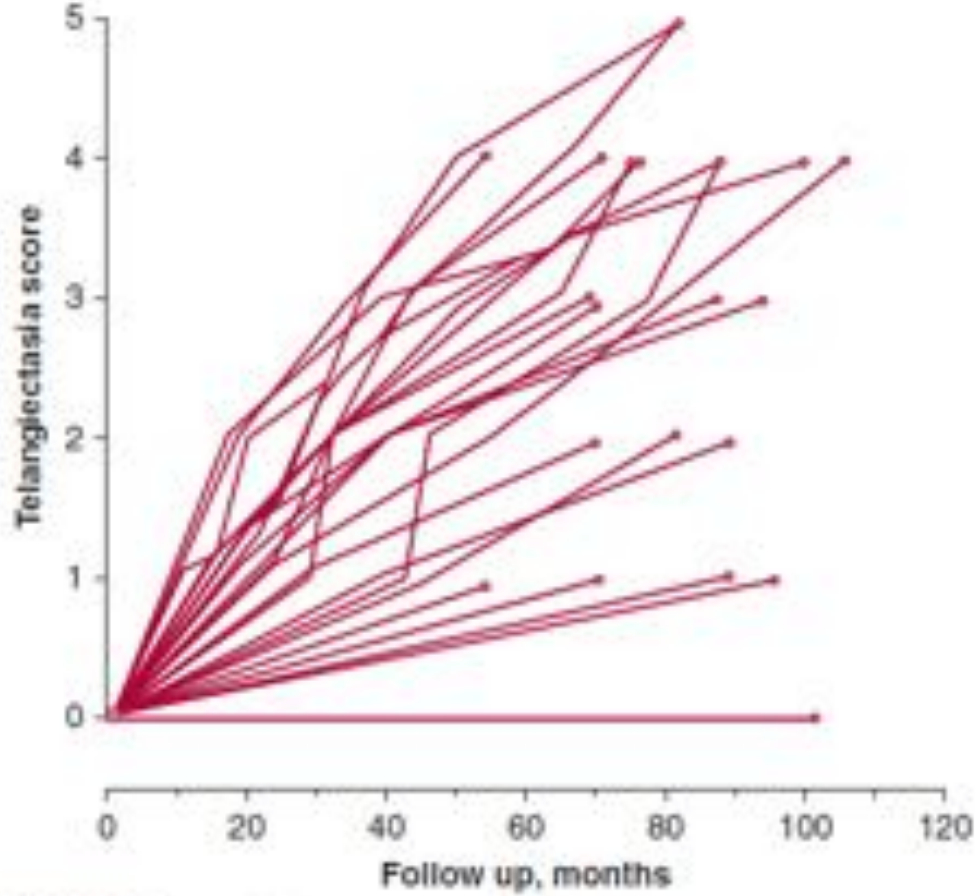
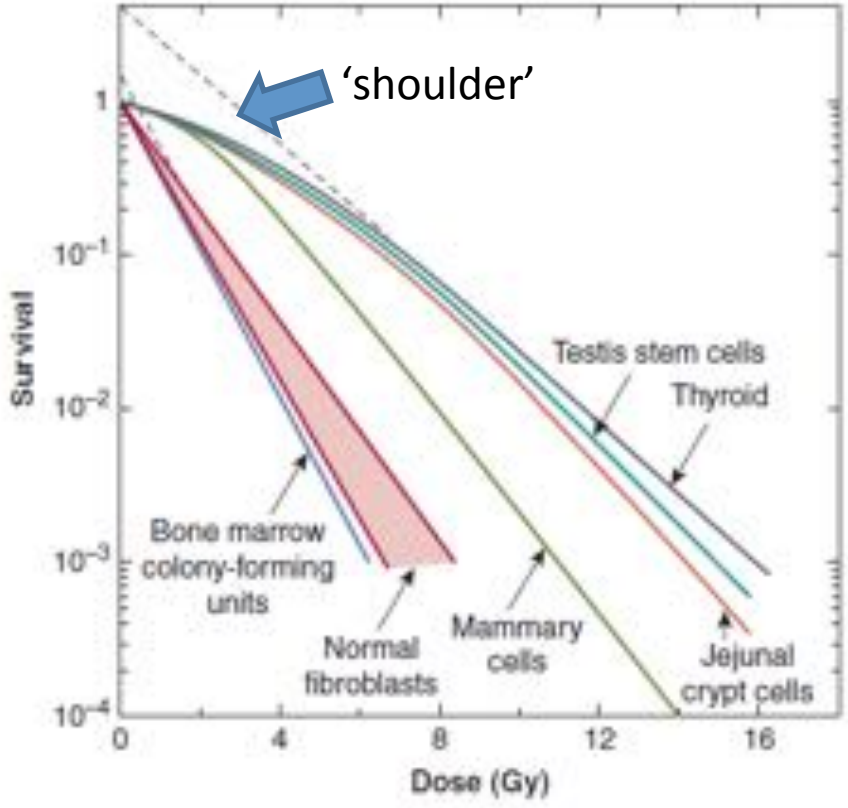


FIGURE 16–17 **Clinical manifestations of skin telangiectasis.** Progression of telangiectasia in individual patients treated with 5 fractions of 1.8 Gy/wk to a total of 35 fractions. (Redrawn from Turesson, 1990.)

