Chapter 20 – Clinical Response of Normal Tissues

11/18/2024

Consent Form (Breast Radiation)

1. General complications of radiation treatment may include:
   - **skin irritation and pigment changes**
   - **organ and normal tissue injuries and scar tissue formation in the areas irradiated**
   - **development of second cancer, such reactions can occur during radiation therapy or a long time after completion of such treatments**

2. Other complications specific to your treatment may include:
   - **Acute**
     - **Fatigue**
     - **Skin redness, itching or blistering**
     - **Swelling of the breast**
     - **Lowered blood count**
   - **Late**
     - **Skin darkening**
     - **Soft tissue hardening**
     - **Swelling of the breast**
     - **Swelling of the arm**
     - **Pain**
     - **Rib fracture**
     - **Damage to the shoulder joint**
     - **Inflammation/scarring of the lung**
     - **Inflammation of the lining of the heart/damage of the heart muscle**

We inform patients of potential **normal tissue injury** from radiotherapy

Radiotherapy may be harmful to an unborn child.

If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before starting radiotherapy process. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not receive radiotherapy.

You should not mother/father a baby while on radiotherapy or for 6 months after completion of treatment.

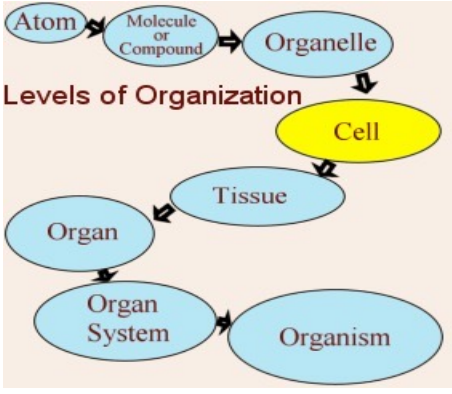
Outlines

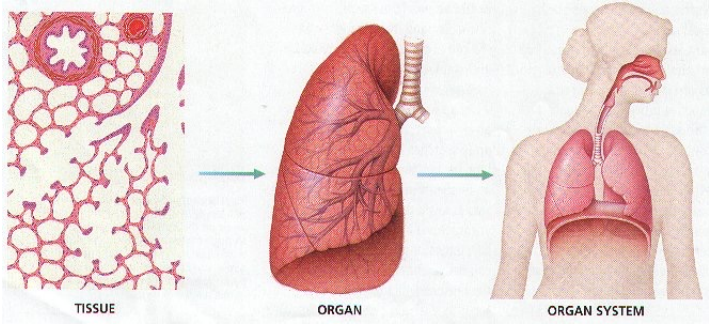
- **Cells and Tissues**
- Early (Acute) and Late Effects
- Functional Subunits in Normal Tissues
- The Volume Effect in Radiotherapy: Tissue Architecture
- Radiation Pathology of Tissues
  - Casarett's Classification
  - Michalowski's H- and F-Type Populations
- Growth Factors
- Specific Tissues and Organs
- Grading of Late Effects

Mechanism

Organ by organ clinical observation

Cells, Tissues and Organs





Lung epithelium Lung Respiratory system

Cells in multicellular organisms depend on each other

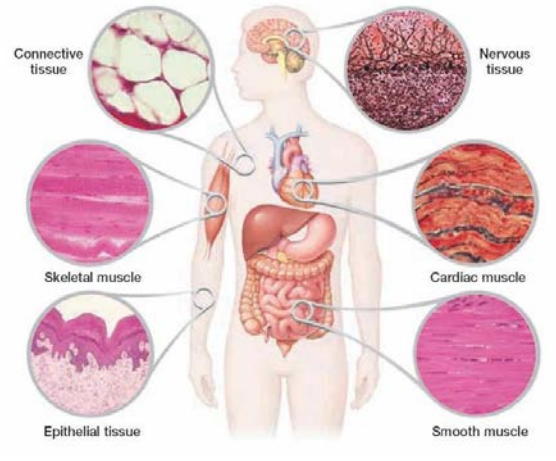
Tissues are groups of cells that perform a particular function

Organs are groups of tissues working together

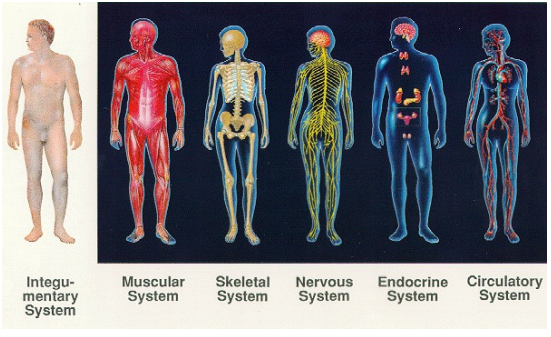
Systems are made of several organs working together to carry out a life process

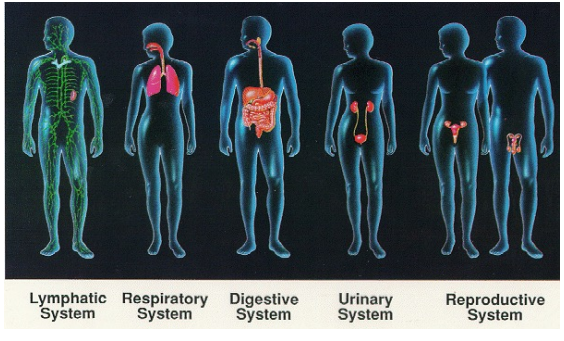
Tissues and Organ Systems

Human Body Tissues



Organ Systems





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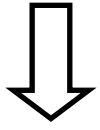
Early vs. Late Effects

Following radiation, most cells die while attempting to divide (i.e., **mitotic death**)



Cells (e.g., stem cells) with *mitotic potential* and *divide rapidly* will die quickly
Tissues containing these cells will also express radiation damage early on

In contrast, cells that *rarely divide* (e.g., kidney tubule cells) will die only when they attempt to divide, which may not occur for a long period of time
Hence, radiation damage to the tissues will be expressed very slowly

Law of Bergonié and Tribondeau

Hence, it appears that **undifferentiated stem cells** are more radiosensitive than the **terminally differentiated cells** (and cells on the road to differentiation)

Law of Bergonié and Tribondeau (1906)

Tissue appear to be more *"radiosensitive"* if their cells are less differentiated, have a greater proliferative capacity and divide more rapidly

Radiosensitivity, Response & Tolerance

Radiosensitivity – often refers to the **sensitivity** of the **individual cells** that make up the tissue

Radioresponse – relates to the **expression** of radiation damage of a **tissue**; i.e., early responding vs. late responding (Latency)

Radiotolerance – is the radiation dose that results in an acceptable level of normal tissue complication

Unfortunately, these terms are often used interchangeably

Normal Tissue Damage Response

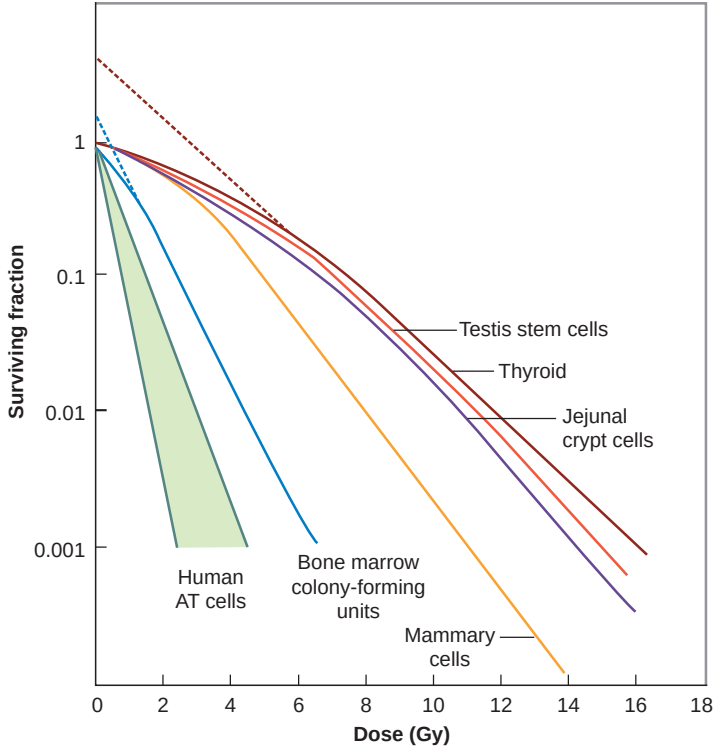
The response of normal tissue to radiation damage is determined by 3 principal factors

1) Inherent cellular radiosensitivity

2) The population kinetics of the tissue

3) The way cells are organized in that tissue

Inherent Cellular Radiosensitivity



There is a wide range of radiosensitivities, with the width of the shoulders being the principal variable

It is important to recognize that cellular radiosensitivity ≠ tissue radiosensitivity, because tissue is made up many cell types that are highly organized

Population Kinetics of Tissue

Population kinetics means the **turnover rate** of a tissue

This is particularly relevant when we discuss radiation response of normal tissue

Radiation damage are commonly divided into 2 categories defined by the *standard clinical treatment time*

- ✓ **Acute-responding (or Early-responding)**
- ✓ **Late-responding**

Early-Responding Tissues

EARLY RESPONDING TISSUES

- **Examples** – gut, skin, bone marrow
- **Latency** – effects are observed within **a few days or weeks** of irradiation
- **Mechanism** – damage result from the death of **stem cells**
- **Population kinetics** – these tissues typically have a **rapid turnover rate**, and the time of onset is determined by the lifespan of the mature functioning cells
- α/β **Ratio** – relatively large

Late-Responding Tissues

LATE-RESPONDING TISSUES

- **Examples** – brain, spinal cord, kidney, lung, heart, bladder
- **Latency** – effects appear after a delay of **months or years**
- **Mechanism** – a combination of loss of parenchymal cells and vascular damage (& ***dysregulated healing response***)
- **Population kinetics** – these are typically **slowly proliferating** tissues
- **α/β Ratio** – relatively small (sensitive to changes in fractionation)

Early and Late Effects

The radiation damage seen in acute-responding tissues are called **early effects**

The radiation damage seen in late-responding tissues are called **late effects**

Because of proliferation of stem cells, acute effects recover rapidly, often completely, whereas late damage is often (but not always) irreversible

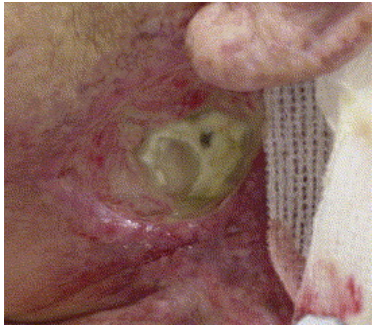
Exception: Consequential Late Effect

Consequential Late Effect

If intensive radiation regimen deplete the stem-cell population below levels needed for tissue restoration, an early reaction in a rapidly proliferating tissue may persist as a chronic injury. This has been termed a consequential late effect, i.e., a late effect consequent to, or evolving out of, a persistent severe early effect

Examples

- Stenosis consequent to mucosal ulceration in the bowel
- Necrosis or fibrosis consequent to desquamation or acute ulceration in the skin or oropharynx



Consequential late radiation dermatitis with chronic telangiectasia, ulcer, and exposed bone

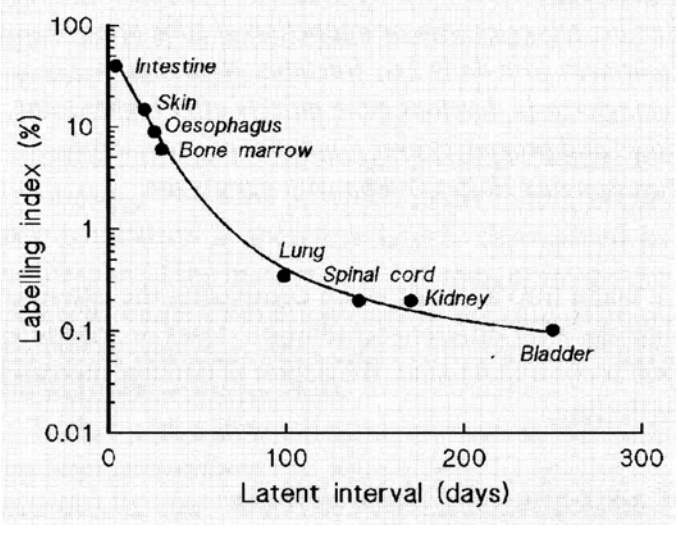
J Am Acad Derm 54(1): 28-46

Early and Late Responding Tissues

TABLE 4–3.

Acutely Responding and Late Responding Normal Tissues

Tissue	Target Cells
Acutely responding	
Skin	Basal cells of the epidermis
Hair	Follicle
Lip mucosa	Basal cells
Jejunum	Crypt cells
Colon	Crypt cells
Testis	Spermatogonia
Bone marrow	Stem cells
Late responding	
Kidney	? Epithelial cells of proximal tubules
Lung	? Type 2 pneumonocytes
Spinal cord	Glial cell
Brain	?
Bladder	?



