Early and Late deterministic effects of Ionizing Radiation

Concepts and variables

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Outline:

- Introduction deterministic effects
- Early responding tissues, and recovery of damage
- Late responding tissues
- Consequential late effects
- Factors that influence the radiation sensitivity of tissues/organs

Deterministic effects; tissue reactions

Deterministic effect: *An effect for which the severity of the effect in affected individuals varies with the dose and for which a threshold exists.*

Radiobiology for the Radiologist, 7th edition 2012, Hall & Giaccia

ICRP INTERNATIONAL COMMISSION ON RADIOLOCICAL PROTECTION

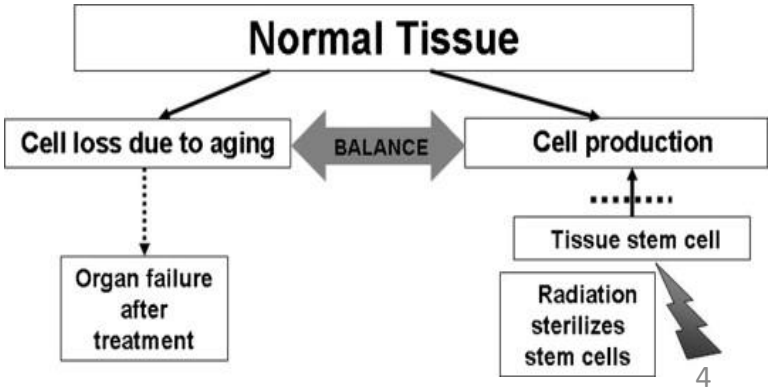
- The Commission issued new recommendations on radiological protection in 2007 (ICRP, 2007), which formally replaced the Commission's 1990 Recommendations (ICRP, 1991a). The revised recommendations included consideration of the detriment arising from **non-cancer effects** of radiation on health. These effects, previously called **deterministic effects**, are now referred to as **tissue reactions** because it is increasingly recognised that some of these effects are not determined solely at the time of irradiation but can be modified after radiation exposure.

Statement on Tissue Reactions (Approved by the Commission on April 21, 2011)

Deterministic effects; tissue reactions

- Are relevant in case of radiation accidents
- Are often seen as a side effect of radiotherapy
- May also occur as a result of diagnostic procedures (i.e. interventional radiology)
- May occur when dose limits have been violated

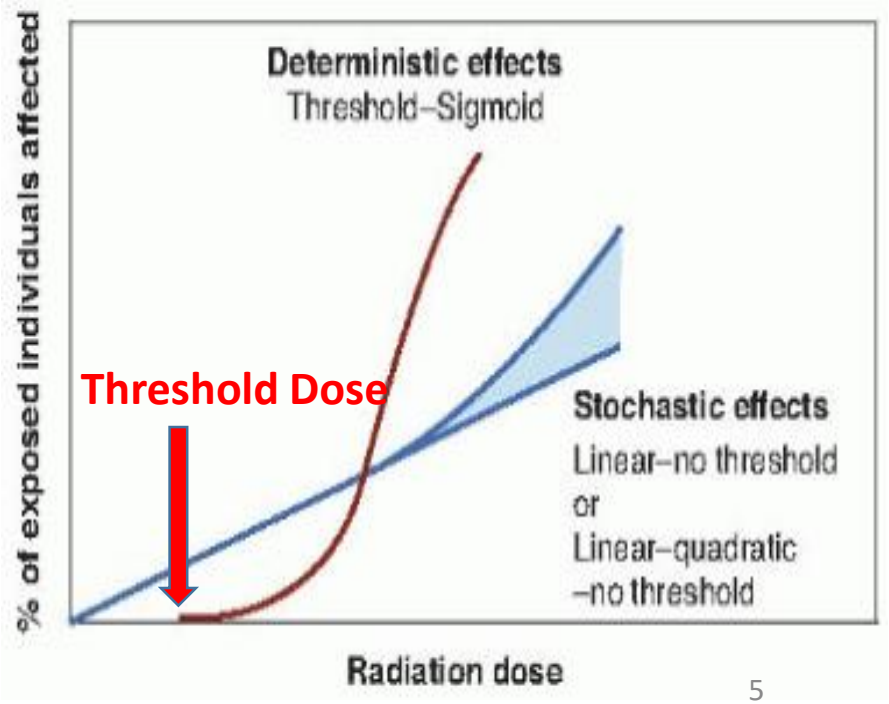
Deterministic effects *are caused by significant tissue /organ damage ("extra" cell death instead of normal cell turn-over rate)*



Dose response relations

Deterministic effects *(or tissue reactions)* of ionizing radiation are related directly to the absorbed radiation dose and the severity of the effect increases as the dose increases

- A deterministic effect typically has a **threshold** below which the effect does not occur
- The shape of the dose response-curve is **sigmoid**
- The steepness of the dose-response curves differs from tissue to tissue



Early versus Late responding tissues

Acute/early reactions

- Oral mucosa
- Intestinal mucosa
- Skin (epidermis)
- Bone marrow
- Testis
- Parotid (salivary) gland

Late (chronic) reactions

- Skin (dermis)
- Vasculature
- Connective tissue
- Spinal cord
- Lung
- Kidney
- .....