Hill and Bristow (in *Basic Science of Oncology*)

Varying radiosensitivity of different cell types – repair capacity



- Different 'shoulder' regions suggests intrinsic differences in **DNA repair** capacity

Hill and Bristow (in *Basic Science of Oncology*)

Late effects

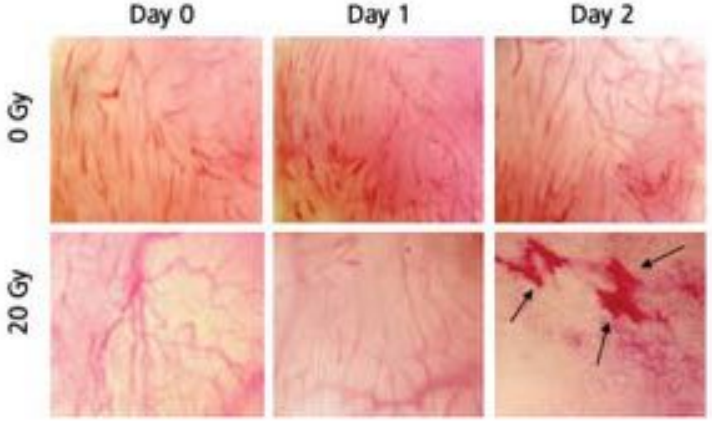
- Earlier onset and increased severity with higher dose
- Results from complex interactions between many cell types
- **DNA repair** (as opposed to repopulation) plays major role in late normal tissue effects
- **Dose fraction size** is an important factor, with more damage seen with larger dose/fraction

Late effects – an ongoing process

- Late effects are generally ***irreversible*** and ***progressive***
- Increasing severity seen with time
- Importance of considering life span of patient – longer survival time = higher risk of developing late effects