Latency vs. mitotic activity (Target Cells)

Latency in Early-Responding Tissue

In **early-responding tissues**, **latency** is determined by cell turnover kinetics in a tissue

Latency is **NOT** an indicator of **radiation tolerance**

Latency in Late-Responding Tissue

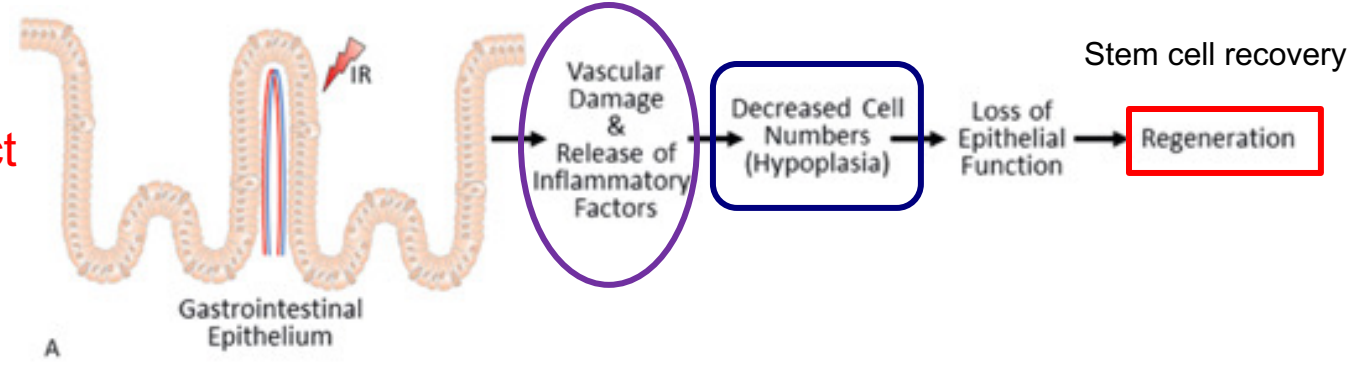
In **late-responding tissues**, **latency** is a function of **dose**

If the dose is small, the expression of damage is **delayed** because cells divide infrequently; consequently, the damage may be hidden for a long time

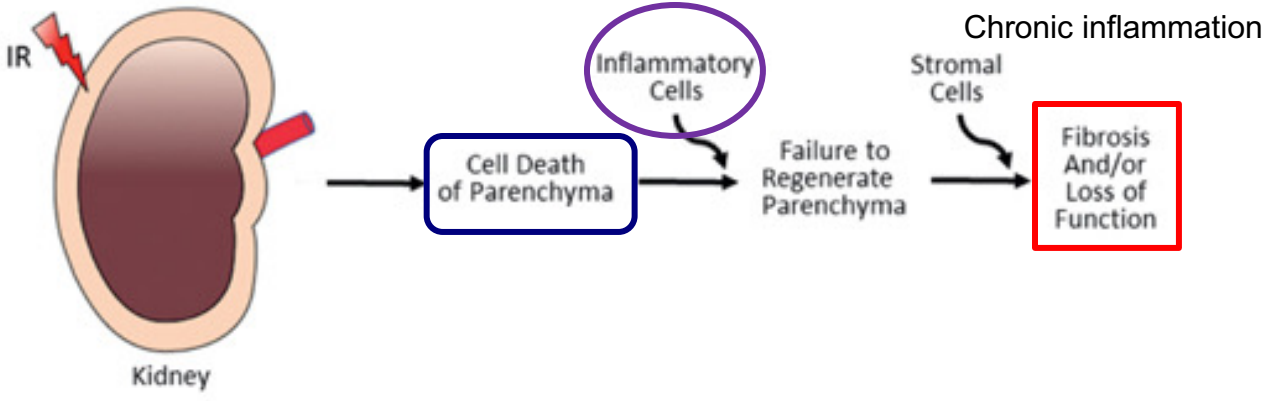
As dose increases, the latency period with late reacting tissues **decreases**. As a ***compensatory*** *response* to massive depletion of mature functioning cells after high doses, cells in late reacting tissues that are normally not part of the growth fraction are recruited into the cell cycle.

Early vs. Late Effects

Early Effect



Late Effect



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Normal Tissue Damage Response

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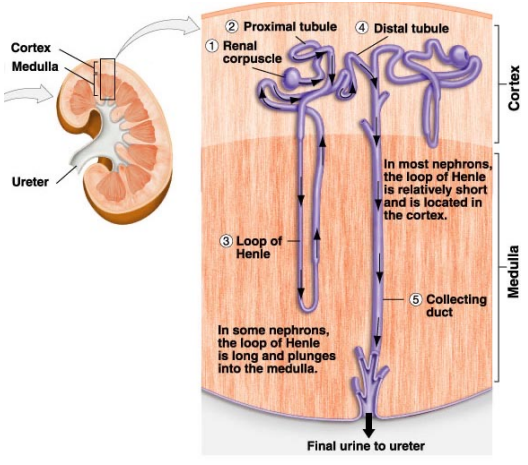
Structurally Defined Functional Subunits (FSUs)



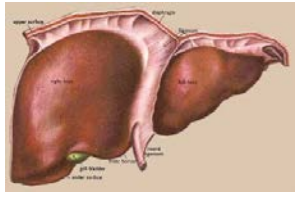
The kidney is composed of functional units called **nephrons**

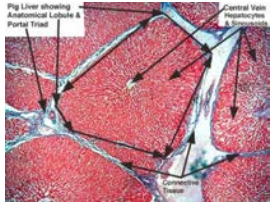
Each nephron consists of a glomerulus, and a long U-shaped tubule (the loop of Henle) which connects to the collecting tubule

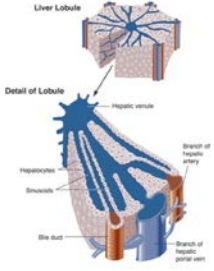
Each nephron is a self-contained entity **independent** of its neighbors – surviving clonogens **cannot migrate** from one to the other

Survival of a nephron after radiation depends on the **survival of at least one clonogen within it** and therefore on the initial number of renal tubule cells per nephron and their radiosensivitity

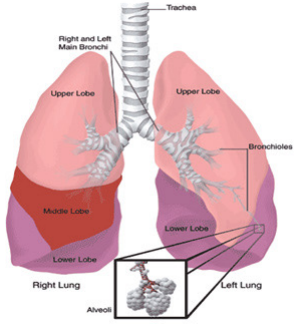
Structural Defined FSUs

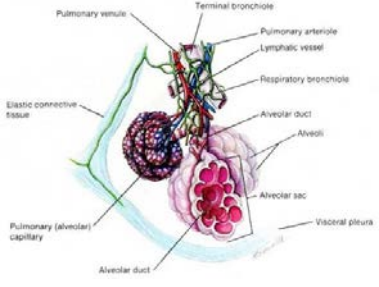


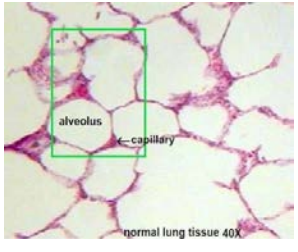




Liver consists of hexagonal shaped functional units called hepatic lobules







Bronchi branches many times to become alveolar sacs, which are made up of clusters of alveoli where gas exchange occurs

Structurally Defined FSUs

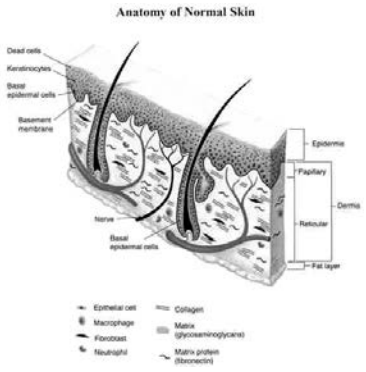
Radiation Tolerance

Because each FSU is relatively small, it is completely depleted of clonogen by low doses

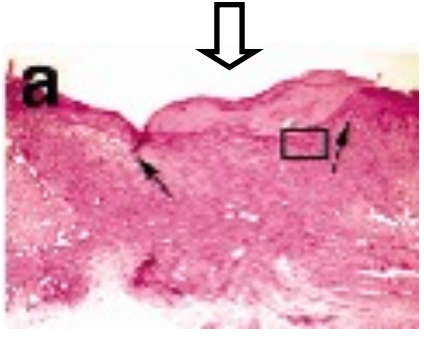
For example, each kidney tubule contains 1,000 cells, which are depleted to 1 clonogen by 3 decades of killing

This accounts for the low tolerance dose of the kidney and some of the other tissues with similar tissue architecture

Structurally Undefined FSUs



Area depleted of clonogenic cells



Migration of epithelium visible at the edge = reepithelialization

The clonogenic cells are **not confined** to one particular FSU
Rather, clonogenic cells **can migrate from one FSU to another** and allow repopulation of depleted FSU
This is how denuded area of skin heal

Other examples include spinal cord and mucosa

Tissue Rescue Unit

Tissue rescue unit is defined as the minimum number of FSUs required to maintain tissue function

This is a concept proposed to link the **survival** of clonogenic cells and **functional** survival of a tissue

Assumptions

1) The number of tissue rescue units in a tissue is proportional to the number of clonogenic cells
2) FSUs contain a constant number of clonogens
3) FSUs can be repopulated from a single surviving clonogen

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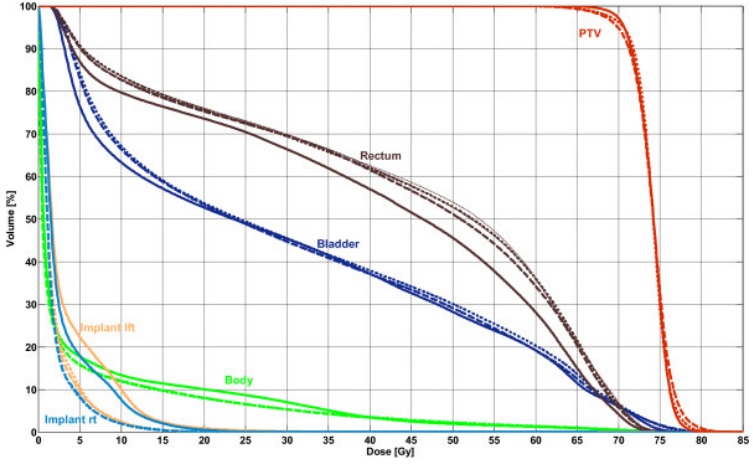
The Volume Effect

An Example of Planning Directives

Structure	Dose–volume constraints
Prostate PTV	$D_{95\%} \geq 66.5$ Gy
	$D_{2\%} \leq 74.9$ Gy
Nodal PTV	$D_{95\%} \geq 47.9$ Gy
Rectum	$V_{65Gy} \leq 15\%$
	$V_{45Gy} \leq 45\%$
Bladder	$V_{65Gy} \leq 25\%$
	$V_{45Gy} \leq 50\%$
Femoral heads	$D_{2\%} \leq 50$ Gy
Bowel bag	$D_{2\%} \leq 52$ Gy
	$D_{max} \leq 55$–60 Gy

D_{max}, maximum dose to the structure; $D_{n\%}$, minimal dose to n% of the structure; PTV, planning target volume; V_{nGy}, percentage structure volume receiving $\geq n$ Gy.

An Example of Dose Volume Histogram



The total dose that can be tolerated depends on the volume of tissue irradiated

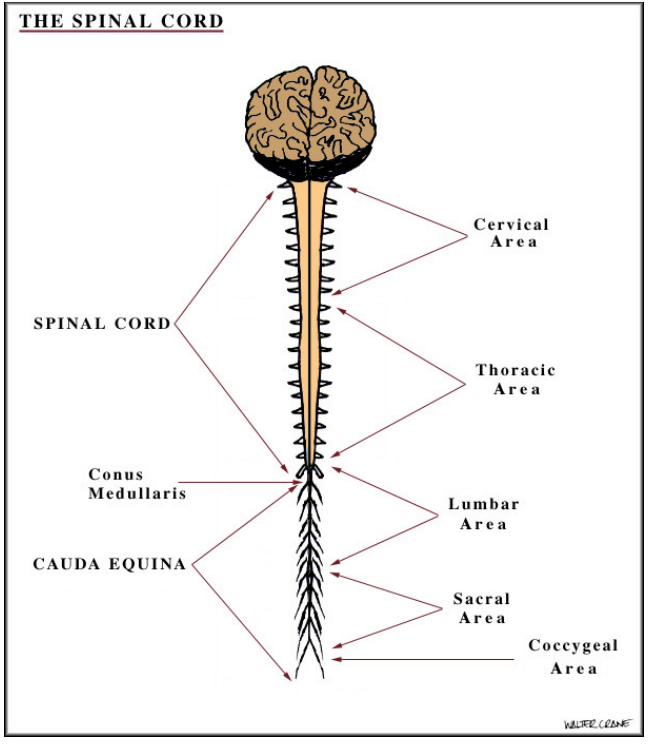
Spatial Arrangement of FSUs

In addition to the FSU being structurally defined or undefined, the spatial arrangement of these FSUs are also critical, especially concerning the effect of radiation volume

Serial organs are those in which the FSUs are arranged ***in tandem*** and destruction of a single FSU will impair function

In **parallel organs**, the FSUs are not arranged serially

FSU in Series

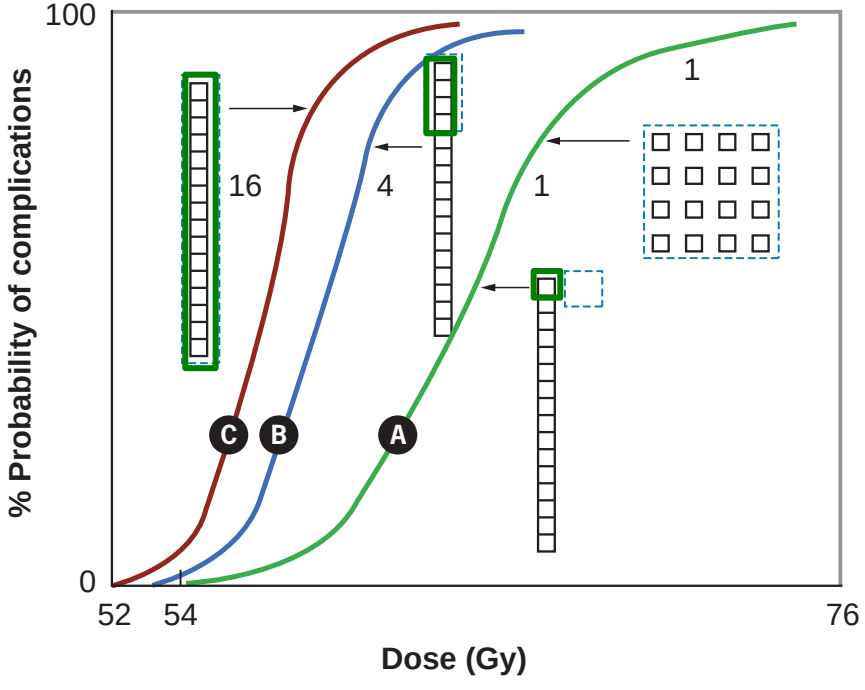


FSUs are arranged like the links of a chain

The integrity of each FSU is critical to organ function, and elimination of any one FSU results in a measurable probability of a complication