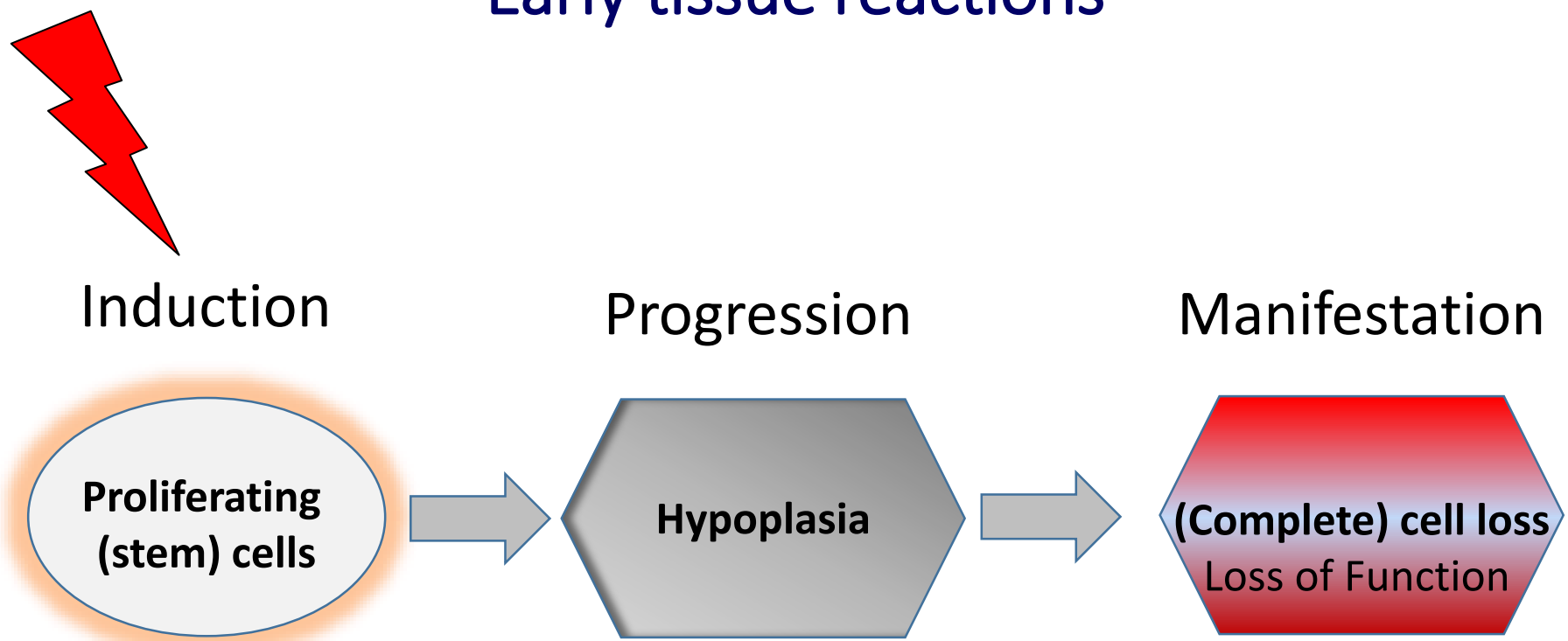
90 days

Early (Acute) Effects

Common features of Acute responding tissues

- Occur within weeks to days after irradiation in tissues with a rapid rate of cell "turn-over". Result from DEATH of a large number of *(functional)* cells; "Target cells" have rapid "turn-over" and high mitotic activity
- Cell loss eventually leads to FUNCTION LOSS
- Function loss, in general, is TRANSIENT *(reversible)*
- Affected tissues/organs RECOVER and their functions are restored completely because of rapid proliferation of surviving stem cells or by recruitment from other sites *(non-irradiated/non-damaged areas)*

Early tissue reactions



Maximum severity:	*dose dependent*
Latent time to effect:	*independent from dose* *dependent from lifespan of functioning cells*

Tissue reactions

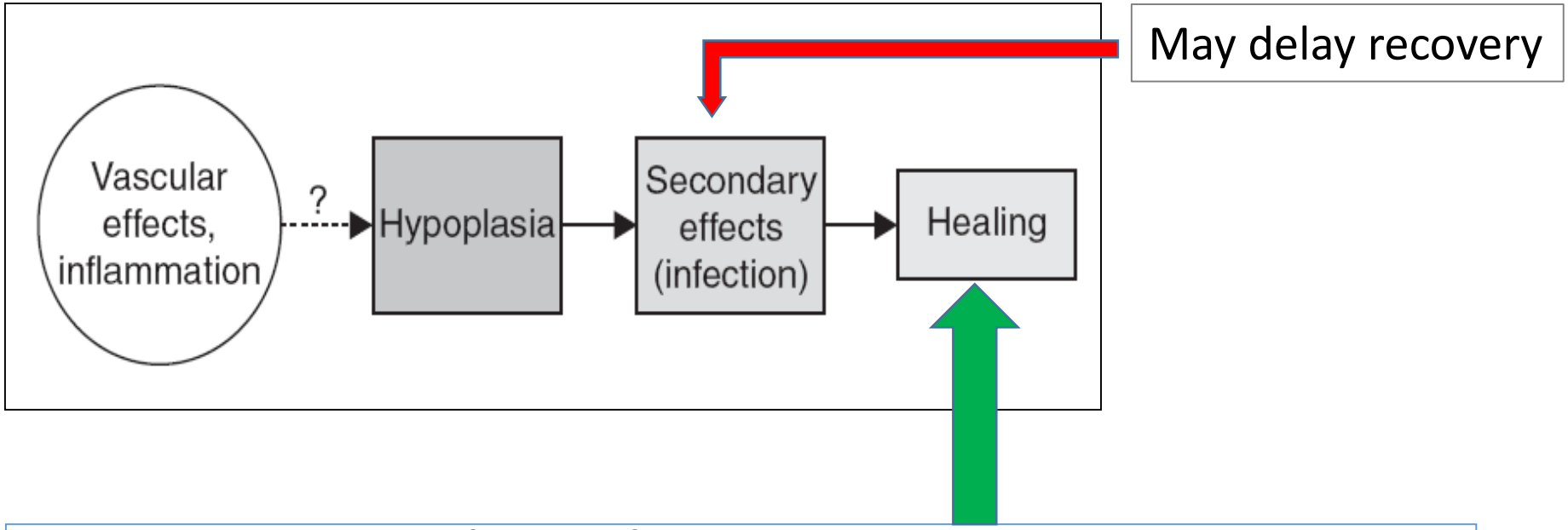
Acute / early responding tissues

Tissue	Target cells	Threshold dose (acute single exposure)	Latency
Epidermis:	Basal cells	>15 Gy	2 - 3 weeks
GI-tract:	Crypt cells	5 - 10 Gy	< weeks
Bone marrow:	BM stem cells	0.5 - 2 Gy	0.5 – 2 weeks
Testes:	Spermatogonial SC	0.15 (3.5) Gy	2 - 4 weeks

Latent time to effect: ~~— dose~~

— tissue biology

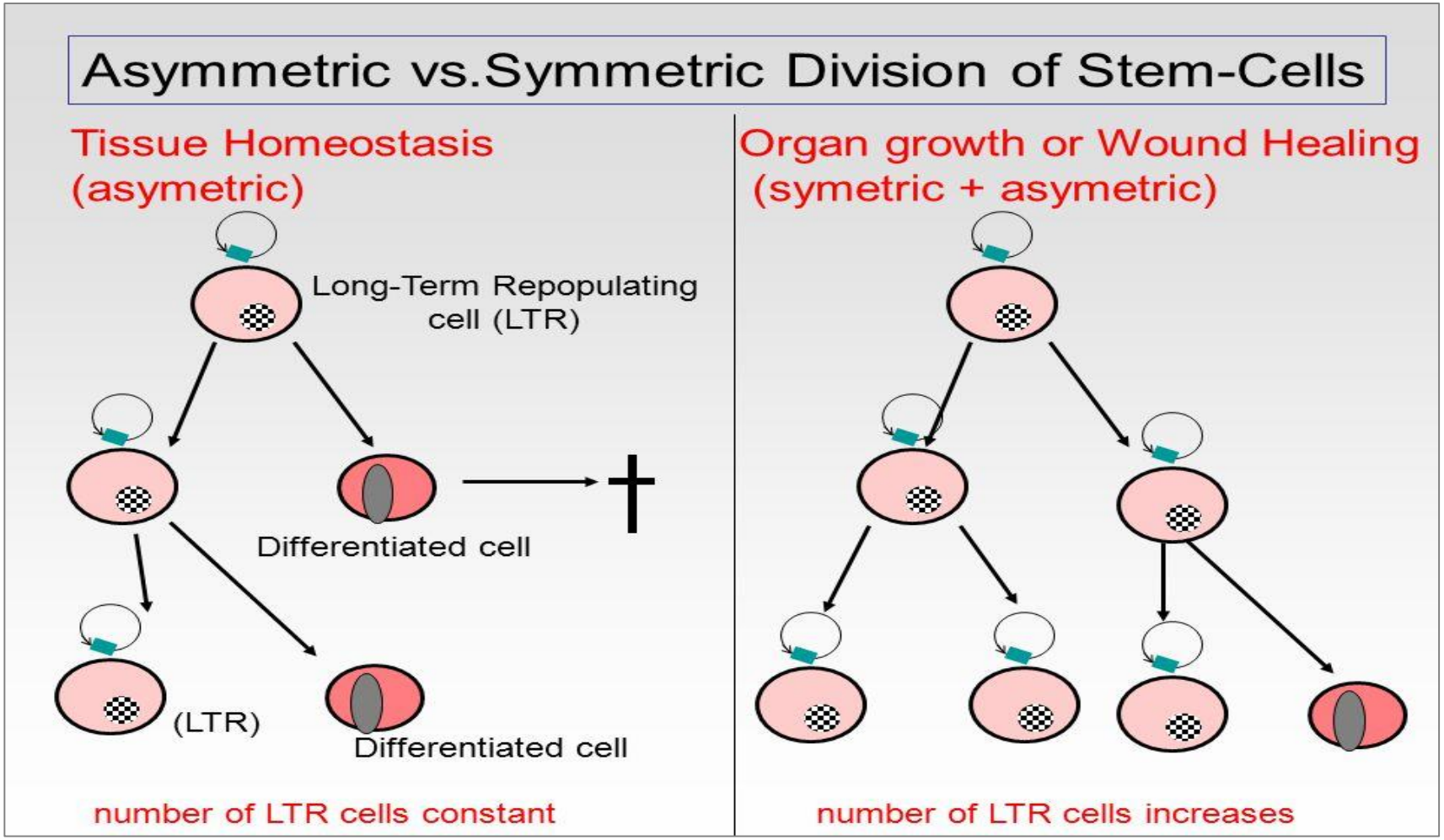
Early tissue reactions; healing/recovery