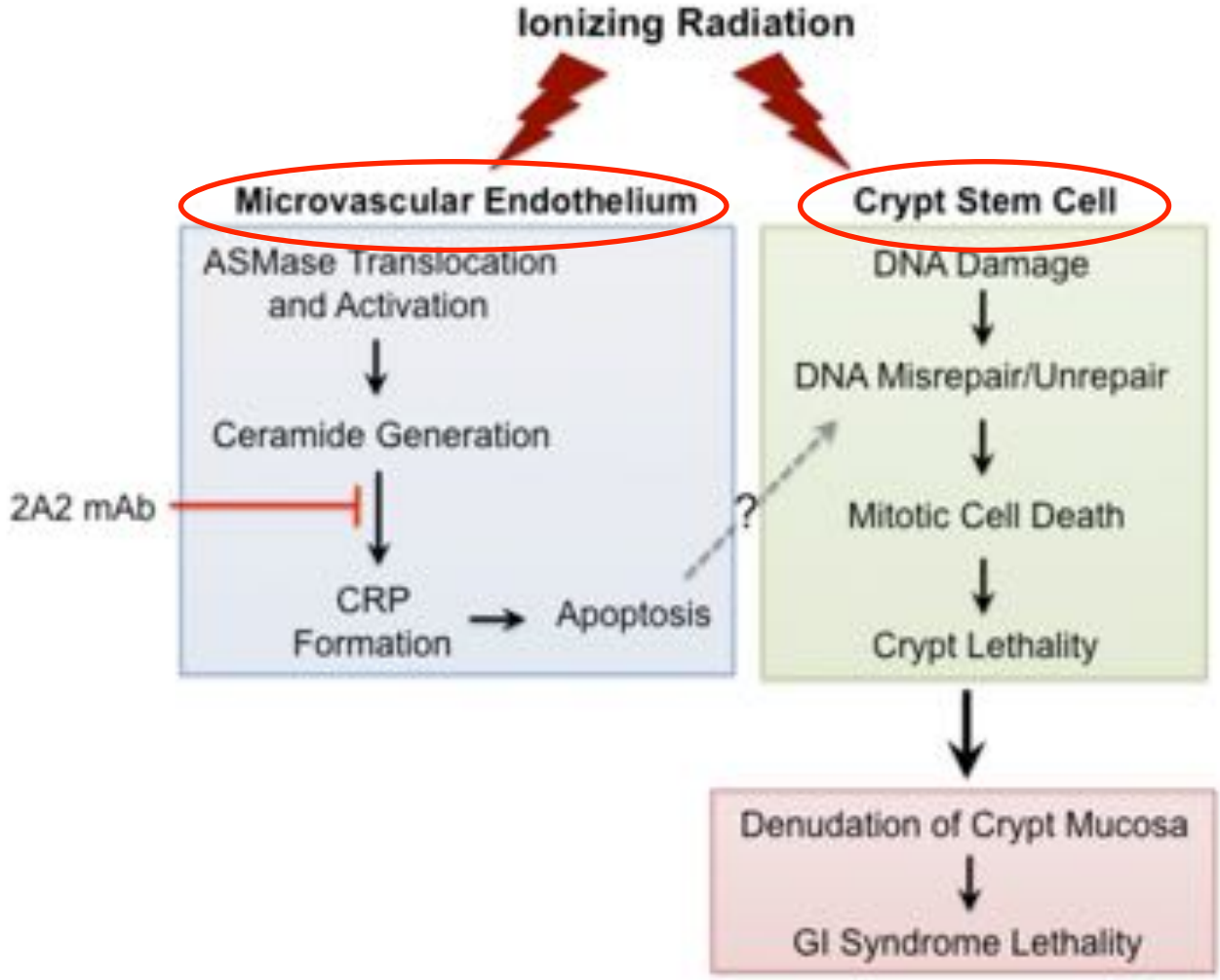
Role of vasculature in tissue toxicity

- With high dose 'ablative' radiotherapy (e.g., SABR), there may be **endothelial cell apoptosis** and disruption of tissue perfusion.
- This may contribute to late tissue toxicity, especially in small intestine (contro



Kim et al., *J US Med* 2006.

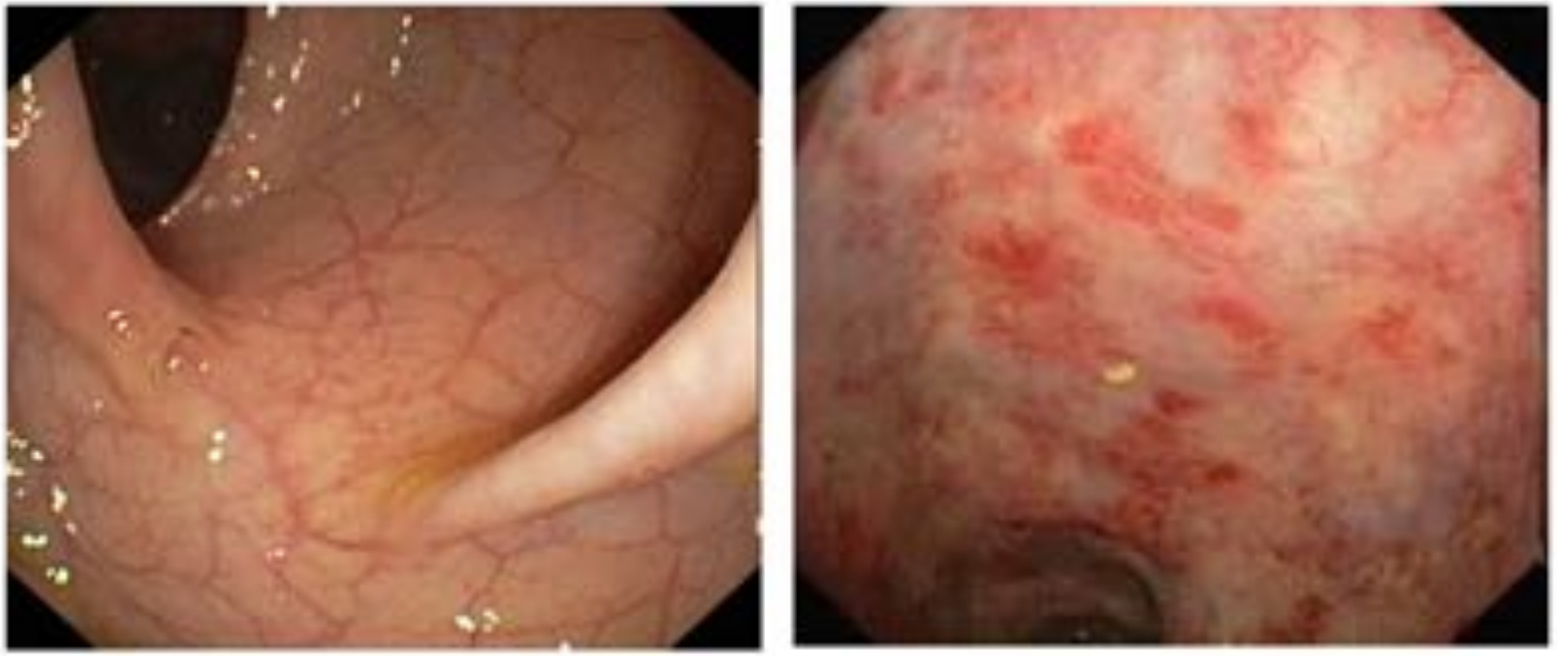
Contribution of endothelial radioresponse to normal tissue toxicity