With serial organs, the effect seems to be all-or-nothing

FSU in Series – Volume Effect

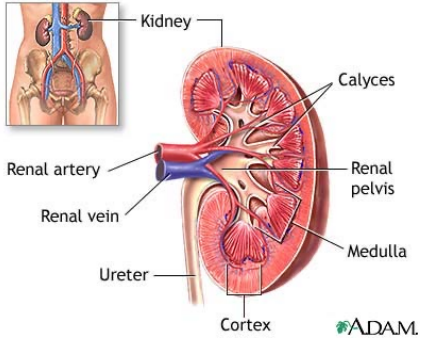


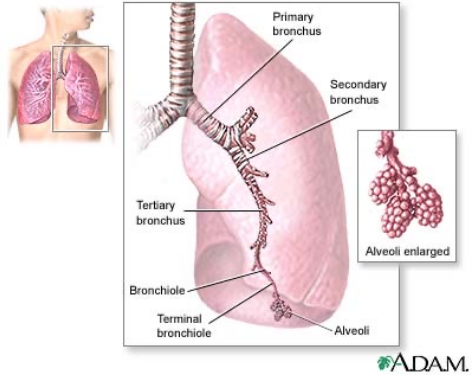
Dose response curve for irradiation of 1 FSU is sigmoidal and is relatively shallow

(as is for FSU in parallel)

As the field size increases to include a greater number of FSU – 4, 16 – the curve relating probability of a complicating to dose rises much more steeply with dose and moves to a lower dose. This is because damage to any one of the 16 FSU leads to organ dysfunction

Parallel Organs



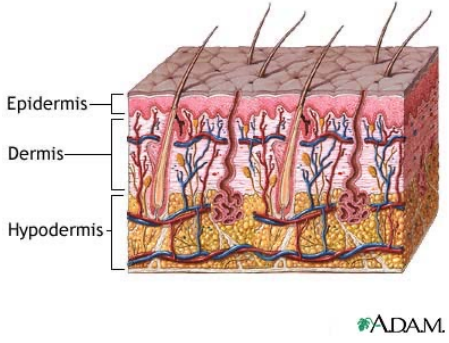


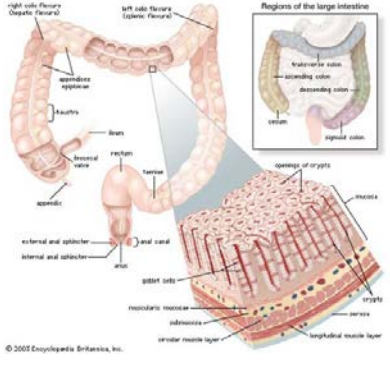
For kidneys and lungs, entire volume tolerates a relatively low dose

Partial volumes can be treated to a much higher dose due to the parallel organization of functional nephrons and alveolar subunits

Thus, a threshold volume can be expected

Parallel Organs





Radiobiologically, skin and mucosa do not show a volume effect at lower levels of injury because they do not have well defined FSU and healing can occur from surviving clonogens scattered throughout the treatment volume

However, at higher doses, **clinical tolerability** does depend on the volume irradiated – if a larger area of skin or mucosa is ulcerated, the prolonged healing time plus the increased potential for infection are more debilitating than similarly severe ulceration in a smaller area

Question 1

Examples of FSUs arranged in parallel include

A. Lung, liver, kidney
B. Skin, peritoneal sheath
C. Spinal cord, nerves
D. Kidney, spinal cord

Question 2

The arrangement of functional subunits (FSU) can sometimes explain the “volume effect”. If FSUs are arranged in parallel

A. Low dose exposures to a small volume may be devastating

B. Low dose exposures to a large volume may be innocuous

C. High dose exposures to a small volume may be innocuous

D. A strong volume effect is predicted

Question 3

Assuming that the target cells do not have a pro-apoptotic tendency, the time to the expression of radiation damage in early-responding tissues typically correlates best with the:

A. radiosensitivity of the cells
B. lifespan of the mature functional cells of the tissue
C. ability of the cells to perform homologous recombinational repair of DNA damage
D. lifespan of the stem cells comprising that tissue
E. type of radiation used to irradiation the organ

Question 4

The tolerance doses for the kidney and lung are highly dependent on the volume of tissue irradiated. Both of these normal tissues are very sensitive to irradiation of their entire volume. In contrast, small volumes can be irradiated to high doses without loss of function. All of the following explanations are consistent with this observation, EXCEPT, that:

A. both organs have considerable reserve capacity
B. these organs have functional subunits arranged in series
C. a functional deficit is not observed in these organs until a critical number of functional subunits are inactivated by exposure to radiation
D. above a certain threshold dose, radiation injury is usually expressed as a graded response rather than as an all or nothing response

Question 5

With regard to the latency period for the expression of radiation-induced normal tissue injury, which of the following statements is CORRECT?

A. The latency period for early-responding tissues decreases markedly with increasing radiation dose

B. Shortening the overall treatment time by accelerating radiotherapy substantially reduces the latency period for early-responding tissues

C. Shortening the overall treatment by accelerating radiotherapy tends to increase the latency period for late-responding tissues

D. The higher the total radiation dose, the shorter the latency period for many late-responding tissues

E. The latency period for early-responding tissues depends on the rate of vascular endometrial cell turnover

Latency in Late-Responding Tissue

In **late-responding tissues**, **latency** is a function of **dose**

If the dose is small, the expression of damage is **delayed** because cells divide infrequently; consequently, the damage may be hidden for a long time

As dose increases, the latency period with late reacting tissues **decreases**. As a ***compensatory*** *response* to massive depletion of mature functioning cells after high doses, cells in late reacting tissues that are normally not part of the growth fraction are recruited into the cell cycle.

Question 6

For normal tissues such as spinal cord, a small dosimetric hotspot could be disastrous in terms of increasing the likelihood for a serious late complication. However, a small volume receiving a high dose during lung irradiation may not lead to any late sequelae. The best explanation for this observation is that:

A. The spinal cord has a large functional reserve, but the lung does not
B. Target cells in the lung are better able to repair radiation damage than their counterparts in the spinal cord
C. Surviving clonogens in the lung can repopulate rapidly, whereas those in the spinal cord cannot
D. Migration of cells from outside the irradiated volume helps to augment lung function, but this process does not occur in the spinal cord
E. The putative functional subunits in the lung are arranged in parallel, whereas those in the spinal cord are arranged in series

Question 7

In normal tissues, the radiation tolerance dose is hypothesized to depend on the ability of tissue clonogens to maintain an adequate number of mature functioning cells. The relationship between organ function and clonogenic cell survival is dependent on the structural organization of functional subunits (FSUs) within the particular tissue. Which of the following statements concerning FSUs is TRUE. FSUs:

A. Contain a relatively set number of clonogens
B. Cannot be repopulated from a single surviving clonogen
C. Are defined as units with clear anatomical demarcation
D. Are usually dependent on one another in a functional sense
E. Cannot be repopulated from an adjacent FSU

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The response of normal tissue to radiation damage is determined by 3 principal factors

1) Inherent cellular radiosensitivity

2) The population kinetics of the tissue

3) The way cells are organized in that tissue

Radiation **Pathology** of Tissues

Two systems are typically used to classify **tissue radiosensitivity** in terms of *population kinetics* and *tissue architecture*

Cassarett's Classification of Tissue Radiosensitivity
(Cellular level)

Michalowski's H- and F-Type Population
(Tissue level)

Cassarett's Classification

- Based on histopathologic observations of early cell death (i.e., fixed section of tissue under the microscope)
- Parenchymal cells are divided into 4 major categories

Cassarett's Classification

Cellular level

TABLE 20.1 Categories of Mammalian Cell Sensitivity

Cell Type	Properties	Examples	Sensitivity[a]
I. Vegetative intermitotic cells	Divide regularly; no differentiation	Erythroblasts Intestinal crypt cells Germinal cells of epidermis	High
II. Differentiating intermitotic cells	Divide regularly; some differentiation between divisions	Myelocytes	
Connective tissue cells[b]			
III. Reverting postmitotic cells	Do not divide regularly; variably differentiated	Liver	
IV. Fixed postmitotic cells	Do not divide; highly differentiated	Nerve cells Muscle cells	Low

[a]Sensitivity decreases for each successive group.

[b]Intermediate in sensitivity between groups II and III.

Cassarett's Classification – Group I

Cell Type	Properties	Examples	Sensitivity[a]
I. Vegetative intermitotic cells	Divide regularly; no differentiation	Erythroblasts Intestinal crypt cells Germinal cells of epidermis	High

These are **stem cells** of the classic self-renewing system

Because they divide regularly, a moderate dose causes a proportion of them to "die" in **attempting mitosis** → they are considered **vulnerable to radiation**

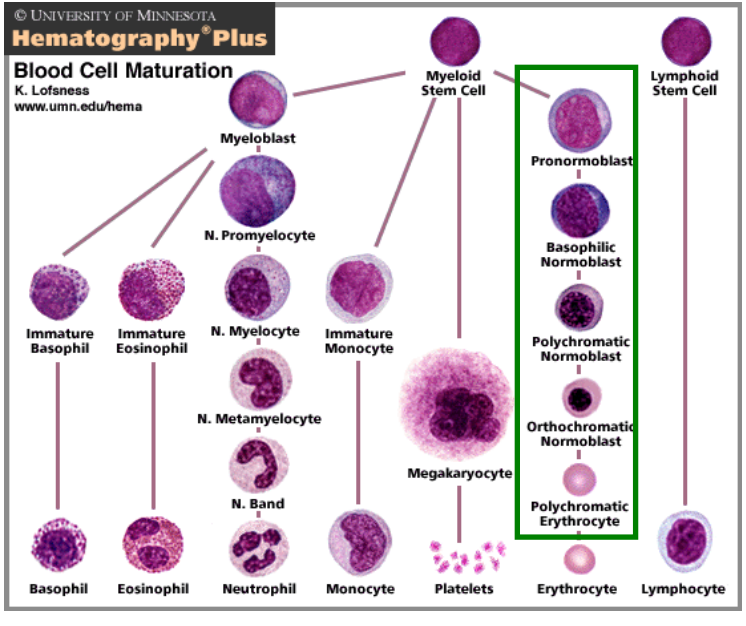
For the **entire tissue**, this translates into early expression of radiation damage (i.e., **early-responding tissue**)

The time interval between irradiation and the crisis depends on the life span of the mature functioning cells

Depending on the dose, the organ or tissue may not survive the critical time at which the number of functioning cells reaches a minimum value (e.g., GI syndrome following TBI)

Cassarett's Classification – Group II

Cell Type	Properties	Examples	Sensitivity[a]
II. Differentiating intermitotic cells	Divide regularly; some differentiation between divisions	Myelocytes Spermatocytes	

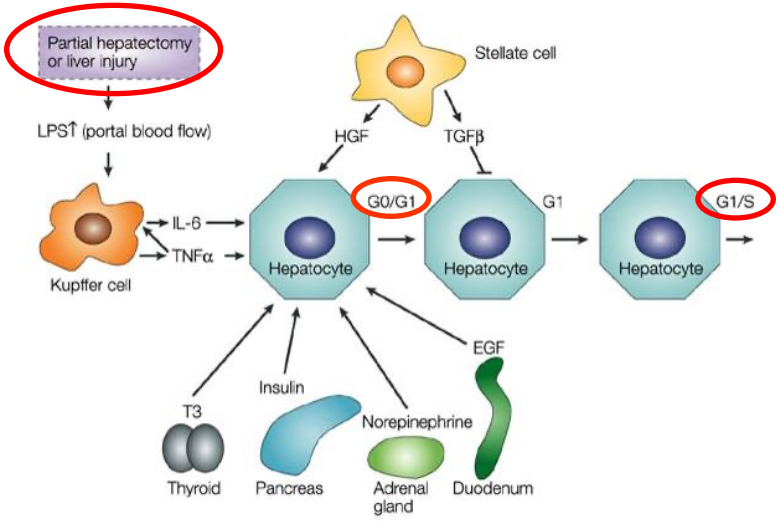


These are cells produced by division of vegetative intermitotic cells

They divide regularly, but also mature and differentiate between divisions

Cassarett's Classification – Group III

Cell Type	Properties	Examples	Sensitivity[a]
III. Reverting postmitotic cells	Do not divide regularly; variably differentiated	Liver Kidney, pancreas, adrenal, thyroid, pituitary	



Liver regeneration

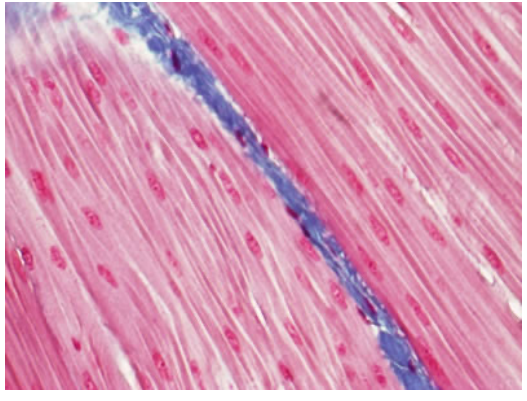
They ordinarily do not undergo mitosis, but are capable of dividing with the appropriate stimulus

They are relatively radioresistant

Tissues consist of these cells would be **late-responding**

Cassarett's Classification – Group IV

Cell Type	Properties	Examples	Sensitivity[a]
IV. Fixed postmitotic cells	Do not divide; highly differentiated	Nerve cells Muscle cells	Low
		Granulocytes, epithelial cells of the gut	