Recovery of function (healing) depends on:

- Number of surviving stem cells *(depending on volume & dose)*
- Turn over times of the stem cells *(shortening cell cycle?)*
- (A)symmetric division of stem cells
- Recruitment *(cells capable of dividing, entering the cycling pool)*

Healing/recovery by (rapid) proliferation

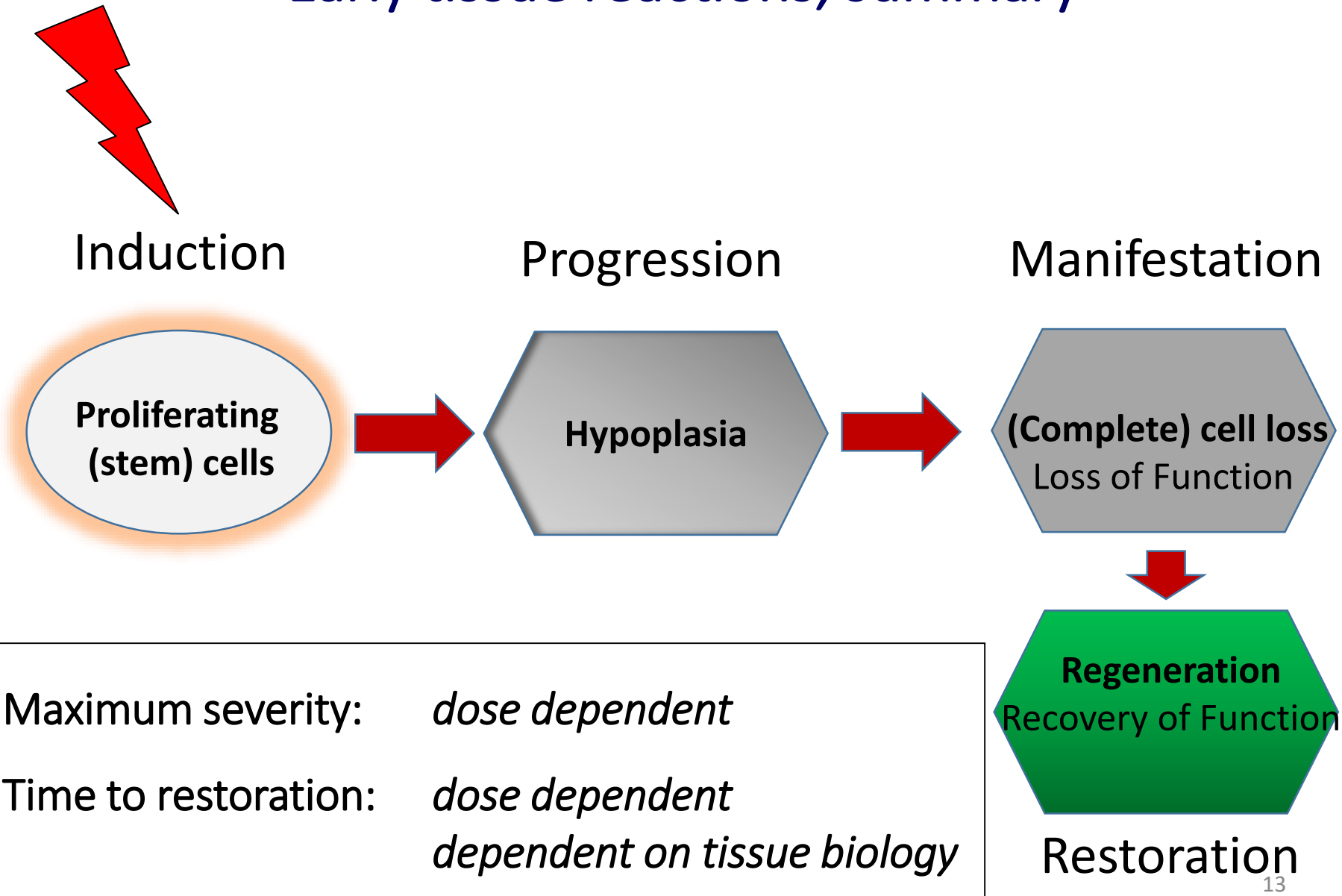


Relation between manifestation & recovery of damage (renewal time)

Tissue	Cell type	"turn-over" time	Manifestation of damage	
			damage	*recovery*
Oral mucosa	*basal cell*	2 - 3 days	few days	1-2 weeks
Bone Marrow	*stem cell*	~ 5 days	about a week	2-4 weeks
Skin; Epithelium	*basal cell*	10 - 12 days	about 3 weeks	1-2 months

**) minimal - partial (functional) recovery*

Early tissue reactions; summary



Maximum severity:	*dose dependent*
Time to restoration:	*dose dependent* *dependent on tissue biology*