Rotolo et al, J Clin Invest, 2012

Shun Wong

Example of late effect



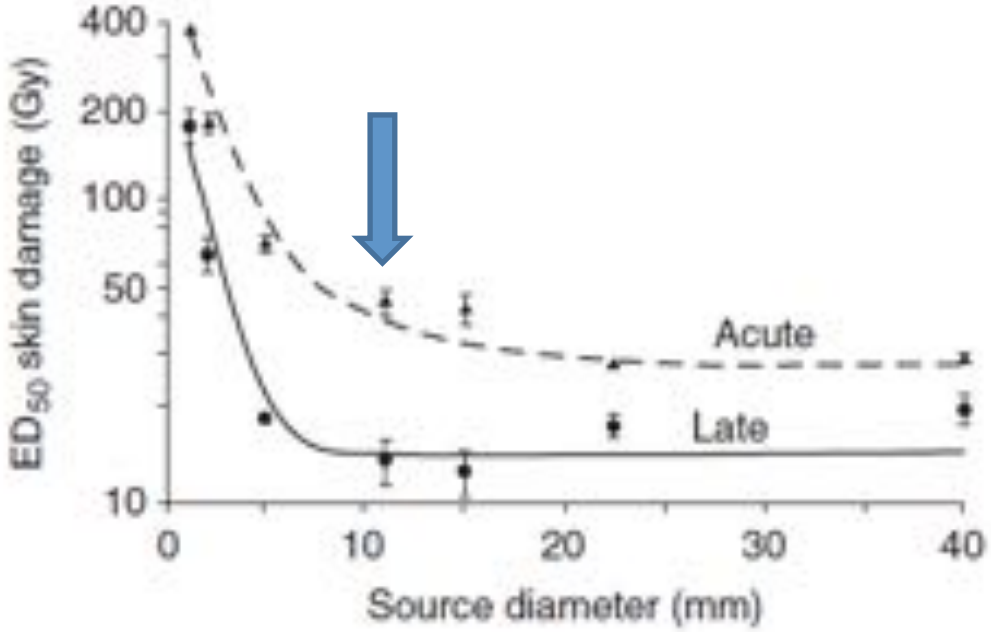
Normal rectal mucosa

Radiation proctitis

Note: edema, pallor, telangiectasia, loss of organized vasculature

Volume dependency for acute and late effects (skin)

- Migration effect of stem cells from adjacent unirradiated regions is important for repopulation (acute effects)
- Steep increase in normal tissue tolerance with small field sizes



From W. Dorr – Basic Clinical Radiobiology

Serial vs Parallel organs

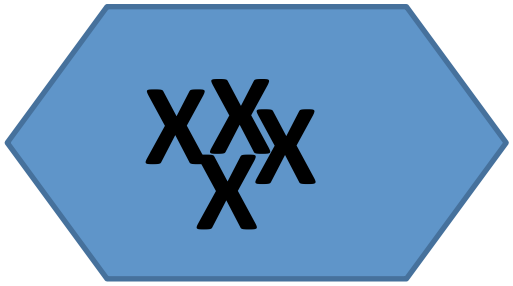
- Analogy with an electrical circuit
- Serial organ – disruption of section results in inability to transmit signal or contents

  e.g., spinal cord, esophagus, bowel

- Risk of complications influenced by high-dose regions and dose ‘hot spots’