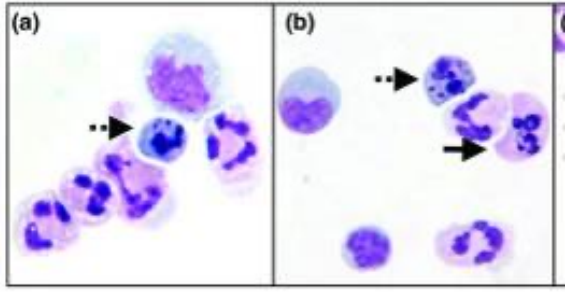
Muscle

They are highly differentiated and appear to have lost their ability to divide

Some have a long lifespan (e.g., neurons)
Others have a short lifespan (e.g., white blood cells)

They are generally considered to be the most resistant to radiation

Cassarett's Classification



Apoptotic lymphocytes

Note that **lymphocytes** defy this system of classification

Lymphocytes never divides at all, yet they are exquisitely radiosensitive

It is believed that they die by interphase death (by the process of **apoptosis**)

Radiation **Pathology** of Tissues

Two systems are typically used to classify **tissue radiosensitivity** in terms of *population kinetics* and *tissue architecture*

Cassarett's Classification of Tissue Radiosensitivity
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Michalowski's H- and F-Type Population
(Tissue level)

Michalowski's H- and F-Type Populations

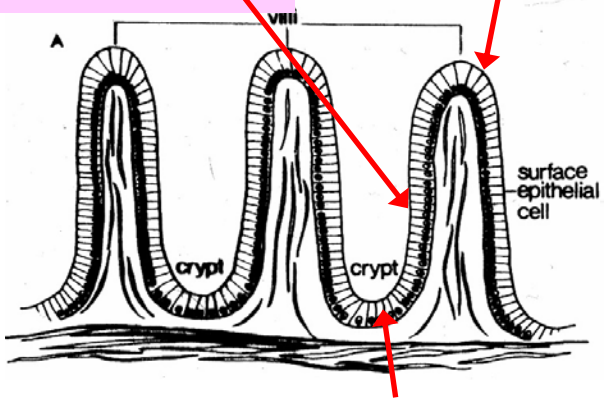
Hierarchical Type (H-Type) Tissue

Descendants of the stem cells
Still multiply as they complete the process of differentiation

Fully differentiated
Usually incapable of further division and die after a finite lifespan

Mature, functioning

Maturing, partially differentiated



Dividing stem cells

Capable of unlimited proliferation
Escape senescence by expression of telomerase

Examples – hematopoietic bone marrow, intestinal epithelium, epidermis

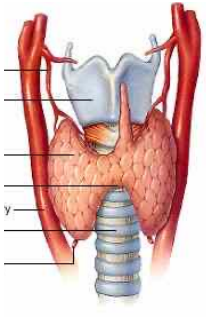
3 distinct categories of cells
(What groups do they belong in Cassarett's classification?)

These are typically early-responding tissues

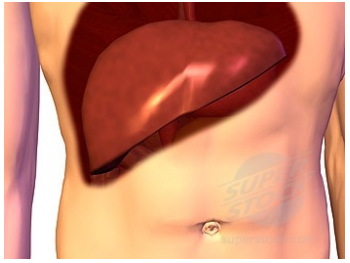
Latency is determined by life span of functioning cells

Michalowski's H- and F-Type Populations

Flexible Type (F-Type) Tissue



Thyroid gland



Liver

Tissues such as liver, thyroid, dermis, are composed of cells that rarely divide under normal conditions but can be triggered to divide by damage

These **flexible tissues (F-type population)** have no compartments and no strict hierarchy

After damage to the tissue, all cells, including those that are functional, enter the cell cycle

These tissues are typically late-responding, and **latency** is a function of **dose**
If the dose is small, the expression of damage is delayed because cells divide infrequently

H- vs. F-Type Populations

	Hierarchical	Flexible
Turnover rate	Rapid with a high rate of cell loss	Slow
Stem cell	Rich stem cells and proliferative progenitor cells that differentiate into functional cells	Play a smaller role in regeneration Generally, it is the functional cells that are induced to proliferate on demand after a long lag time
Damage expression	Acute responding tissues mainly fall into this category; and they recover rapidly from the effects of irradiation by regeneration	Late responding tissues fall mainly into this category
Examples	Gut, skin, bone marrow	Brain, spinal cord, kidney, lung, bladder

Michalowski's H- and F-Type Populations

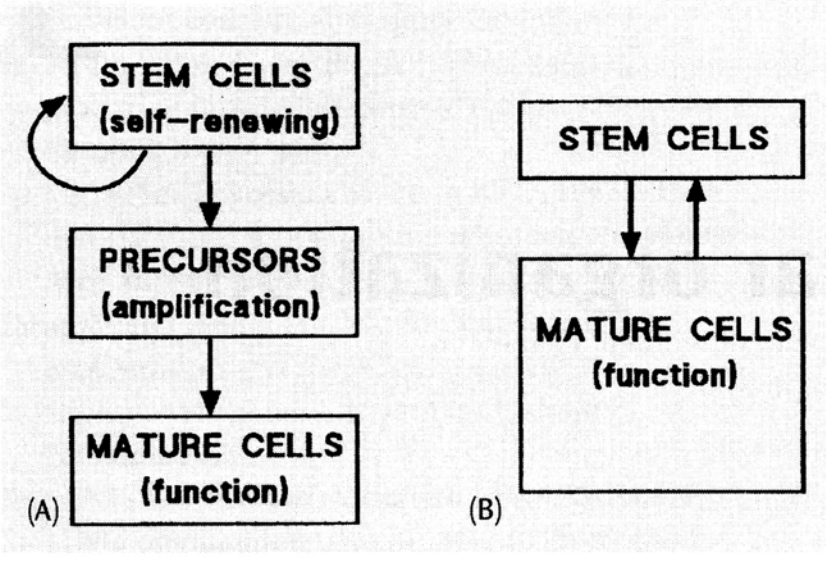


Figure 3.1 *Schematic outline of the proliferative organization of (A) hierarchical and (B) flexible normal-tissue systems.*

Many tissues are hybrids of these two extreme models, with most cells able to make a few divisions and a minority of the population behaving as stem cells

Normal Tissue Damage Response Summary

When analyzing the the response of normal tissue to radiation damage, always think about these three factors:

1) **Inherent cellular radiosensitivity** (A tissue may consists of several types of cells with varying radiosensivity)

2) **The population kinetics of the tissue** (e.g., rapid turnover vs. slow turn over)

3) **The way cells are organized in that tissue** (e.g., serial vs. parallel; hierachical vs. flexible)

Outlines

- Cells and Tissues
- Early (Acute) and Late Effects
- Functional Subunits in Normal Tissues
- The Volume Effect in Radiotherapy: Tissue Architecture
- Radiation Pathology of Tissues
  - Casarett's Classification
  - Michalowski's H- and F-Type Populations
- **Growth Factors**
- Specific Tissues and Organs
- Grading of Late Effects

Mechanism

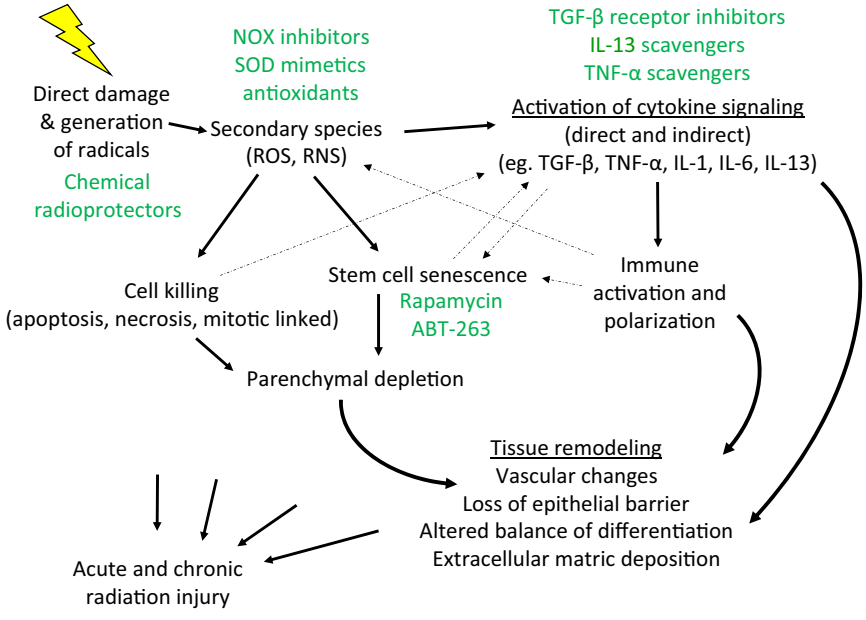
Organ by organ clinical observation

Modern Meets Classic

- Radiation-induced normal tissue injury is a complex process that spans *acute* and *late* injury in biologically diverse tissues
- Classical radiobiological understanding of normal tissue injury has provided a framework into which **molecular biologic, immunologic, and tissue homeostatic** understanding is now being integrated

Mostly for medical residents

Pathways of Radiation Injury

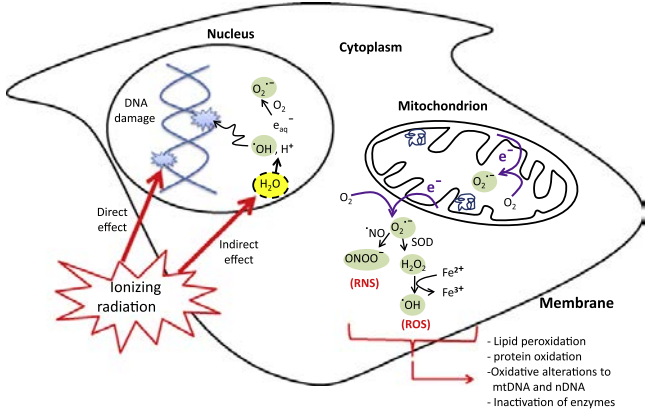


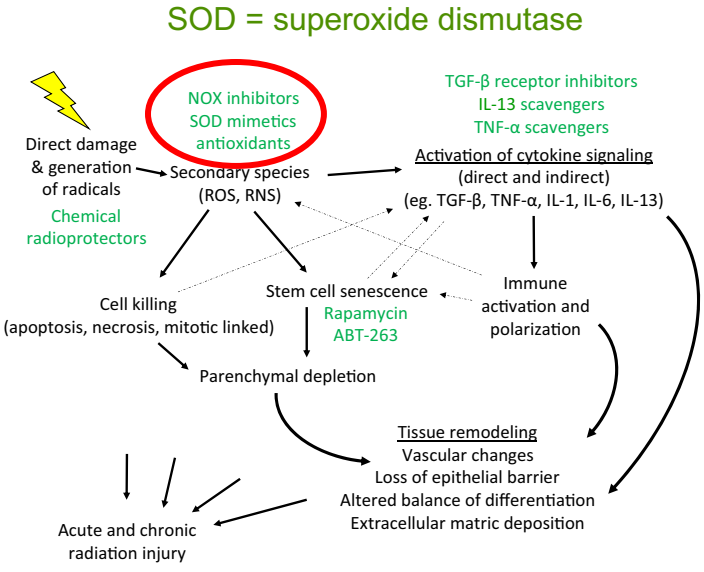
The molecular events that lead to normal tissue injury span a variety of biologic processes, including

- Oxidative stress
- Inflammation
- Depletion of injured cells
- Senescence
- Elaboration of proinflammatory and profibrogenic cytokines
- Epigenetic modulators

Citrin & Mitchell 2017; Semin Radiat Oncol 27:316-324

Oxidative Stress





Besides direct ionization, secondary reactions result in chronic elevation of reactive oxygen species **(ROS)**
In addition, ROS can be generated by a host of cell types in the setting of injury and inflammation, which can contribute to ongoing oxidative injury through the generation of reactive nitrogen species (**RNS**).

Many attempts at minimizing injury from irradiation have focused on reducing oxidative stress by inhibiting the production of free radicals and delivering compounds capable of scavenging deleterious free radicals.