Generic Late (chronic) Effects

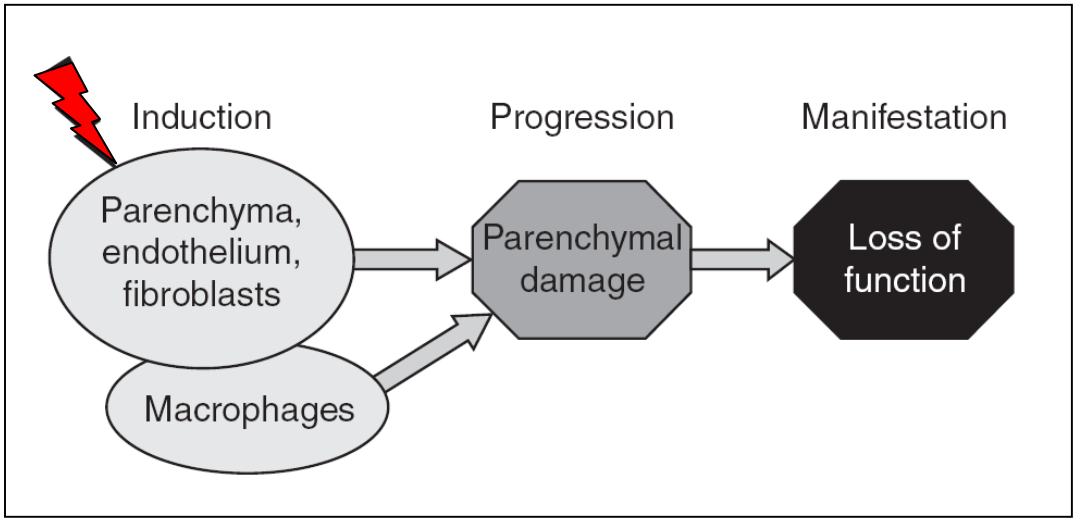
- Occur *(very)* late after irradiation *(months – years)*
- Tissues with slow cell turn-over rate
- Result of COMPLEX INTERACTION of different mechanisms including inflammation, development of fibrosis, vascular alteration and slow cellular depletion
- Are PERSISTANT *(CHRONIC)* or even PROGRESSIVE: Organ function may improve during a certain period but will deteriorate later

Late responding tissues

Tissue	Target cells	Threshold dose *(acute single exposure)*	Latency Time
Dermis	myofibroblasts, endothelium	> 10 Gy	3 – 6 months
Spinal Cord	glia cells, endothelium	~ 15 Gy	0.5 – 2 years
Lung	pneumocyte type II	7 - 10 Gy	0.5 – 2 years
Eye lens	lens epithelium	0.5 Gy	many years

No recovery: Tissue response is irreversible *(chronic)* and *(very often) progressive*

Example of generic Late responding Tissues



- Late effects appear after delay of months or years. These effects occur predominantly in slowly proliferating tissues. Target cells: parenchymal cells, vascular endothelial cells, mesenchymal cells *(fibroblasts)*

Latency period shortens with increasing Dose
Severity is dependent on Dose

Consequential Late Effects (CLE)

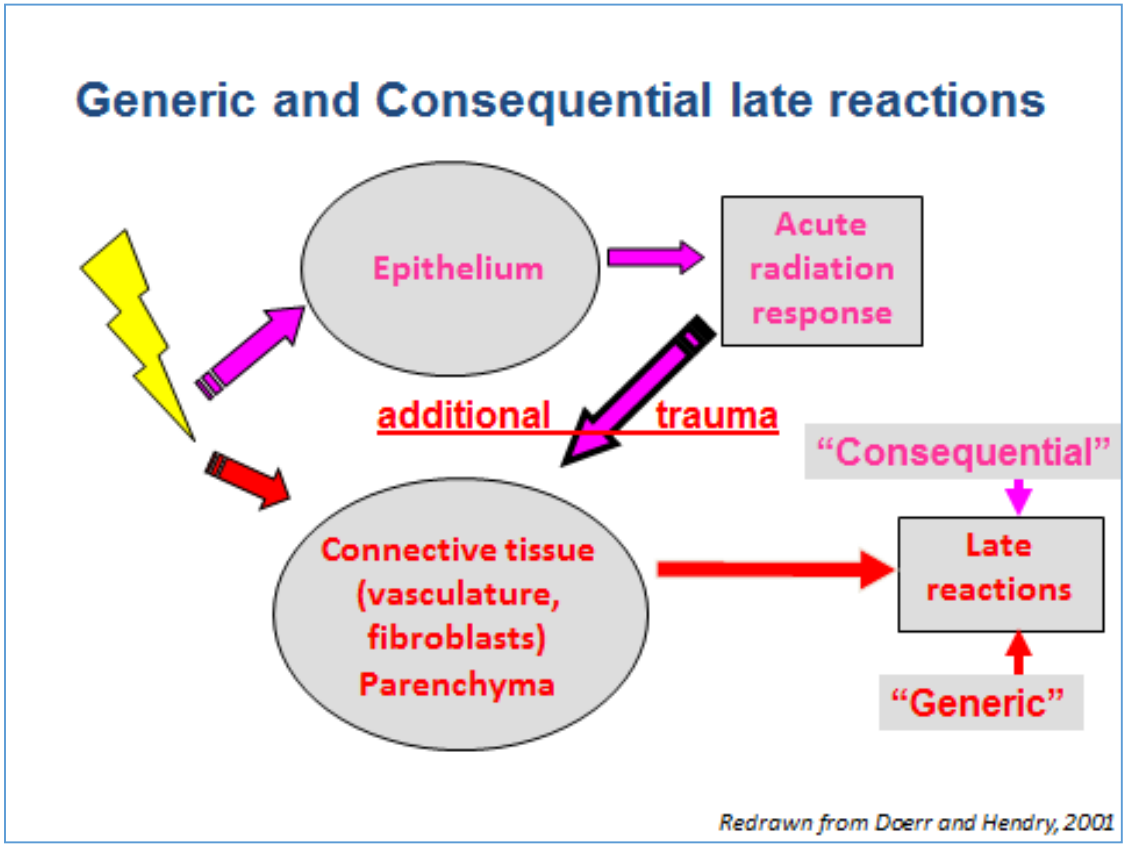
- Occur when EARLY effects are so severe that sufficient HEALING does not take place *(persistent severe early damage)*

- Represent LATE effects, which in their frequency or severity are influenced by the severity *(i.e. grade, duration)* of the ACUTE changes in the same tissue

- Is very often the consequence of damage to an overlying acutely responding epithelial surface - **loss of "BARRIER" function** - i.e. necrosis or fibrosis of skin consequent to desquamation and acute ulceration