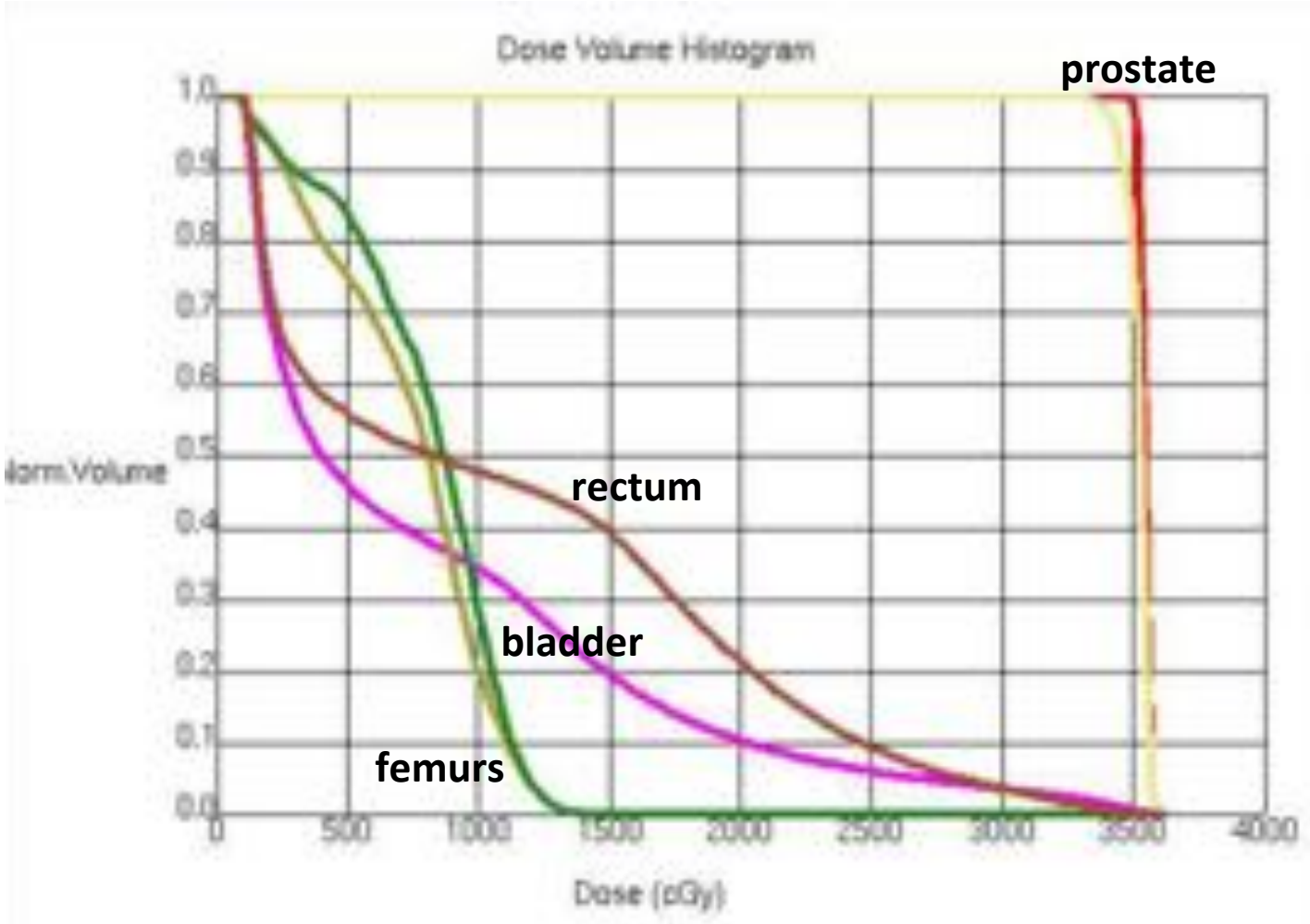
Serial vs Parallel organs

- Parallel organ – since it is made of autonomous units, can still function (e.g., liver, kidney)

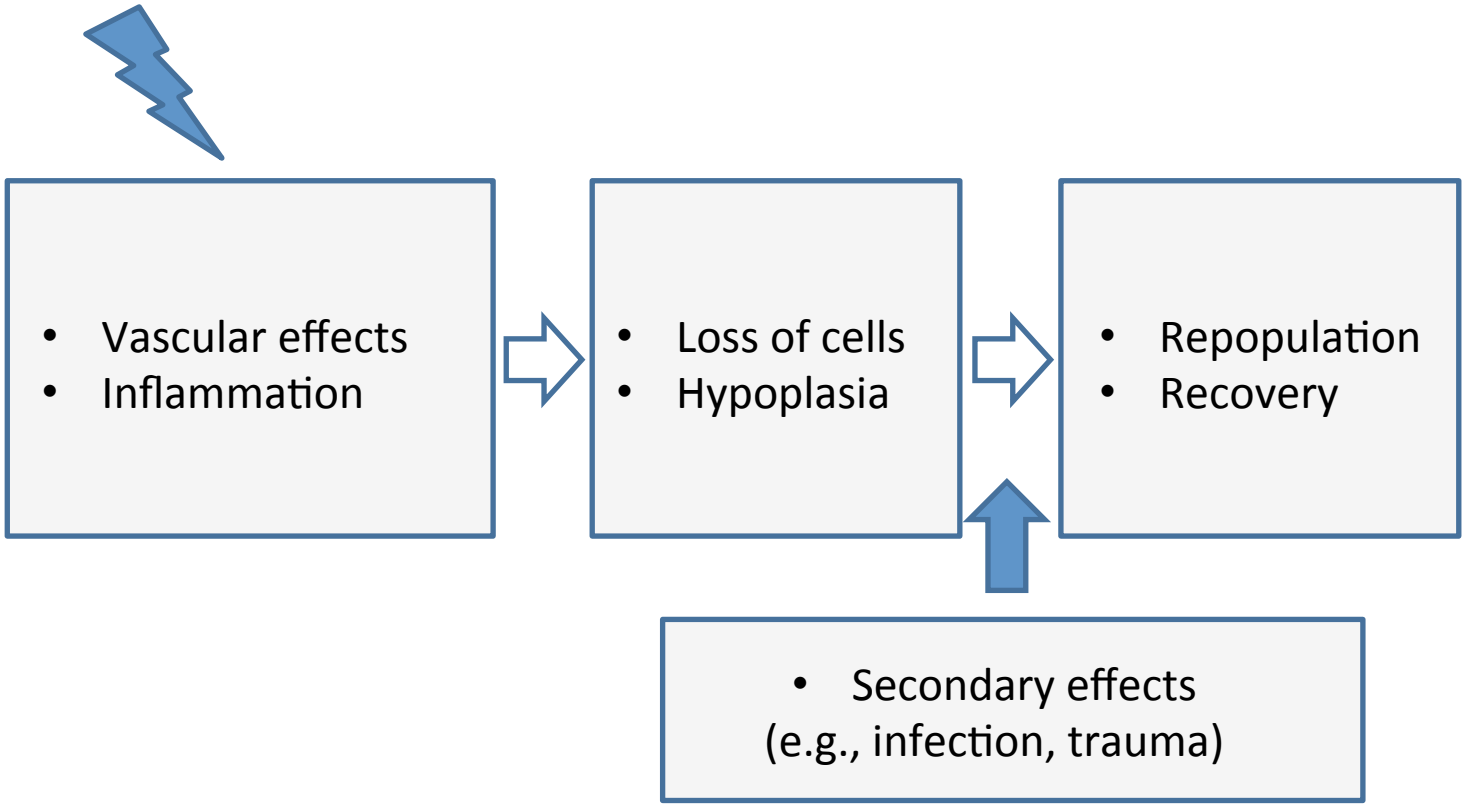


- Risk of complications show dose volume effect – depends on dose distribution throughout the whole organ rather than maximum dose to small area