Azzam 2012; Cancer Letters 327:48-60

Cytokines and Growth Factors

Cytokines and **growth factors (GF)** are secreted proteins which mediate cellular responses through binding to specific receptors

They are involved in important processes such as ***immunity***, ***inflammation***, ***hematopoiesis***, and ***wound healing responses*** that lead to tissue regeneration

They may also play a role in **pathogenesis of complications** and are probably responsible for some side effects or irradiation, such as fatigue, nausea/vomiting, acute edema or erythema, somnolence

Cytokines

Cytokines are produced in response to an immune stimulus; they can also be induced by radiation

They generally (though not always) act over short distances and short time spans and at very low concentrations

They act by binding to **specific membrane receptors**, which then signal the cell via **second messengers**, often tyrosine kinases, to **alter gene expression**

Cytokines

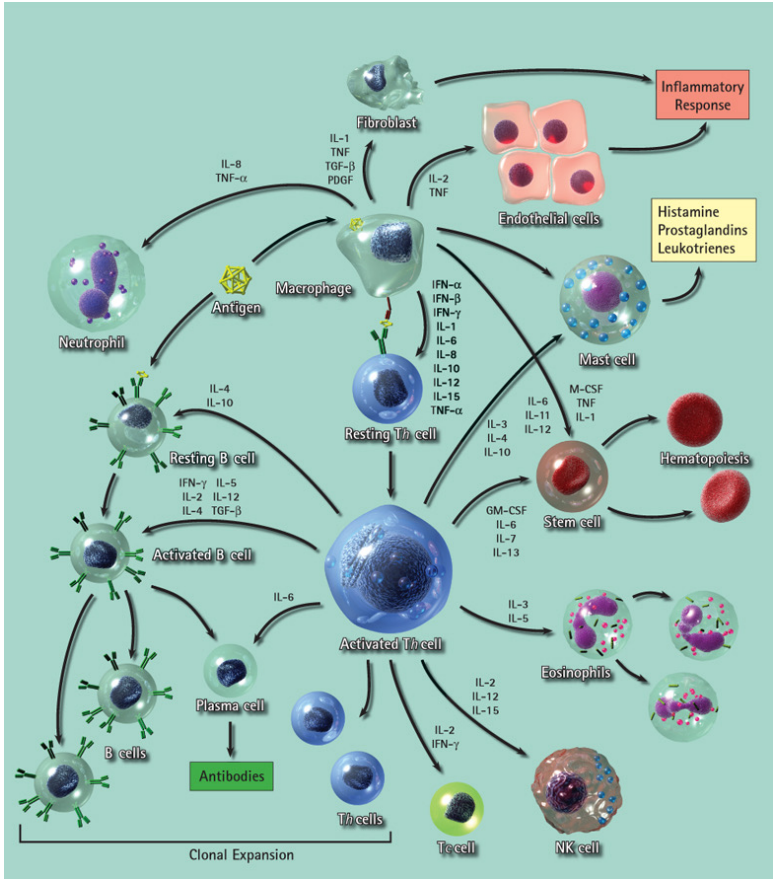
It is common for different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types (**pleiotropy**)

Cytokines are **redundant** in their activity, meaning similar functions can be stimulated by different cytokines

Cytokines are often produced in a **cascade**, as one cytokine stimulates its target cells to make additional cytokines

Cytokines can also act **synergistically** (two or more cytokines acting together) or **antagonistically** (cytokines causing opposing activities)

Cytokines



Cytokine is a general name; other names include

Lymphokine – made by lymphocytes

Monokine – made by monocytes

Chemokine – cytokines with chemotactic activities

Interleukin – made by one leukocyte and acting on other leukocytes

Cytokines may act on the cells that secrete them (**autocrine action**), on nearby cells (**paracrine action**), or in some instances on distant cells (**endocrine action**)

Cytokines

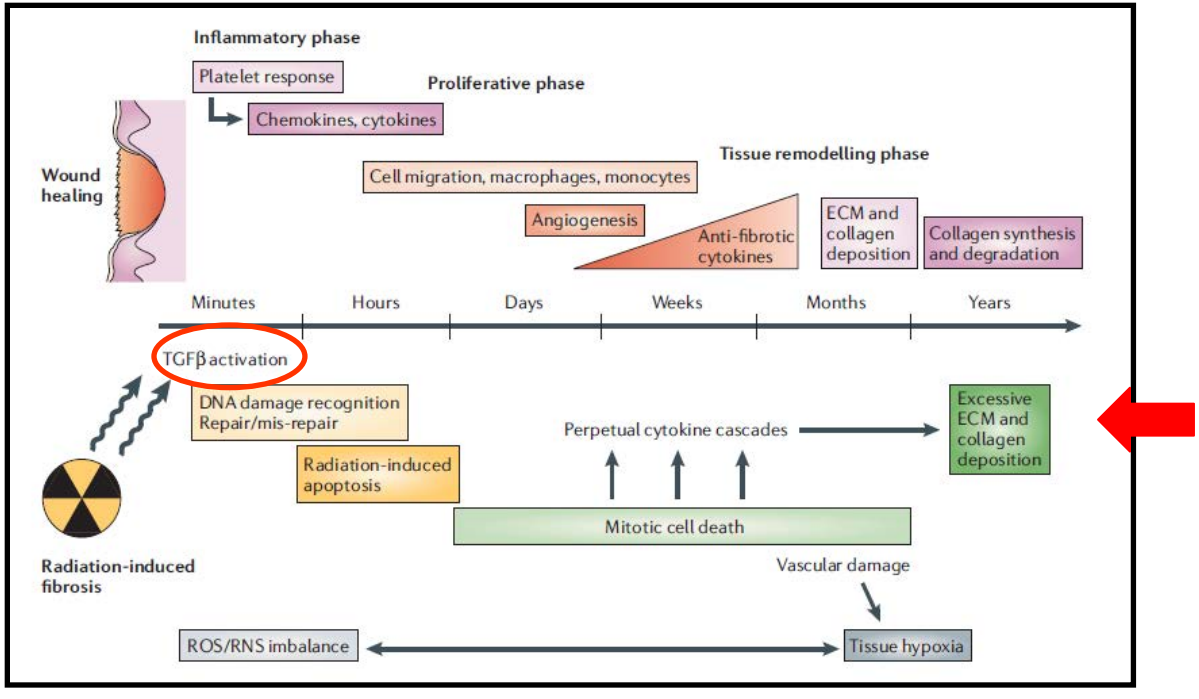
Inflammatory Cytokines	Tumor necrosis factor (**TNF-α**) Interleukin-1 (**IL-1**)
Angiogenesis	Vascular Endothelial Growth Factor (**VEGF**) Basic Fibroblast Growth Factor (**bFGF**) **TNF-α**
Immune Cytokines	**IL-2** **IL-4**
Fibrotic Cytokines	Transforming Growth Factor (**TGF-β**) **bFGF** **IL-6**
Growth Factors	Colony Stimulating Factors (**G-CSF, GM-CSF, IL-3, EPO**) Epidermal Growth Factor (**EGF**), **TGF-α**, **bFGF**

Cytokines and Late Effects – Paradigm Shift

In the past (classical target theory) there was considerable discussion as to whether *parenchymal cell loss* or *vascular damage* was the main reason for late effects

It is more sensible to consider symptoms to result from **a dysregulated healing response**, the manifestations of which may change with time after RT and involve all cellular compartments

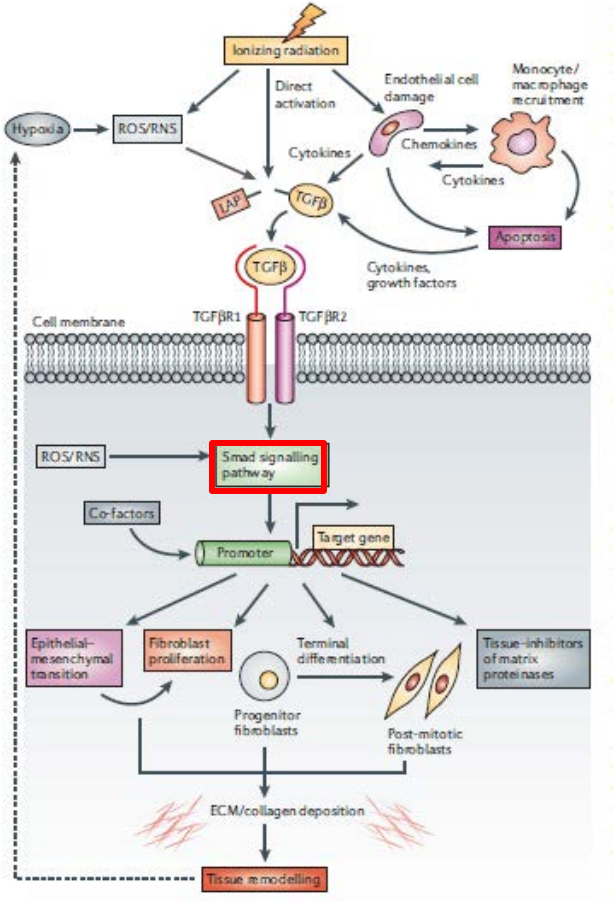
Wound Healing and Radiation-Induced Fibrosis



Radiation activates the whole wound-healing machinery, but in addition, also initiates a series of unique processes

This continued interference with the normal control of wound healing leads to excessive deposition of extracellular matrix and collagen that is characteristic of radiation fibrosis

Key Process in Radiation Fibrosis

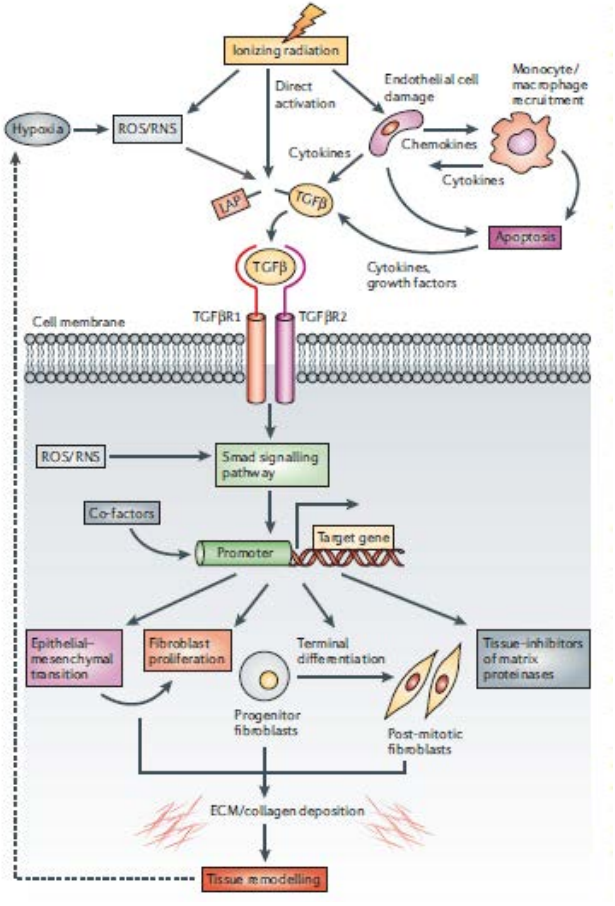


Ionizing radiation directly activates **TGF-β**

Radiation damages endothelial cells, which in turn initiate a cellular response that also leads to the release of pro-fibrotic cytokines, including **TGF-β**

Radiation perturbs the homeostatic control of the reactive oxygen and nitrogen species (**ROS** and **RNS**), which again leads to the activation of **TGF-β** and directly interferes with the Smad signaling pathway

Radiation Fibrogenesis



All these extracellular events activate the **TGF-β** signaling pathway, which in turn produces various transcriptional responses, all of which lead to increased extracellular matrix and collagen deposition

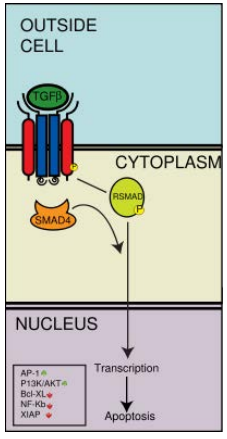
The radiation-induced vascular damage and uncontrolled tissue remodeling can lead to tissue hypoxia, which could be one of the mechanisms perpetuating the fibrogenic response

TGF-β

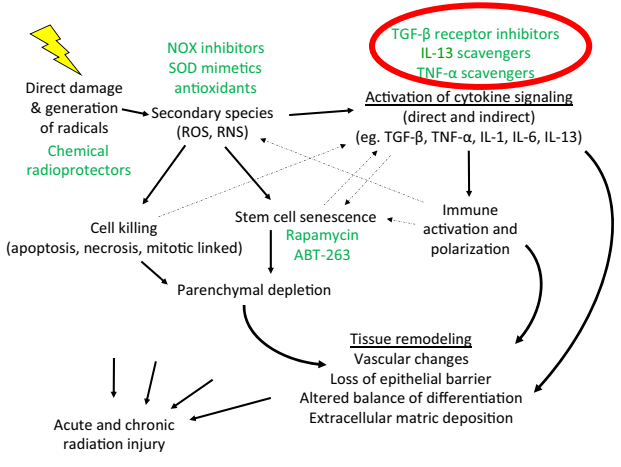
TGF-β is a 25 kDa polypeptide

TGF-β pathway plays a key role in radiation fibrogenesis

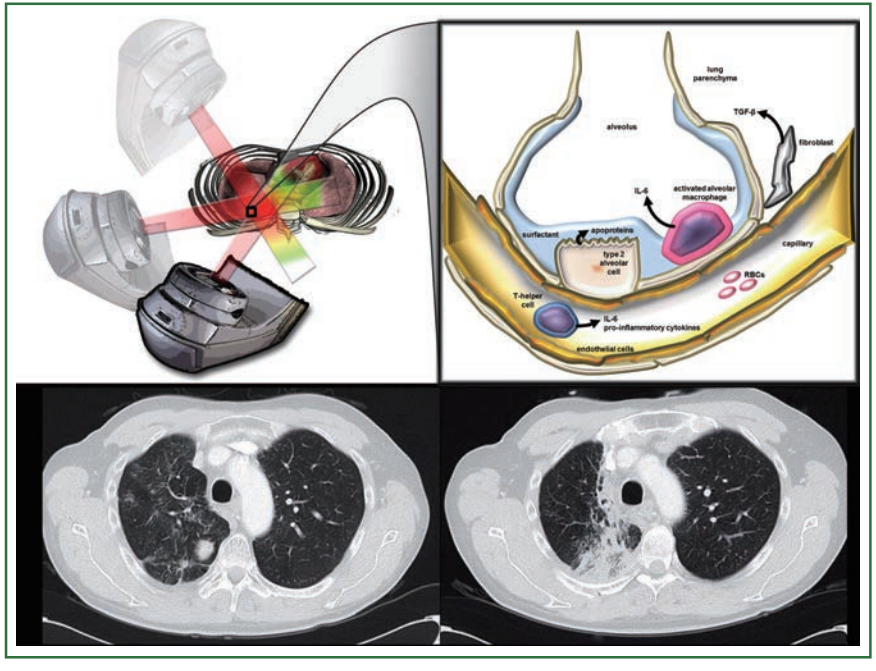
Patients with persistent high serum levels of TGF- β, before and during a course of therapy for lung cancer have a higher risk of developing pneumonitis



It is an attractive target for developing novel pharmaceuticals aimed at preventing or reducing late radiation effects



Mechanism of Pulmonary Toxicity



Radiation therapy is targeted at a right lower lobe lung mass

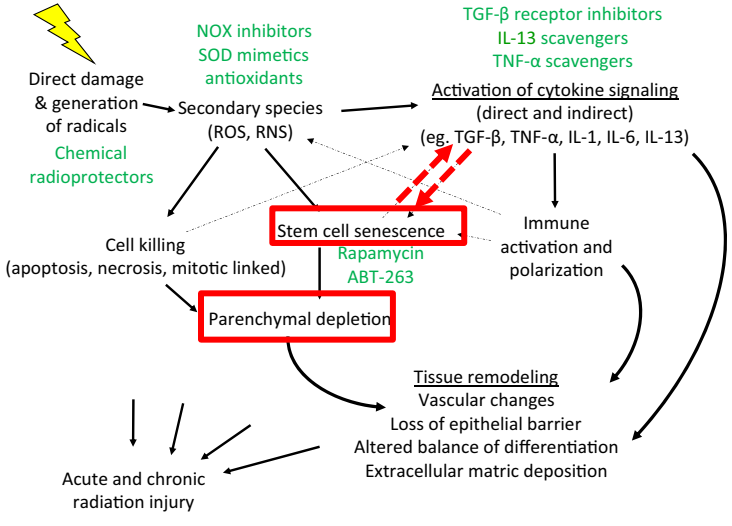
The irradiation of normal tissue during radiotherapy causes certain patients to develop radiation pneumonitis, which is associated with release of **IL-6** from neutrophils, **TGF-β** from fibroblasts, and **apoproteins** in surfactant from type II alveolar cells.