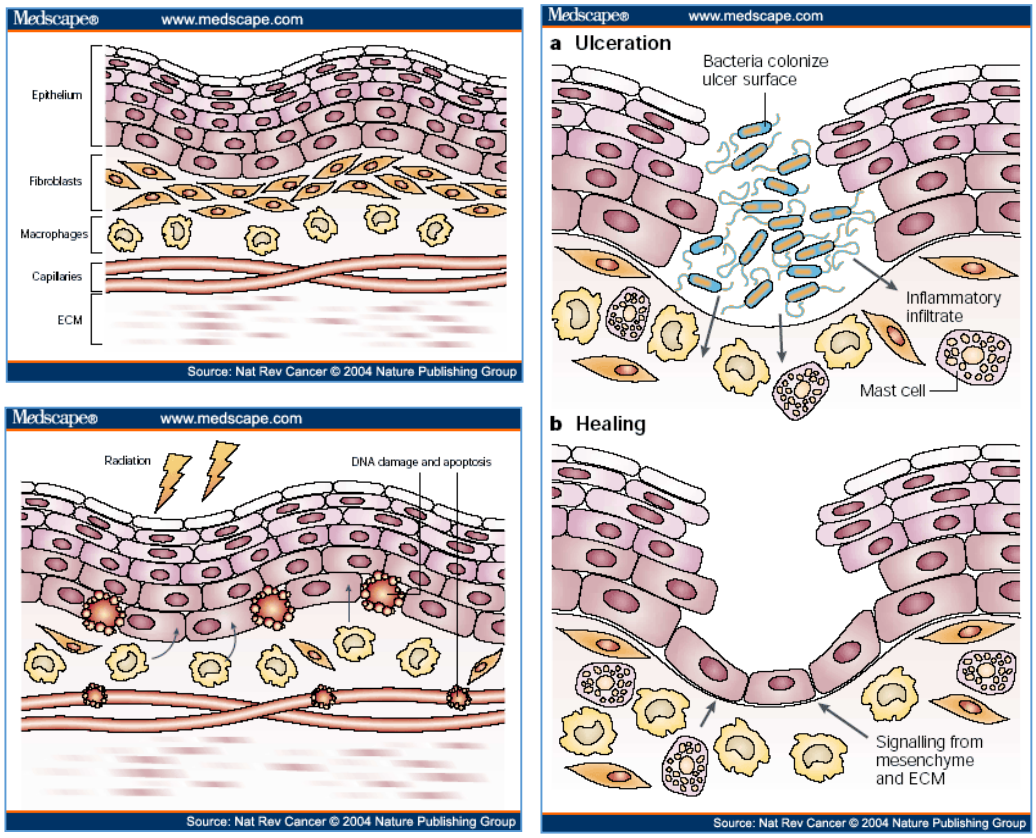
Pathogenesis of Consequential late effects

- Both phases are manifestations of an ongoing sequence of events initiated immediately after injury
- Autocrine, paracrine messages resulting in dysregulation of the tissue environment are of major importance



Radiopathology of Mucositis

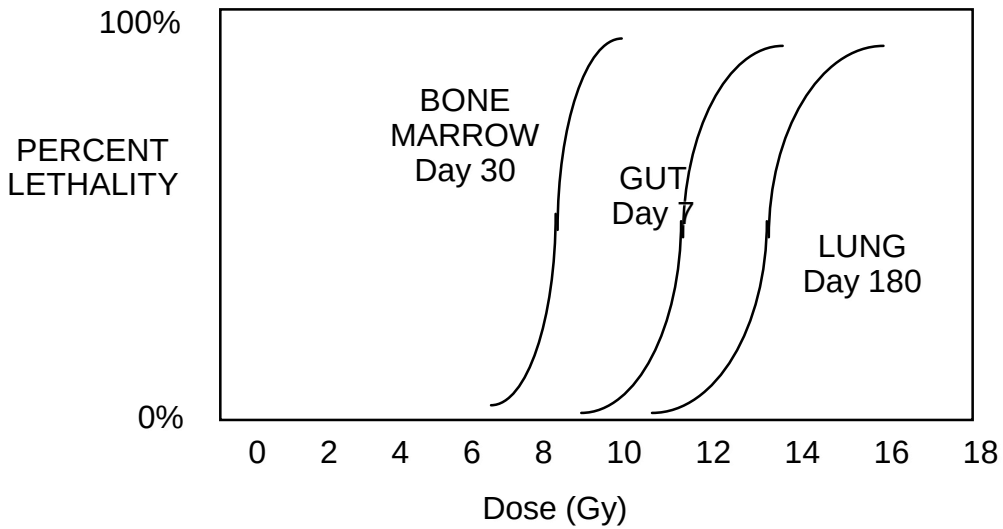
- LEFT TOP: Normal mucosa: squamous epithelium overlying the lamina propria; barrier function
- LEFT BOTTOM: Radiation induced mucositis: direct injury to basal epithelial cells; loss of renewal capacity; thinning of epithelium
- RIGHT TOP: Integrity loss of epithelium: ulceration phase, release of cytokines, inflammatory infiltrate, macrophages
- RIGHT BOTTOM: Healing *(via migration of viable cells from wound margins)* or NO healing**:**



Nat Rev Cancer, 2004

Consequential Late Damage (CLE)

There is no Relationship between Latency and Tolerance



- Different tissues have different tolerances to irradiation and fail at different times (latency) after irradiation
- Latency is determined by cell turnover kinetics in a tissue. It is NOT an indicator of radiation sensitivity.
- After moderate doses, gut fails first, then bone marrow, then lung, but the hematopoietic system is the most RADIOSENSITIVE

**) In these experiments, mice were given varying doses of whole body, abdominal, or thoracic irradiation, and the dose and time to failure assessed.*

Factors that influence the radiation sensitivity of tissues/organs

- Intrinsic radiation sensitivity; individual differences in radiation sensitivity: anatomical differences
- Proliferative organization of tissues (H-and F-type tissues)
- Functional subunits & Volume effects
- Repair capacity between fractions *(fractionation [LQ] parameter; α/β ratio)*