Example of Dose-Volume evaluation



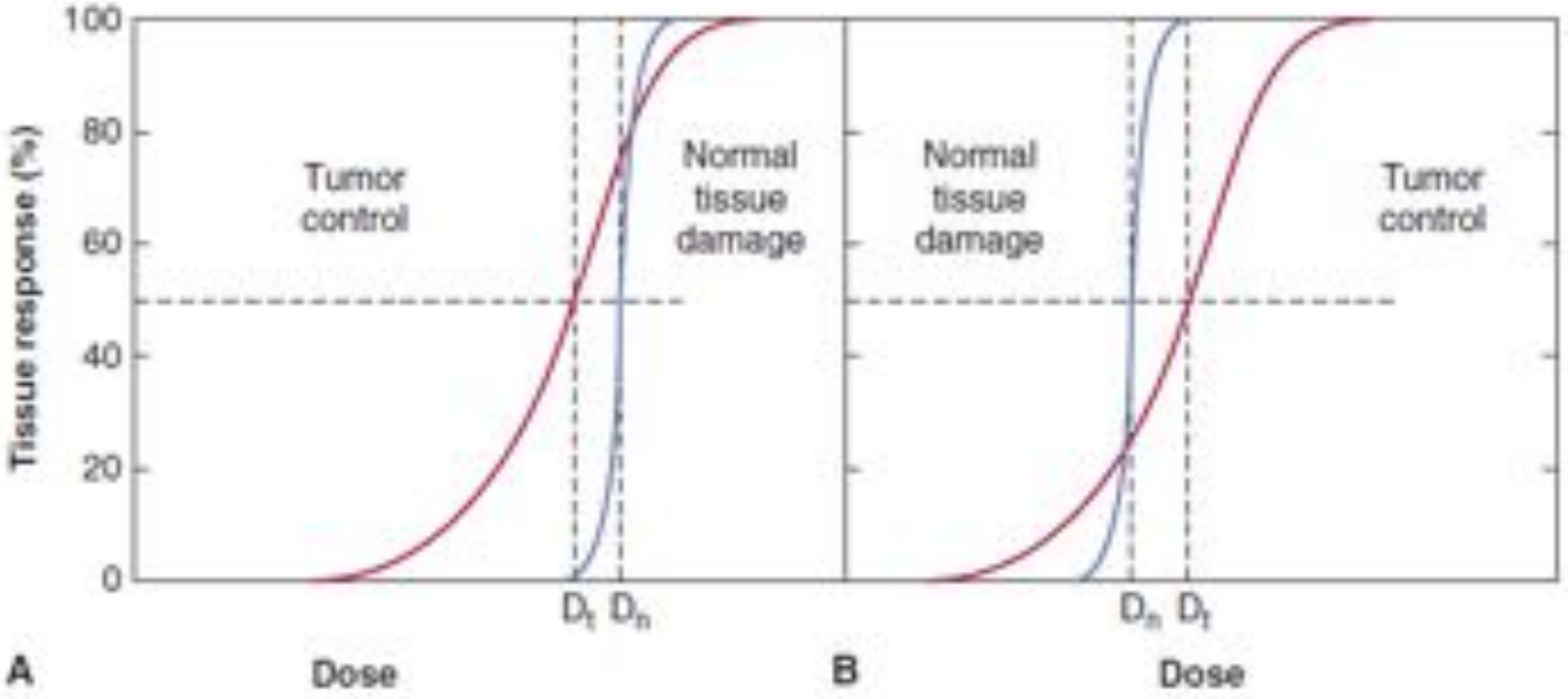
Consequential late effects



Consequential late effects

- If a **severe** acute reaction occurs (e.g., ulceration, infection which compromises underlying neurovasculature), this can predispose to the development of significant late effects
- This occurs primarily in organs where barrier function is important (e.g., bowel, bladder, skin)

Therapeutic Ratio



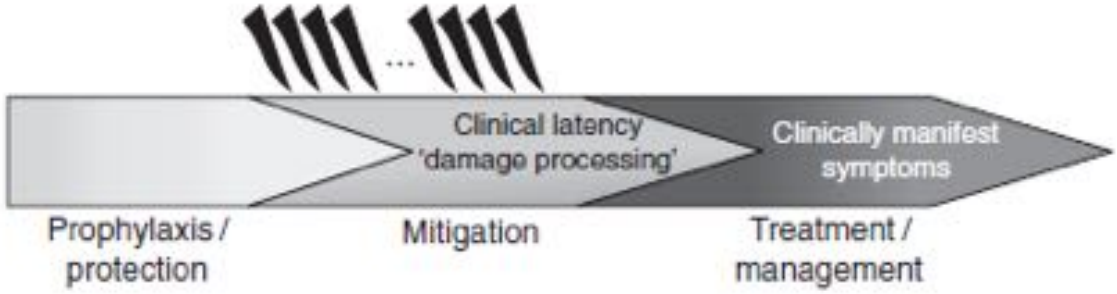
Favorable ratio

Unfavorable ratio

- As dose increases: probability of tumor control and normal tissue damage increase
- There is a steep dose-response portion to the curve