J Thorac Dis 2014;6(4):387-398.

Other Important Cytokines

TNF	Induces proliferation of fibroblasts, inflammatory cells, and endothelial cells and so is **associated with complications** Serum concentrations of TNF correlate with severity of **pneumonitis, hepatic dysfunction, renal insufficiency, and demyelination** Radiation induces TNF via protein kinase C-dependent pathway **Protects hematopoetic cells** and sensitizes tumor cells to radiation A cachexin – responsible for fatigue, anorexia, weight loss, and transient leukopenia
bFGF	Induces endothelial cell growth, inhibits radiation-induced apoptosis, and therefore protects against microvascular damage Produced in response to stress and tends to **reduce late effects**
PDGF-β	Increases damage to vascular tissue
IL-1	A radioprotectant of hematopietic cells by increasing both the shoulder and the D_0 of the survival curve
IL-6	A potent pro-inflammatory cytokine
IL-10	**An anti-inflammatory cytokine**

Stem Cell Senescence



In addition to **parenchymal depletion**, senescent cells secrete a complex mixture of proangiogenic, mitogenic and proinflammatory/immunomodulatory molecules, commonly referred to as the **secretory profile of senescence** (SASP).

Importantly, several molecules of the SASP have been associated with normal tissue injury after irradiation, including **interleukin (IL) 1, IL-6, TGF-β, epidermal growth factor, vascular endothelial growth factor,** and **TNF-α**.

Thus, senescent cells may further enhance or perpetuate normal tissue injury through the elaboration of these molecules with resulting paracrine effects such as inflammation, tissue remodeling, and secondary senescence and cell death.

Question 1

Which one of the following statements is NOT a correct characterization of radiation-induced fibrosis?

A. There is a chronic overproduction of pro-inflammatory cytokines.
B. There is a chronic overproduction of pro-fibrotic cytokines and growth factors.
C. There are chronic increases in reactive oxygen and nitrogen species.
D. Once present, radiation-induced fibrosis is fixed and untreatable.
E. Complex and dynamic interactions between several cell types are involved in the development of fibrosis.

Medical Residents Only

Question 2

Which of the following cytokines or growth factors is *least* likely to be associated with the development of radiation-induced late effects?

A. TNF-α
B. IL-1
C. IL-6
D. TGFβ
E. VEGF

Medical Residents Only

Question 3

Which of the following cytokines is generally considered both anti-inflammatory and immunosuppressive?

A. Interleukin 1
B. Interleukin 6
C. Interleukin 8
D. Interleukin 10
E. Tumor necrosis factor alpha (TNFα)

Other Important Cytokines

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Question 4

Which of the following statements concerning radiation-induced late effects is TRUE?

A. Most late effects develop primarily as a direct result of endothelial killing
B. Most late effects are due to the loss of parenchymal cell clonogens
C. Radiation-induced late effects produce unique pathological response
D. The development of late effects shares many elements in common with both acute and chronic wound-healing responses in normal tissues
E. Once present, late effects are irreversible

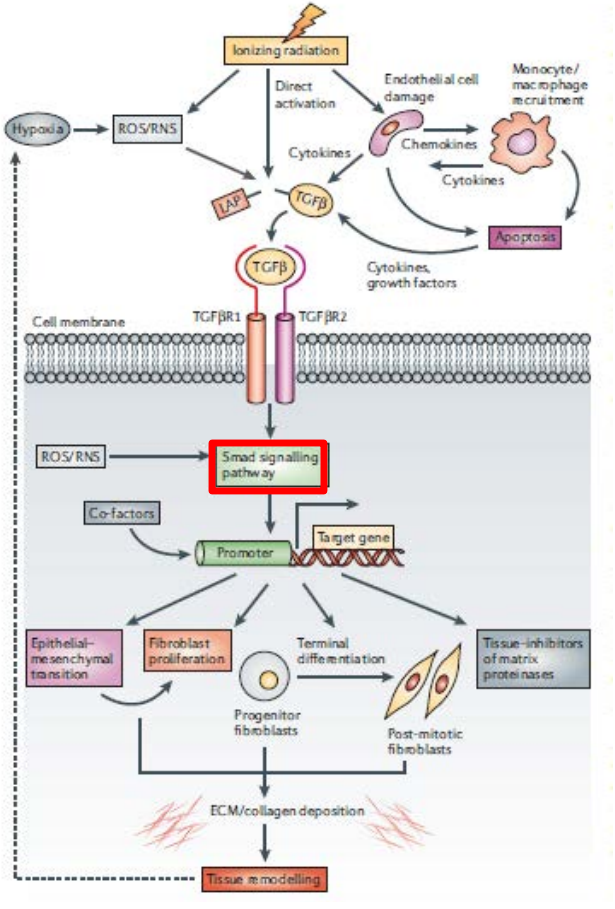
Medical Residents Only

Question 5

Which statement concerning transforming growth factor beta 1 (TGF-β1) and basic fibroblast growth factor (bFGF/FGF2) is TRUE?

A. The pro-fibrotic activities and role in radiation-induced fibrosis of TGF-β1 are mediated by SMAD3
B. Stimulation of TGF-β1 synthesis should improve the therapeutic ratio
C. bFGF has been shown to sensitize endothelial cells to radiation-induced apoptosis
D. The serum concentration of TGF-β1 always decreases following lung irradiation
E. TGF-β1 promotes the radiation-induced inflammatory response

Key Process in Radiation Fibrosis



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TGF-β

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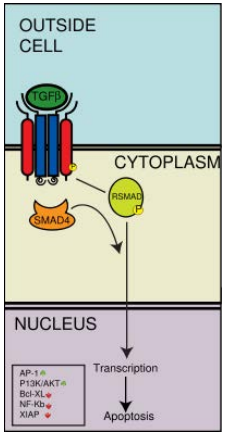

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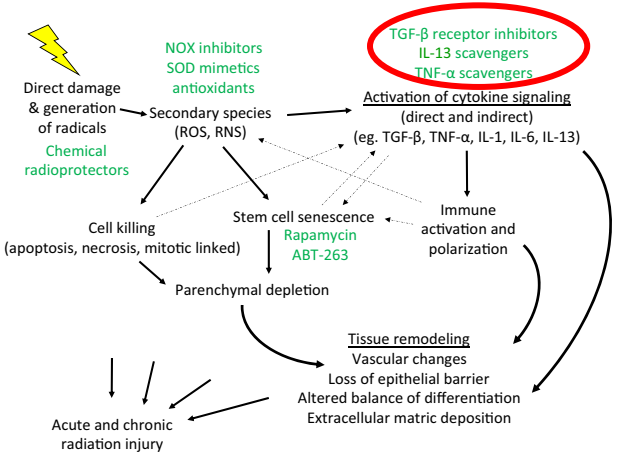

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Question 6

Transforming growth factor-beta (TGF-β) protein levels in the plasma of patients exposed to radiotherapy has been extensively correlated to which of the following?

A. Acute radiation lung injury
B. Acute radiation dermatitis
C. Radiation mucositis
D. Radiation induced gliosis
E. Leukemia

Medical Residents Only

Question 7

Regarding radiation fibrosis, which of the following statements is TRUE?

A. Fibrosis occurs in only a select few tissues and organs

B. The severity of late fibrosis can be predicted based on radiotherapy treatment parameters and is NOT tissue-dependent

C. Radiation fibrosis is typically inhomogeneous; some affected areas could be densely collagenous whereas others may have only a few fibrous bands, despite both areas having received the same dose

D. Irradiated bone marrow commonly develops regions of fibrosis

E. Increases in collagen deposition are associated with down-regulation of fibrogenic cytokines.

Role of Tumor Microenvironment

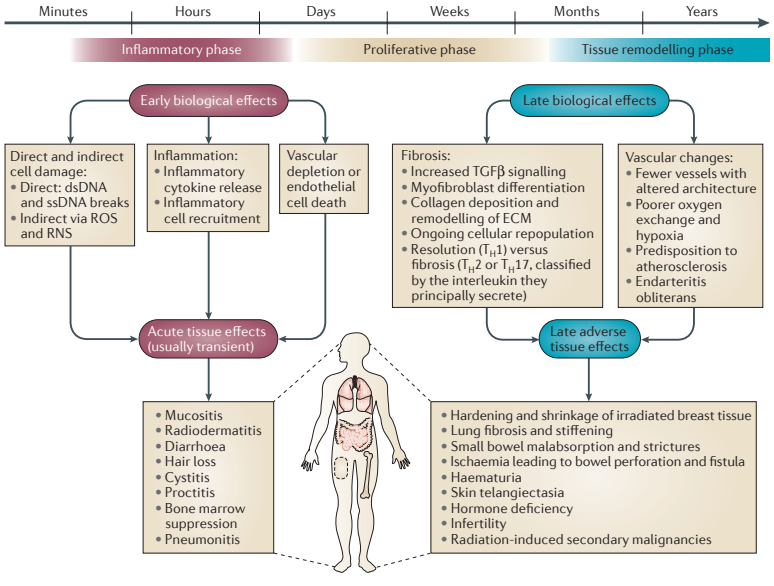
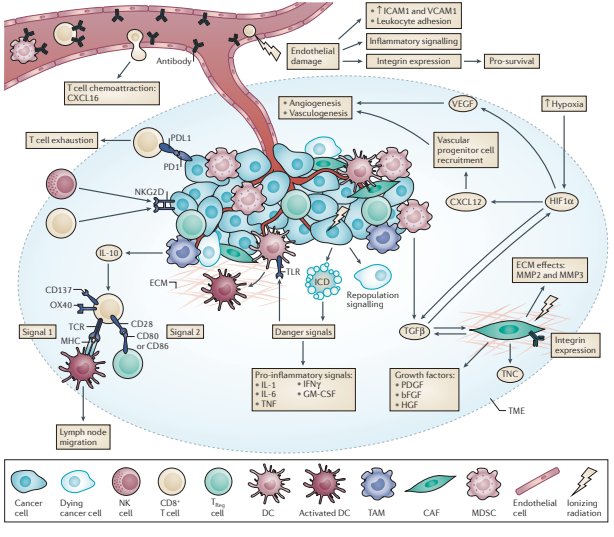


Figure 2 | **Biological effects and normal tissue toxicity after radiotherapy.** Early biological events cause acute tissue effects, which are usually transient and normally resolve within 3 months of completing treatment. These events also result in more protracted biological effects that can manifest in tissues as late biological effects and secondary malignancies. Higher radiation dose per fraction seems to increase the severity of late adverse effects. dsDNA, double-stranded DNA; ECM, extracellular matrix; ROS, reactive oxygen species; RNS, reactive nitrogen species; ssDNA, single-stranded DNA; TGFβ, transforming growth factor-β; T_H, T helper cell.

The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence

Holly E. Barker, James T. E. Paget, Aadil A. Khan and Kevin J. Harrington



Nature Reviews 2015; Vol 15(7): 409-424

Recommended for medical residents only

Outlines

- Cells and Tissues
- Early (Acute) and Late Effects
- Functional Subunits in Normal Tissues
- The Volume Effect in Radiotherapy: Tissue Architecture
- Radiation Pathology of Tissues
  - Casarett's Classification
  - Michalowski's H- and F-Type Populations
- Growth Factors
- **Specific Tissues and Organs**
- Grading of Late Effects

Mechanism

Organ by organ clinical observation

Sensitivities of Selected Organs and Tissues

- **Tolerance doses** for most organs and tissues have been compiled by ***Rubin and Cassarett*** (1968) and ***Emami*** (1991)
- They are empirically derived in humans and take into account many factors that are not necessarily radiobiologically determined, for example medicolegal, psychological, and socioeconomic considerations

Sensitivities of Selected Organs and Tissues

- These are expressed as **$TD_{5/5}$**, which is the dose for 5% complication within 5 years of treatment
- The steepness of the dose response curve is represented by the dose for 50% complication **$TD_{50/5}$**
- The volume effect is represented by the $TD_{5/5}$ and $TD_{50/5}$ values for different fractions of the organ irradiated

Emmi Table

	INJURY	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	FIELD SIZE
Class I organs				
Bone marrow	Aplasia, pancytopenia	2.5	4.5	Whole segment
Liver	Acute and chronic hepatitis	30 50	40 55	Whole 1/3
Intestine	Obstruction, perforation, fistula	40 50	55 60	Whole 1/3 or 1/2
Stomach	Perforation, ulcer, hemorrhage	50 60	65 70	Whole 1/3
Brain	Infarction, necrosis	45 60	60 75	Whole 1/3
Spinal cord	Infarction, necrosis	47 50	— 70	20 cm 5 or 10 cm
Heart	Pericarditis and pancarditis	40 60	50 70	Whole 1/3
Lung	Acute and chronic pneumonitis	17.5 45	24.5 65	Whole 1/3
Kidney	Acute and chronic nephrosclerosis	23 50	28 45	Whole 1/3 or 1/2

QUANTEC – IJROBP 2010

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

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RANDALL K. TEN HAKEN, PH.D.,‡ LOUIS S. CONSTINE, M.D.,§ AVRAHAM EISBRUCH, M.D.,‡
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The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review summarizes the currently available three-dimensional dose/volume/outcome data to update and refine the normal tissue dose/volume tolerance guidelines provided by the classic Emami *et al.* paper published in 1991. A "clinician's view" on using the QUANTEC information in a responsible manner is presented along with a description of the most commonly used normal tissue complication probability (NTCP) models. A summary of organ-specific dose/volume/outcome data, based on the QUANTEC reviews, is included.