Casarett's classification of tissue radiation sensitivity

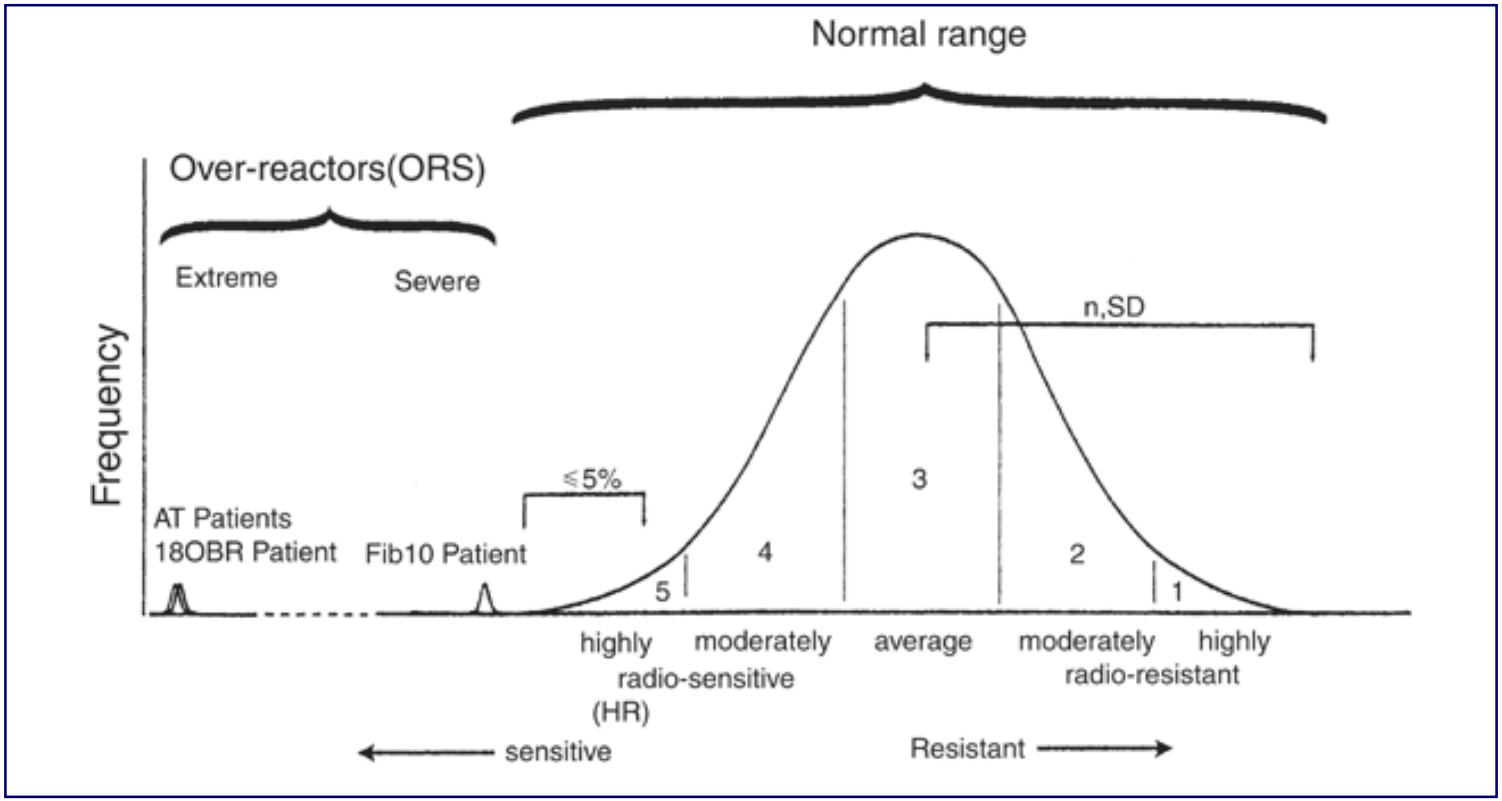
Adapted from Hall and Giaccia, 2006

Categories of Mammalian Cell Sensitivity

Cell type	Properties	Examples	Sensitivity*
I Vegetative inter-mitotic cells	Divide regularly; *no differentiation*	Erythroblasts Intestinal crypt cells Germinal cells of epidermis	High
II Differentiating inter-mitotic cells	Divide regularly; *some differentiation between divisions*	Myelocytes	
Connective tissue cells#			
III Reverting post mitotic cells	Do not divide regularly; *variably differentiated*	Liver	
IV Fixed post mitotic cells	Do not divide; *highly differentiated*	Nerve cells Muscle cells	Low

Individual differences in radiation sensitivity

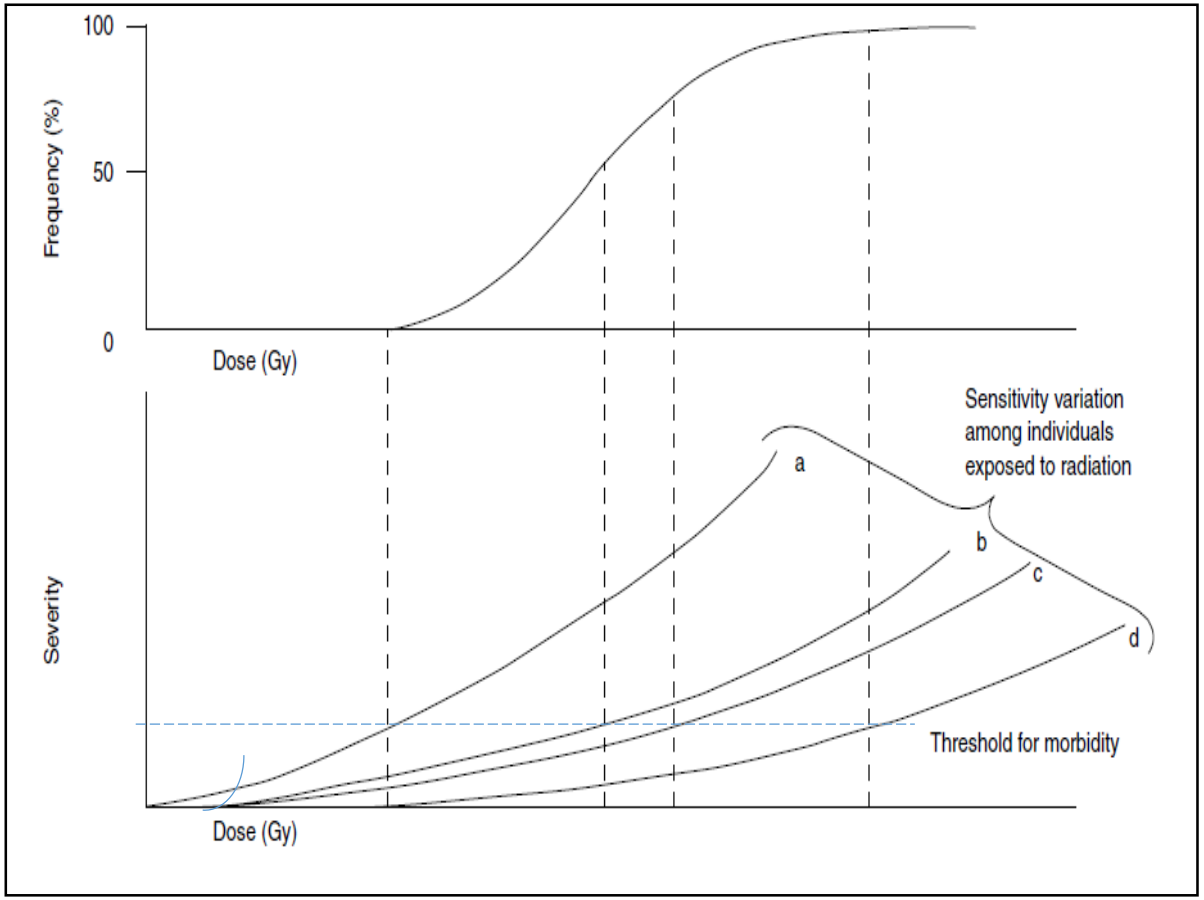
Idealized normal tissue response –relative scale



Genetic factors and radiation sensitivity

Burnet et al., Int. J. Cancer, 79,606

Individual differences in radiation sensitivity



Subpopulations of individuals with different radiation sensitivities

Hendry et al., 2006

Skin reaction: variation of Radiation sensitivity

Biological factors:

- *Genetic factors (individual differences)*
- *Anatomical site*
- *Pre-exposure condition (obscure damage)*
- *Age of exposed individual (young – old)*
- *Oxygen status of the skin and Vascularization*
- *Hormonal status of individual*