Radioprotection

- To improve therapeutic ratio, can improve physical radiotherapy targeting or biologically protect normal tissue:
- Prophylaxis - applied **prior** to exposure
- Mitigation - applied **during** or shortly after exposure (i.e., latent phase)
- Treatment - given **after** symptoms appear



From W. Dorr – Basic Clinical Radiobiology

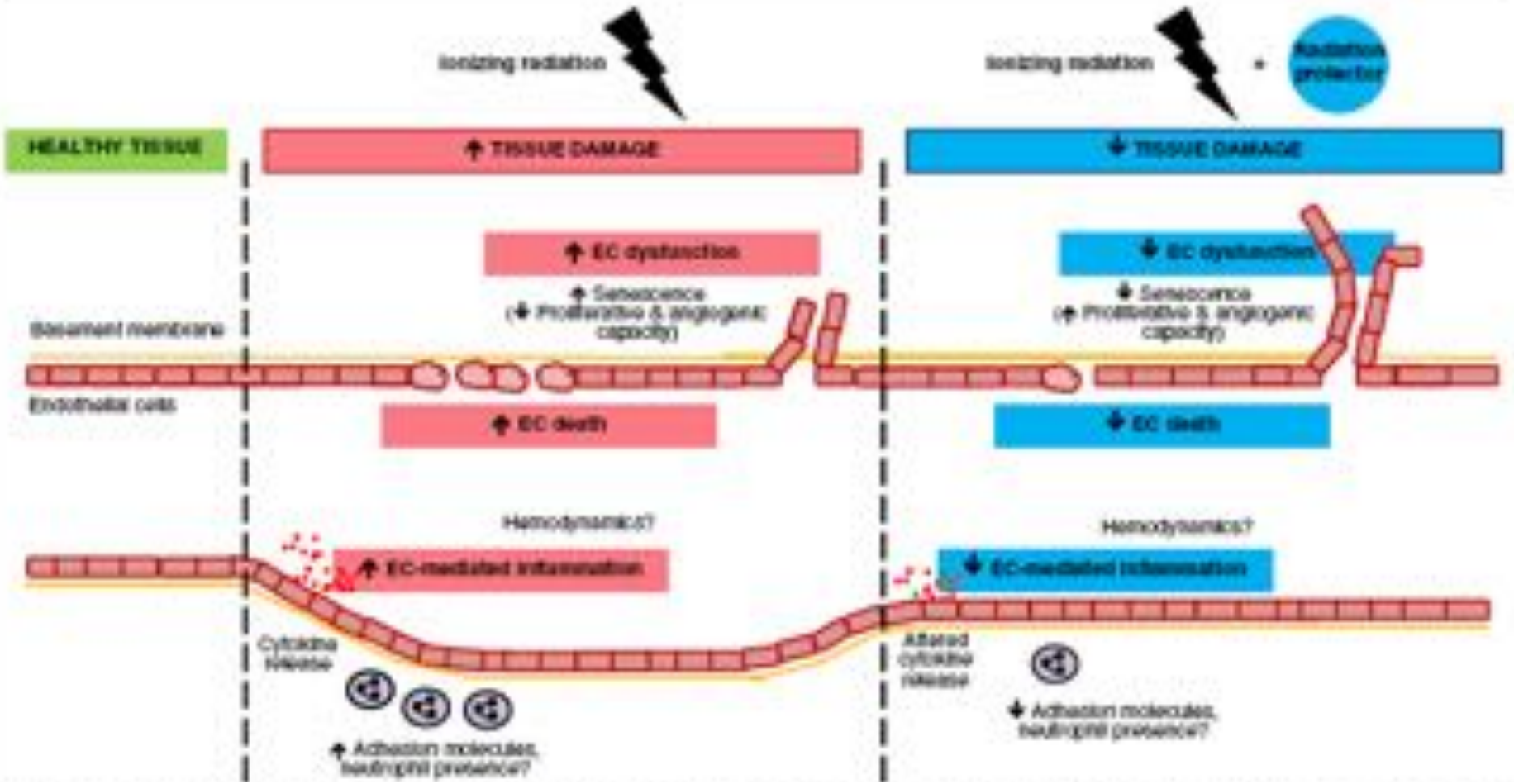
Radioprotection - mitigation

- Free radical scavengers
  - **Amifostine** – organic thiophosphate, preferentially uptaken in normal cells
    - May reduce xerostomia in H&N patients treated with radiotherapy alone, however studies often not blinded.
- Growth factors
  - **Keratinocyte growth factor (palifermin)**
    - Reduces mucositis from chemotherapy. Did not reduce incidence mucositis from chemoradiotherapy in H&N cancers.