Nice Review Articles

Seminars in Radiation Oncology

Volume 27, Issue 4

2017-9-30, Pages 299-392

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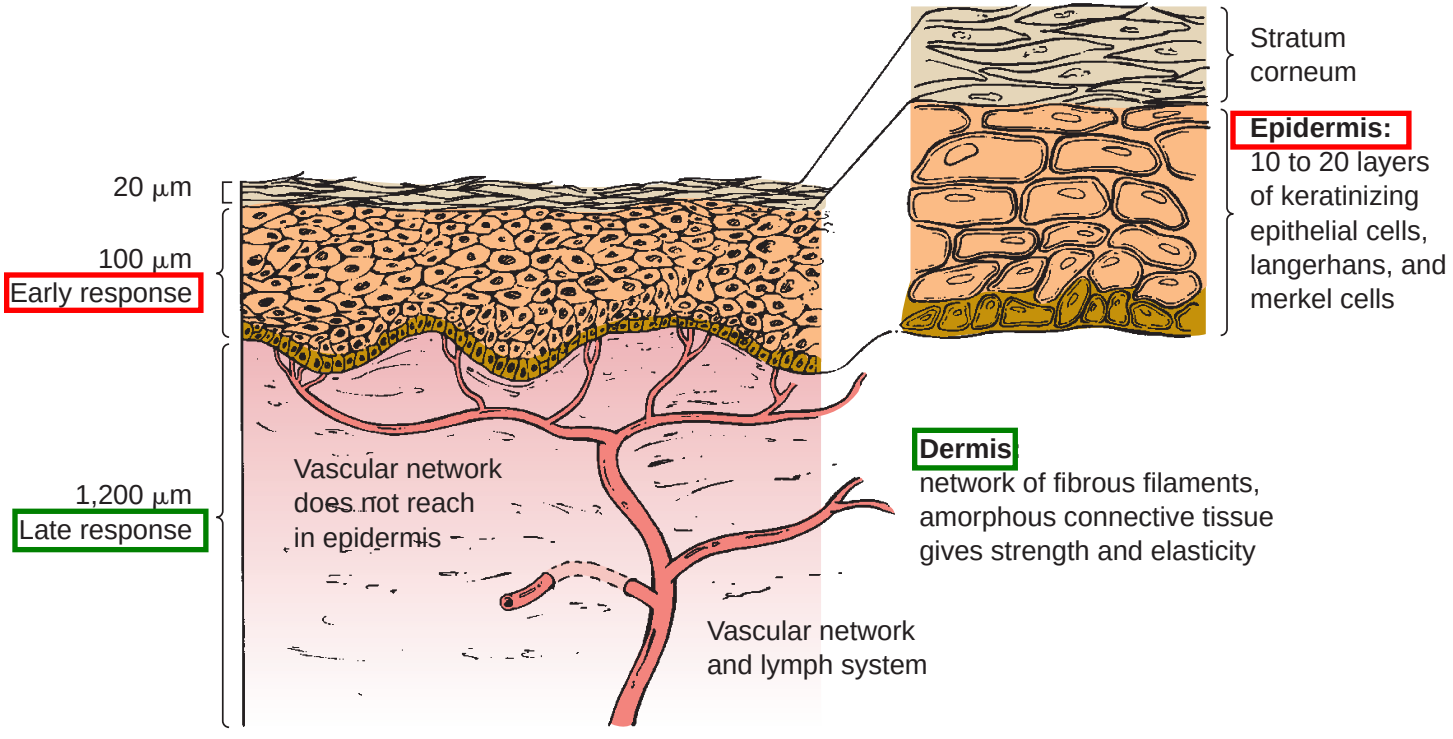
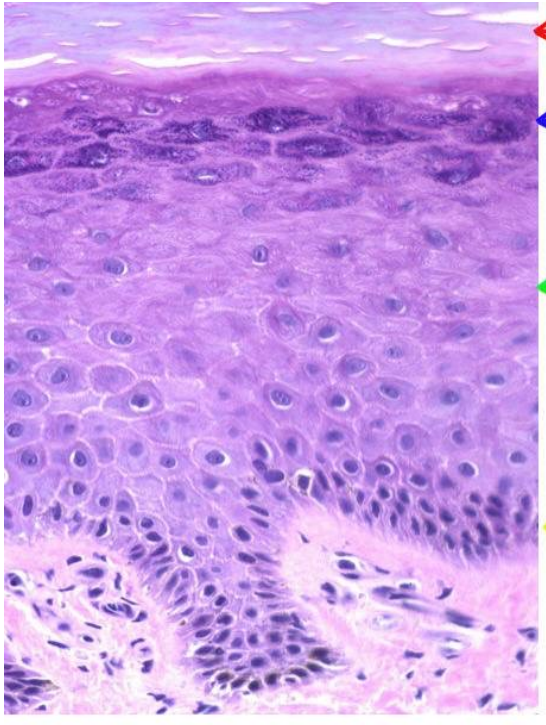
Skin


20 μm
100 μm
Early response
1,200 μm
Late response
Vascular network
does not reach
in epidermis
Vascular network
and lymph system
Stratum
corneum
Epidermis:
10 to 20 layers
of keratinizing
epithelial cells,
langerhans, and
merkel cells
Dermis:
network of fibrous filaments,
amorphous connective tissue
gives strength and elasticity

Skin

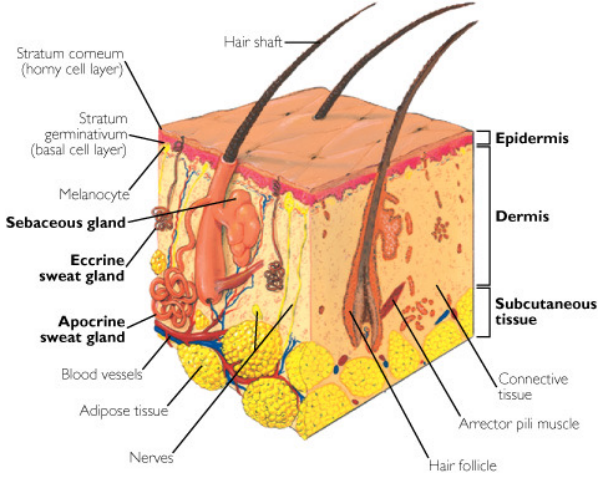
14 days



Target cells for radiation damage
Basal cells (= stem cells)

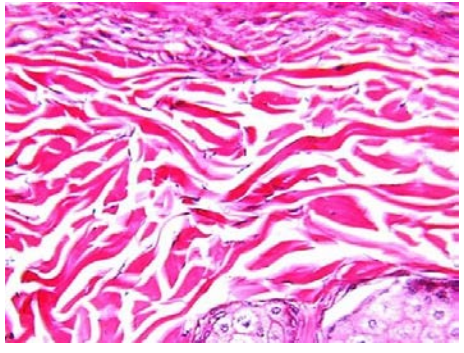
Epidermis H-type Tissue

Skin



Dermis consists of a dense network of collagen produced by scattered fibroblasts

Contains vasculature and lymphatics



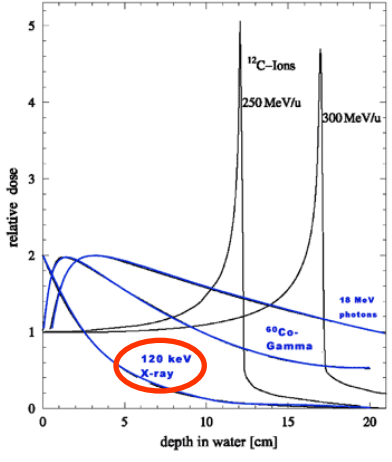
Dermis F-Type Tissue

The vasculature plays a major role in the radiation response

Target cell = fibroblasts & vascular endothelial cells

Skin

Becquerel & P. Curie 1901



During orthovoltage era, skin was frequently dose-limiting

Erythema

↓

Dry desquamation

↓

Moist desquamation

} Due to depletion of basal cell population

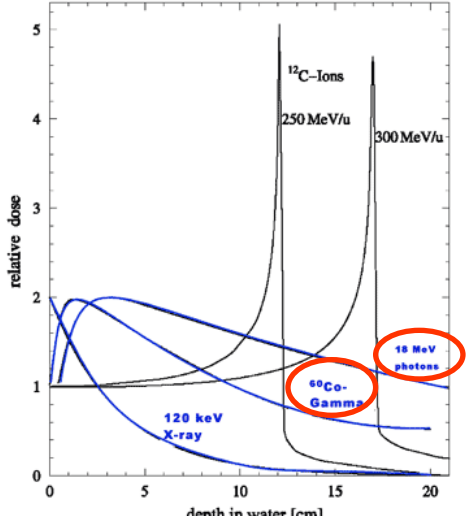
At lower doses, islets of skin may regrow from surviving stem cells

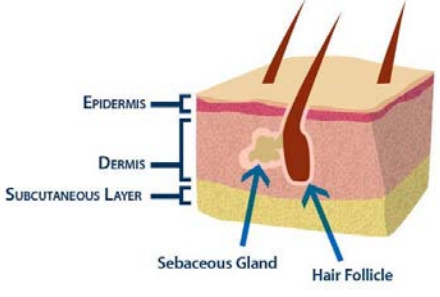
At higher doses, at which there are no surviving stem cells within the area treated, healing must occur migration of cells from outside the treated area

Reepithelialization takes place after 6-8 weeks

Skin

With megavoltage x-ray, D_{max} occur at depths





Epidermis

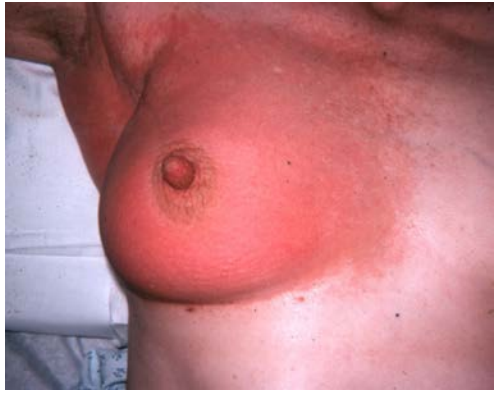
Epidermal reactions usually are limited to dry desquamation and increased pigmentation
60 Gy in fractionated dose are tolerated readily because stem cell regrowth can occur during this time

Dermis

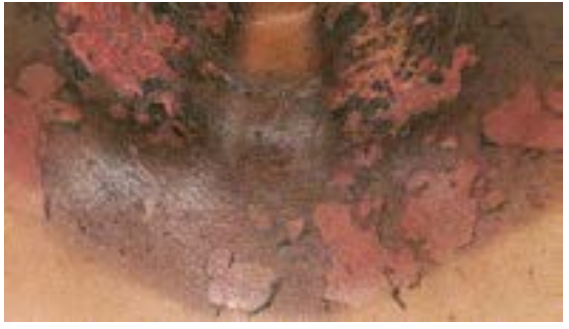
Late damage may occur even in the absence of early reactions in the epidermis

Late effects include fibrosis and telangiectasia (vascular injury)

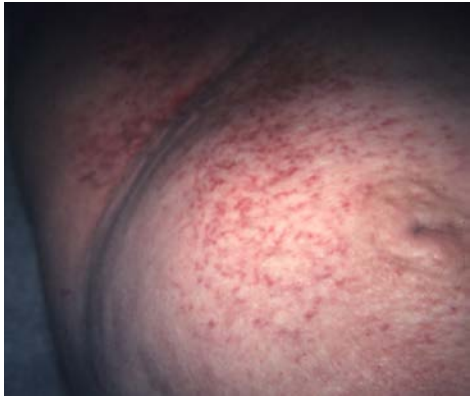
Skin



Erythema



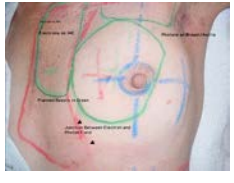
Confluent desquamation

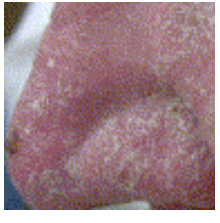


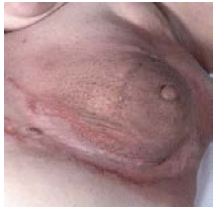
Telangiectasia

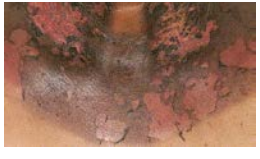
Dermatitis – Common Toxicity Criteria

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases, moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