Skin reaction: variation of Radiation sensitivity

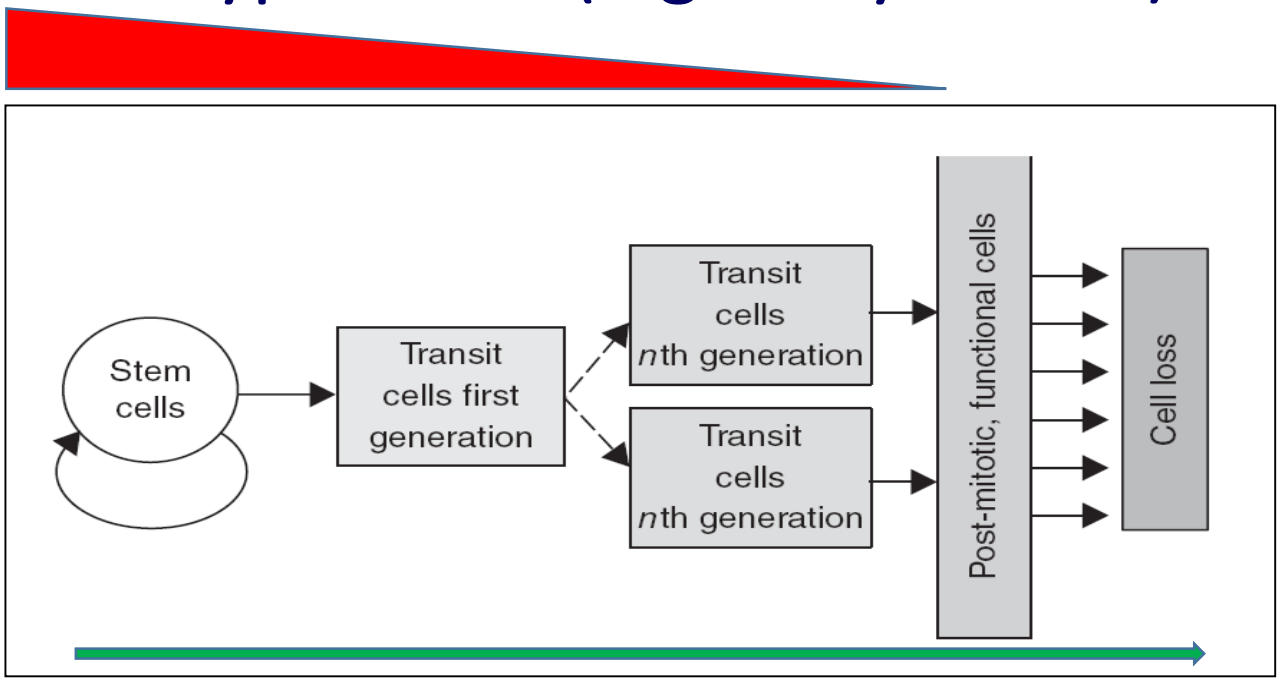
SENSITIVE	***SKIN REACTION***	***HAIR LOSS***
	• *Anterior aspect of neck* • *Flexor surfaces of extremities and trunk* • *Face (fair skin)* • *Back and extensor surfaces of extremities* • *Face (coloured skin)* • *Nape of neck* • *Scalp* • *Palms and soles*	• *Scalp* • *Armpit* • *Beard* • *Pubic hair* • *Eyelash* • *Eyebrow*
RESISTANT		

Proliferative organisation of tissues/organs & Radiation sensitivity

H-type tissue: Hierarchical tissue consisting of a lineage of stem cells, transit cells, and post mitotic *(differentiating) cells*

F-type tissue: Flexible type of tissue which do NOT have compartments with dividing cells and NO strict hierarchy between functioning and/or dividing cells

H-type tissue (e.g. early effects)



- Response is determined by hierarchical cell lineage composed of stem cells and differentiating offspring; dividing stem cell compartment is most radiosensitive
- Time of onset *(latency times)* correlates with lifespan of mature functional cells *(tissue/organ related)*

Latency is independent from Dose
Severity is dependent on Dose

Cell renewal in the Skin (H-type tissue)

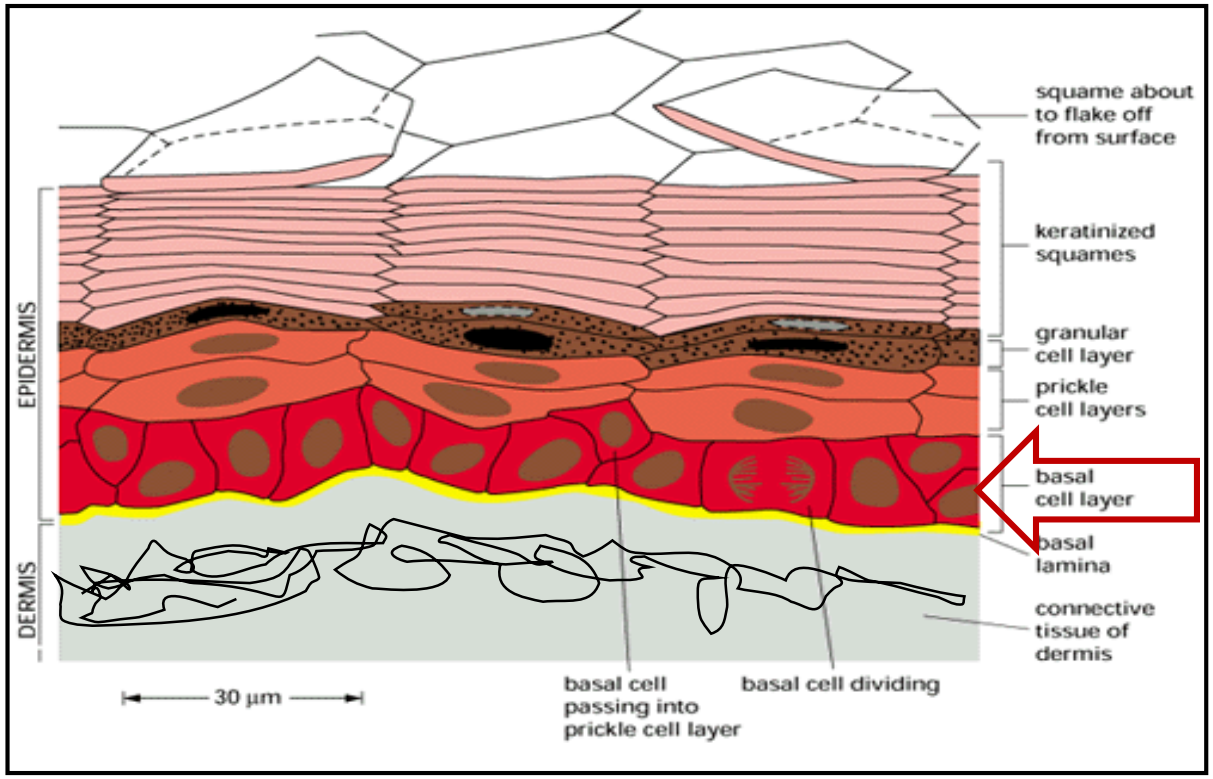
Cell loss

Differentiation

Migration

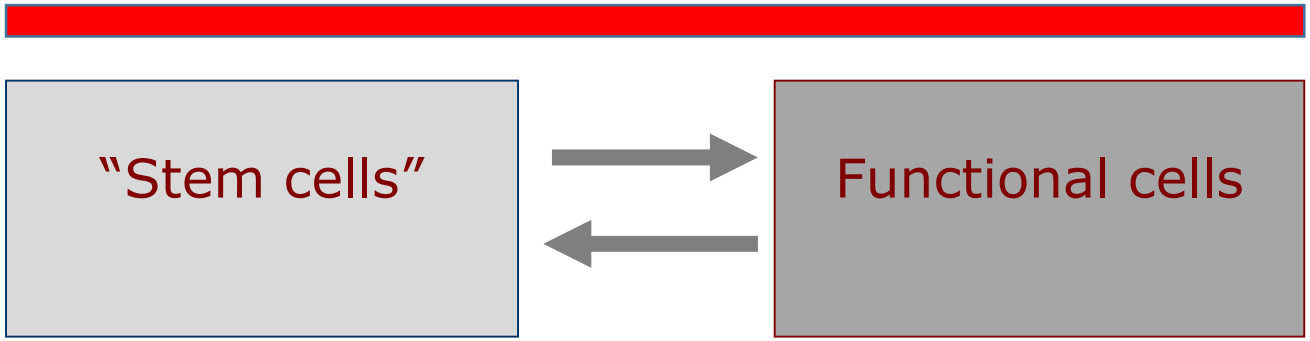
Proliferation

(cell renewal)



The most radiosensitive cells in the skin are those from the *basal stratum of the epidermis*. EPU *(epidermal proliferative unit);* cell cycle time ~ 200 h; transition time ~ 12 – 48 days.