Treatments

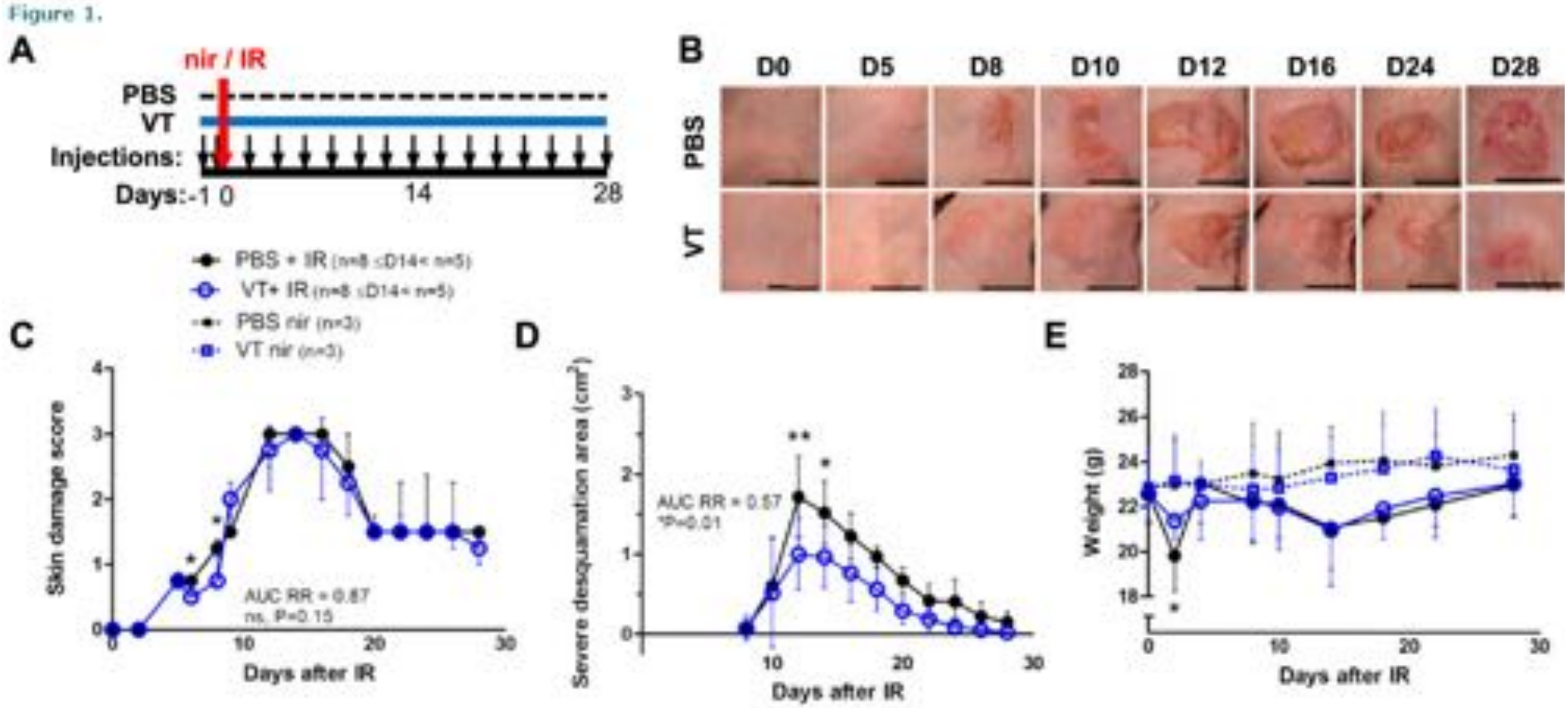
- Anti-inflammatories (5-ASA, corticosteroids)
- Hyperbaric oxygen
- Endoscopic treatment
- Surgical revision
- Stem cell therapy

Endothelial cells and acute radiotoxicity



Korpela & Liu – Rad Onc 2014

Preclinical example of vascular protection agent as a mitigant



Korpela et al – BMC Cancer 2014

Radiation syndromes

- After **whole body** radiation exposure:
  - **Hematopoietic syndrome** 0.7 to 10 Gy
    - death within few months due to loss of bone marrow stem cells causing infection and hemorrhage
  - **Gastrointestinal syndrome** >10 Gy
    - death within days due to damage to GI mucosal lining, causing electrolyte imbalance, dehydration, infection
  - **Neurovascular syndrome** >20 Gy
    - death within hours to days due to collapse of circulatory system and neurological dysfunction

Summary

- **Acute effects**
  - Occur within 90 days of radiotherapy
  - Severity and resolution are ***dose-dependent***
  - **Repopulation** plays important role in acute-responding tissue
  - Generally, complete resolution occurs
  - Severe acute effects may predispose to development of late toxicity (consequential effect)

Summary

- **Late effects**
  - Occur months to years later
  - Seen in acute and late responding tissue
  - Generally ***irreversible*** and ***progressive***
  - Need **prolonged clinical follow up**
  - Importance of considering life span of patient – longer survival time = higher risk of developing late effects

Summary

- **Dose**
  - For acute effects: increases severity and time to recovery
  - For late effects: increases severity and decreases time to clinical onset
- **Fraction size**
  - More of an effect on ***late effects*** than acute effects
- **Time**
  - Prolonging treatment time decrease ***acute effects*** due to repopulation
- **Volume**
  - For certain tissue (e.g., skin), with small field sizes, there is a steep increase in normal tissue tolerance.

Summary

- **Tissue-specific radiosensitivity**
  - Serial (e.g., spinal cord, GI tract) vs parallel organs (e.g., liver, kidney)
  - Stem cell repopulation plays an important role in acute responding tissue

Summary

- **Therapeutic ratio can be improved through radioprotection of normal tissues**
  - Free radical scavengers
  - Growth factors