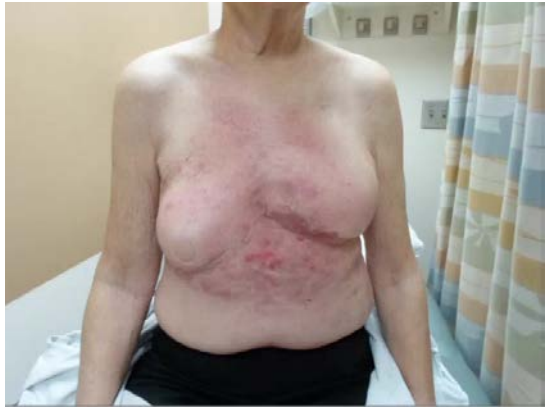




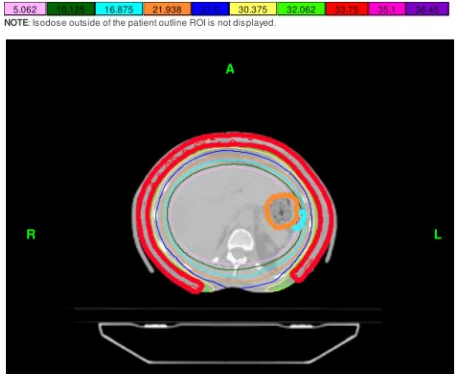


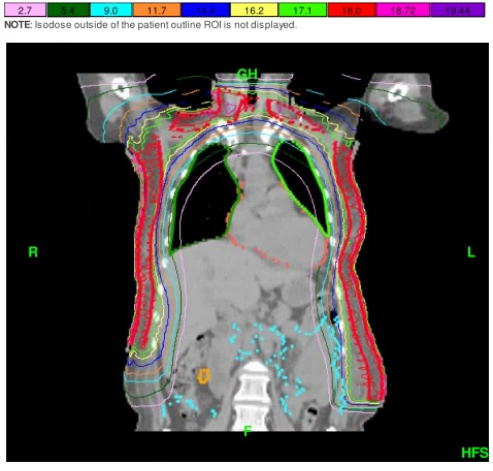


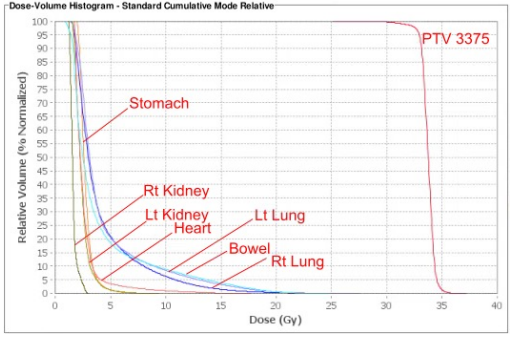
Patient PN



Metastatic Breast Cancer







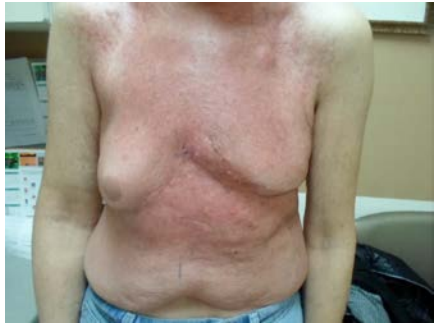
3375 cGy/15 fx

+

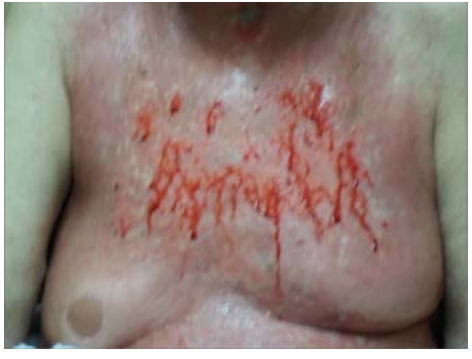
1125 cGy/5 fx

Concurrent Xeloda

Patient PN



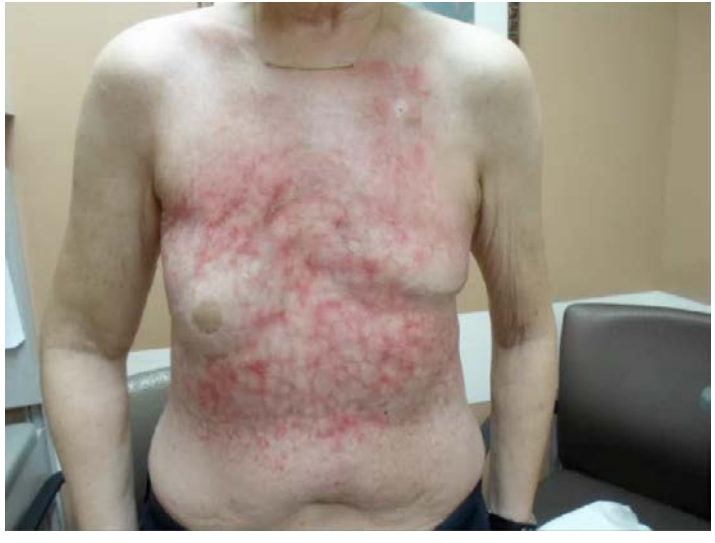
Last day of Treatment



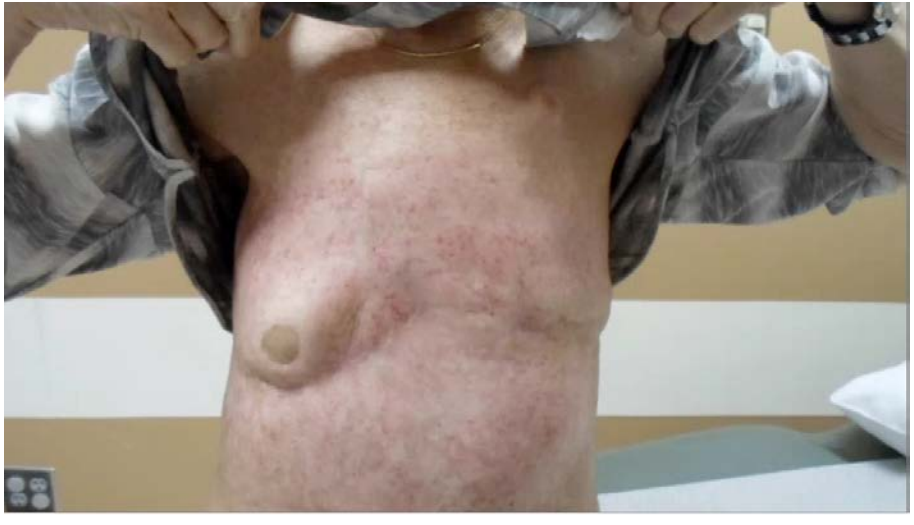
8 days later

- Increase Oxycontin to 30 mg BID
- Continue with oxycodone for breakthrough pain
- Silvadene and Cutecerin BID
- She may bathe herself once or twice a day as long as the water is lukewarm temperature
- Clindamycin 300 mg QID x 10 days
- Benadryl prn for presumed allergic reaction
- 2.5% HC cream for the back and shoulder (itchy area)

Patient PN



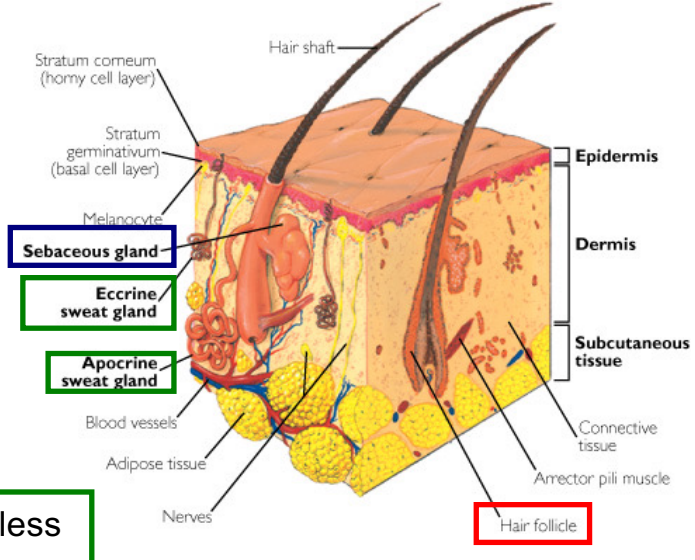
2 months later



8 months later

Skin Appendages

Sebaceous glands are as sensitive as hair



Sweat glands are less radiosensitive

Death of germinal cells results in hair dysplasia
Epilation occurs during the 3rd week
Regrowth may occur after 1-3 months

Skin

TABLE 20.2 A Compilation of Tissue and Organ Sensitivities

		Tolerance dose		
	Injury	**$TD_{5/5}$, Gy**	**$TD_{50/5}$, Gy**	**Field Size**
Skin	Acute and chronic dermatitis, telangiectasia	55	65	100 cm^2

Based on a combination of Rubin P, Casarett GW: Clinical Radiation Pathology, vol 1. Philadelphia, WB Saunders, 1968; and Emami et al., 1991, with permission.
Table compiled by Dr. Richard Miller. The figures in this table are a guide only.

Tolerance dose – dose that produces an acceptable probability of treatment complication

$TD_{5/5}$ = tolerance dose for 5% complications in 5 years

$TD_{50/5}$ = tolerance dose for 50% complications in 5 years

Effects of Fluoroscopic Exposures on the Skin

Early Effects

Epilation

Threshold – 3 Gy (temporary); 7 Gy (permanent)
Time of onset – 3 wks
Mechanism – reduction or destruction of the reproductive integrity of germinal cells or the matrix of the hair follicles

Dry Desquamation

Threshold – 14 Gy
Time of onset – 4 wks
Mechanism – depopulation of clonogenic cells in the epidermis
Healing requires the repopulation of basal cells from surviving clonogens

Effects of Fluoroscopic Exposures on the Skin

Early Effects

Moist Desquamation

Threshold – 18 Gy
Time of onset – 4 wks
Mechanism – depopulation of clonogenic cells in the epidermis
Healing requires repopulation of surviving clonogens or migration of clonogens from the edges of the irradiated area

Effects of Fluoroscopic Exposures on the Skin

Late Effects

Effect	Threshold	Time of Onset
Dermal atrophy (1st phase)	10 Gy	> 12 wks
Dermal atrophy (2nd phase)	10 Gy	> 52 wks
Telangiectasis	10 Gy	> 52 wks
Delayed necrosis	12 Gy?	> 52 wks
Mechanism – damage to the vasculature of the dermis		
Skin cancer	not known	> 15 yrs

Effects of Fluoroscopic Exposures on the Skin

Table 1. Skin effects after a single exposure[8].

Effect	Acute exposure threshold (Gy)	Onset	Peak
Temporary epilation	3	~3 weeks	
Permanent epilation	7	~3 weeks	
Early transient erythema	2	~ hours	~24 hours
Main erythema	6	~10 days	~2 weeks
Dry desquamation	10	~4 weeks	~5 weeks
Moist desquamation	15	~4 weeks	~5 weeks
Secondary ulceration	20	>6 weeks	
Late erythema	15	~6–10 weeks	
Dermal necrosis	18	>10 weeks	
Telangiectasia	12	>52 weeks	

Geleijins & Wondergem 2005; Radiation Protection Dosimetry 114:121-125

Question 1

Radiation-induced epilation occurs before dermatitis because:

A. Basal cells in the epidermis have shorter cell cycle times than the germinal matrix of the hair bulb
B. Cells in the germinal matrix of the hair bulb have shorter cell cycle times than the basal cells of the epidermis
C. Of the exquisite sensitivity of sebaceous glands
D. Of vascular endothelial cell death in the connective tissue at the distal end of the hair follicle
E. Of keratin synthesis inhibition in the hair follicle

Question 2

Which of the following series of skin reactions match the acute single dose and time to elicit the reaction?

A. Temporary erythema - 1 Gy - 7 days
B. Permanent epilation - 7 Gy - 3 months
C. Moist desquamation - 3 Gy - 4 weeks
D. Dry desquamation - 14 Gy - 1 week
E. Temporary epilation - 3 Gy - 3 weeks

Effects of Fluoroscopic Exposures on the Skin

Table 1. Skin effects after a single exposure[8].

Effect	Acute exposure threshold (Gy)	Onset	Peak
Temporary epilation	3	~3 weeks	
Permanent epilation	7	~3 weeks	
Early transient erythema	2	~ hours	~24 hours
Main erythema	6	~10 days	~2 weeks
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Moist desquamation	15	~4 weeks	~5 weeks
Secondary ulceration	20	>6 weeks	
Late erythema	15	~6–10 weeks	
Dermal necrosis	18	>10 weeks	
Telangiectasia	12	>52 weeks	

Geleijins & Wondergem 2005; Radiation Protection Dosimetry 114:121-125

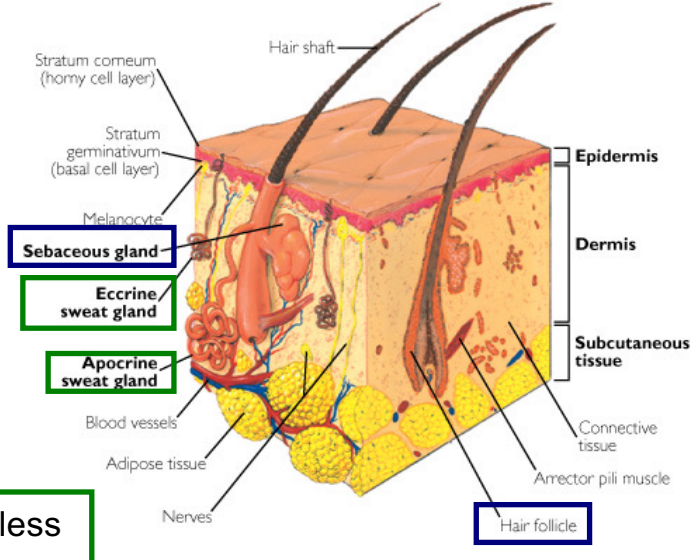
Question 3

Which of the following statements is CORRECT? Following acute irradiation of the skin:

A. Epilation and the loss of sebaceous gland secretions follow similar time courses
B. The first visible reaction is moist desquamation, typically observed within 24 hours of irradiation
C. Epilation is only observed at doses much greater than those that cause the main wave of erythema observed at about one week
D. Pigment changes are typically seen within days due to the high proliferation rate of melanoblasts
E. It is usually possible to predict the extent of late reactions based on the severity of early reactions

Skin Appendages

Sebaceous glands are as sensitive as hair



Sweat glands are less radiosensitive

Death of germinal cells results in hair dysplasia
Epilation occurs during the 3rd week
Regrowth may occur after 1-3 months