F-type tissue (e.g. late effects)



No differences in radiation sensitivity
Both stem cells and/or functional cells are capable of proliferation

Latency is dependent from Dose (reversed)
Severity is dependent on Dose

Proliferative organisation of tissues/organs & Radiation sensitivity

H-type tissues:

- Oral mucosa
- Intestinal mucosa
- Skin (epidermis)
- Bone marrow
- Testis

Radiation Sensitivity:
stem cells > dividing cells > differentiating cells > post mitotic functional cells

F-type tissues:

- Spinal cord (CNS)
- Dermal layer of the skin (fibroblasts)
- Lung
- Kidney
- Liver

Radiation Sensitivity:
No difference in **radiation sensitivity** between functioning cells and dividing cells

Tissue architecture & Tolerance dose

CONCEPT: An *organ* can be considered to be *made up* of several functional subunits (FSUs):

Adapted from Withers et al., 1988

Tissue architecture & Tolerance dose

CONCEPT: An *organ* can be considered to be *made up* of several functional subunits (FSUs):

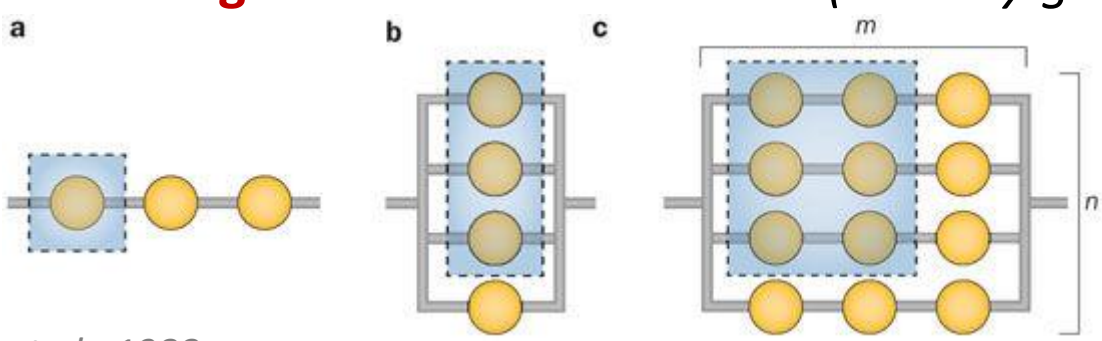
Does tissue architecture influence the radiation sensitivity of an tissue/organ (i.e. Volume effect)?

Adapted from Withers et al., 1988

Tissue architecture

Functional subunits (FSU) & Volume effect

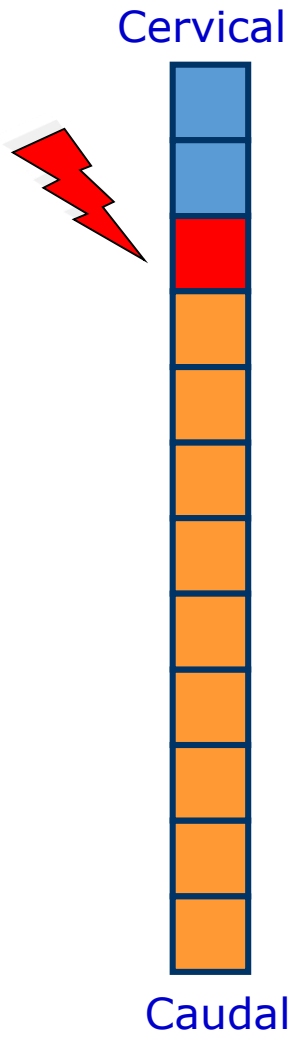
- **Serial organization of FSUs**: in serial organs failure of only one FSU results in loss of function of entire organ/structure *(spinal cord, oesophagus, vasculature)*
- **Parallel arrangement of FSUs:** in parallel organized tissues a critical number of FSUs *(threshold volume)*, must be damaged before a clinical response *(i.e. loss of function)* becomes manifest *(skin, mucosa, liver lung)*
- **Serial-Parallel organ:** has features of both *(salivary gland/heart)*



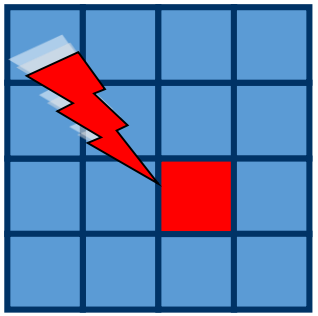
Adapted from Withers et al., 1988

Tissue architecture & Probability of complications

Serial organization of FSUs: failure of only one FSU results in loss of function of entire organ *(Spinal cord, GI-tract, vasculature)*



Parallel arrangement of FSUs: a critical number of FSUs (threshold volume) must be damaged before a clinical response *(i.e. loss of function)* becomes manifest, *(i.e. liver, lung, skin & mucosa)*



Volume and Tolerance dose*,**

Clinical data

Organ	injury	volume	
		1/3	whole
Kidney	nephrosclerosis	50	23
Lung	pneumonitis	45	17.5
Heart	pericarditis; pancarditis	60	40
Esophagus	esophagitis; ulceration	60	55
Stomach	perforation; ulcer	60	50
Intestine	obstruction; perforation	50	40
Spinal cord	infarction, necrosis	50#	47#
Brain	infarction, necrosis	60	45

**) TD5/5: 5% complications in 5 year; 2 Gy/fx; total dose in Gy*

***) Adapted from Emami et al., 1991*

Hall, Giacca, 2006

Take home message I

Deterministic effects:

- Deterministic effects increase with increasing dose *(above threshold dose)*
- Radiation response of a particular tissue/organs depends on the intrinsic radiation sensitivity of their cells; individual differences in radiation sensitivity: anatomical differences
- Proliferative organization of tissues *(H-and F-type tissues)* and architecture *(functional subunits)* influence radiation response
- Radiation response of tissues/organs also depend on its function before the treatment

Take home message II

Early effects:

- Turn-over tissues: rapidly proliferating cells
- Latent time: independent from dose; dependent on tissue biology
- Maximum severity: dependent on dose
- RECOVERY: time to restoration: dependent on dose & tissue biology

Take home message III

Generic Late effects:

- Low-turn-over tissues; complex pathogenesis (parenchyma, fibroblasts, endothelium, macrophages)
- IRREVERSIBLE (chronic)
- Latency: dose-dependent (reversed)
- Progression rate: dose-dependent

Take home message IV

Consequential late effects (CLE):

- Radiobiological characteristics of early effects *(RT: fractionation, overall treatment time)*
- Correlate with markers for early effects
- Modulated by treatment of early effects *(barrier function, irritation level, anti-microbials, anti-inflammatory agents, GF's etc.)*