Radiation Biology and Radiation Protection

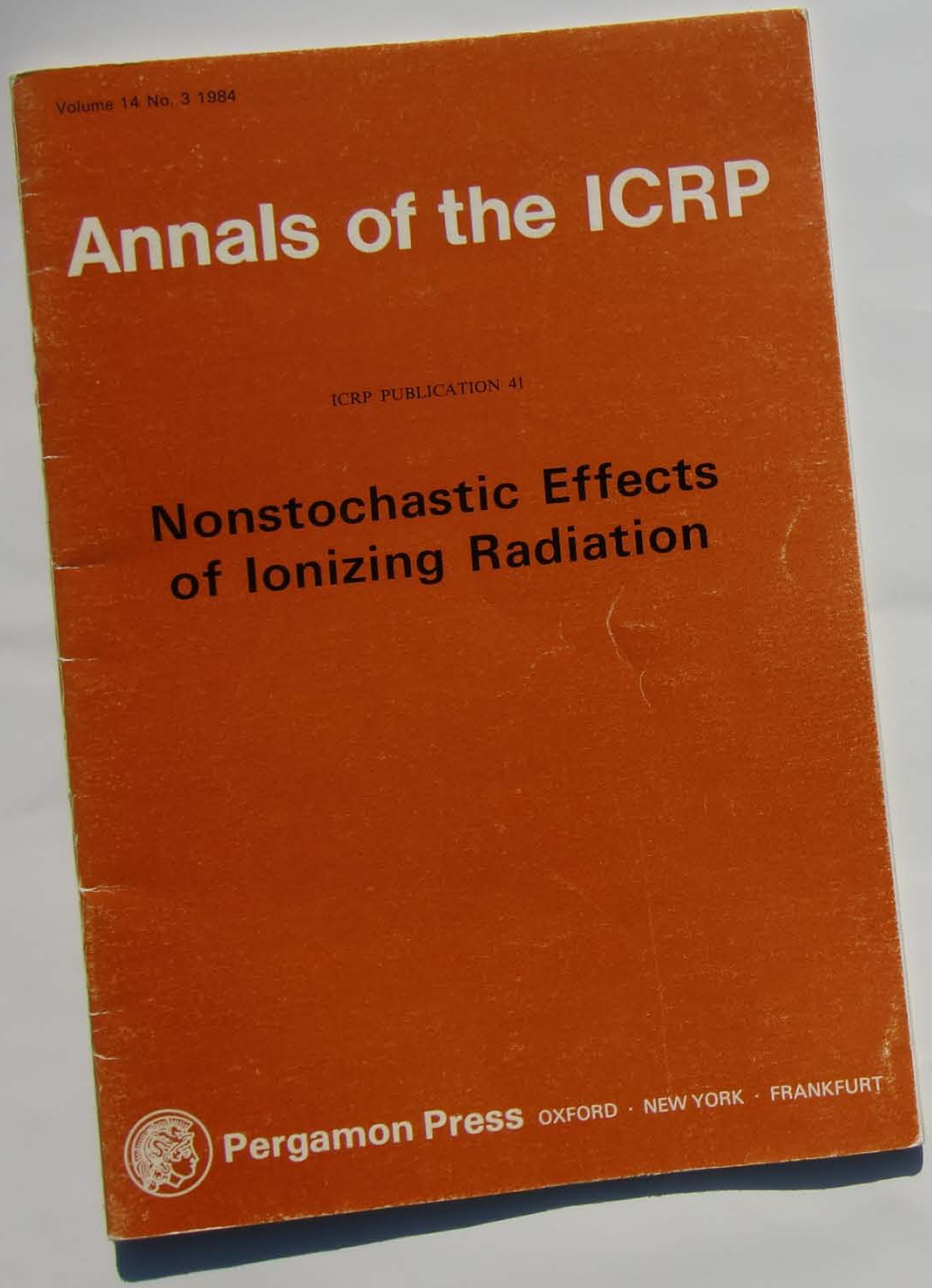
Prof. Jolyon Hendry

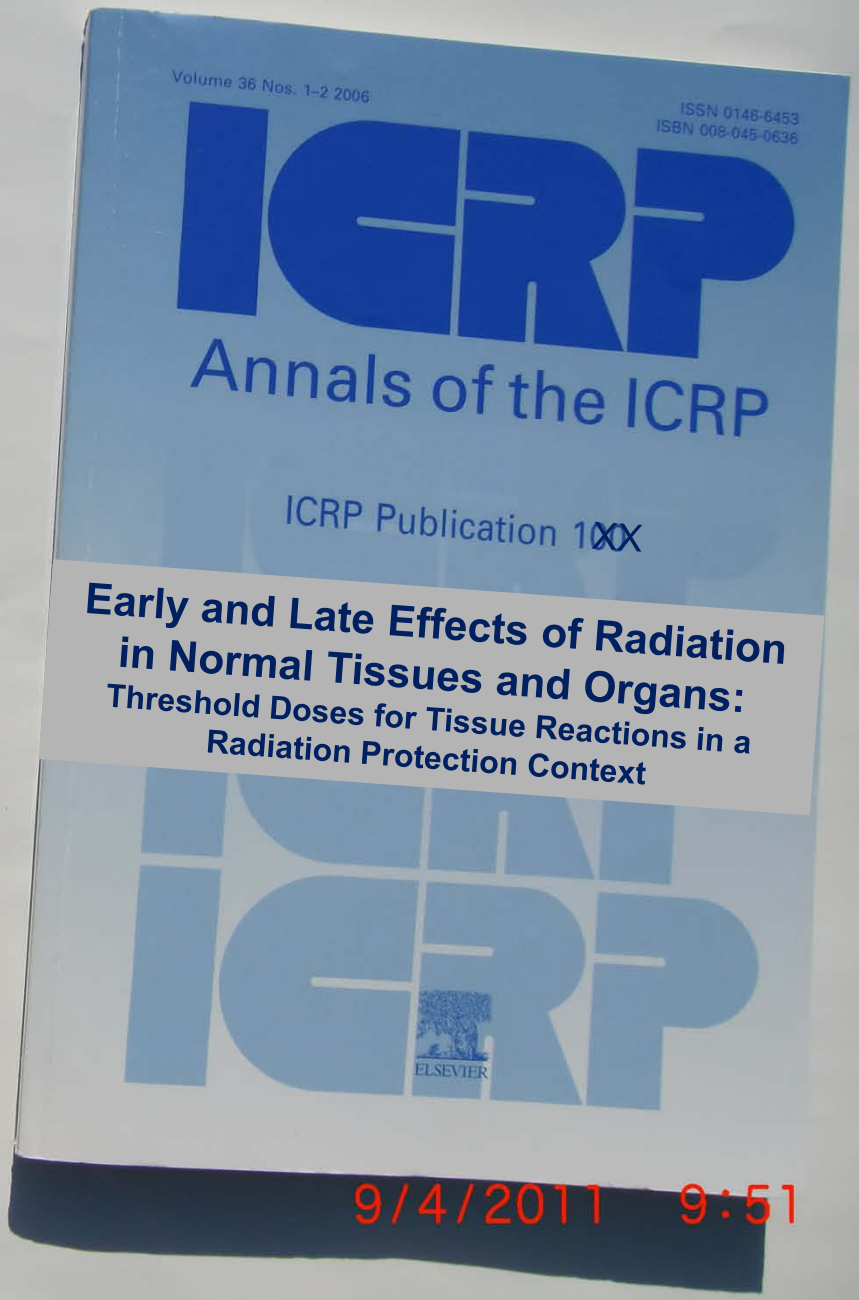
Manchester, U.K.

ICRP Committee 1 in Amsterdam, Netherlands, October 2010

Tissue reactions (Deterministic effects)

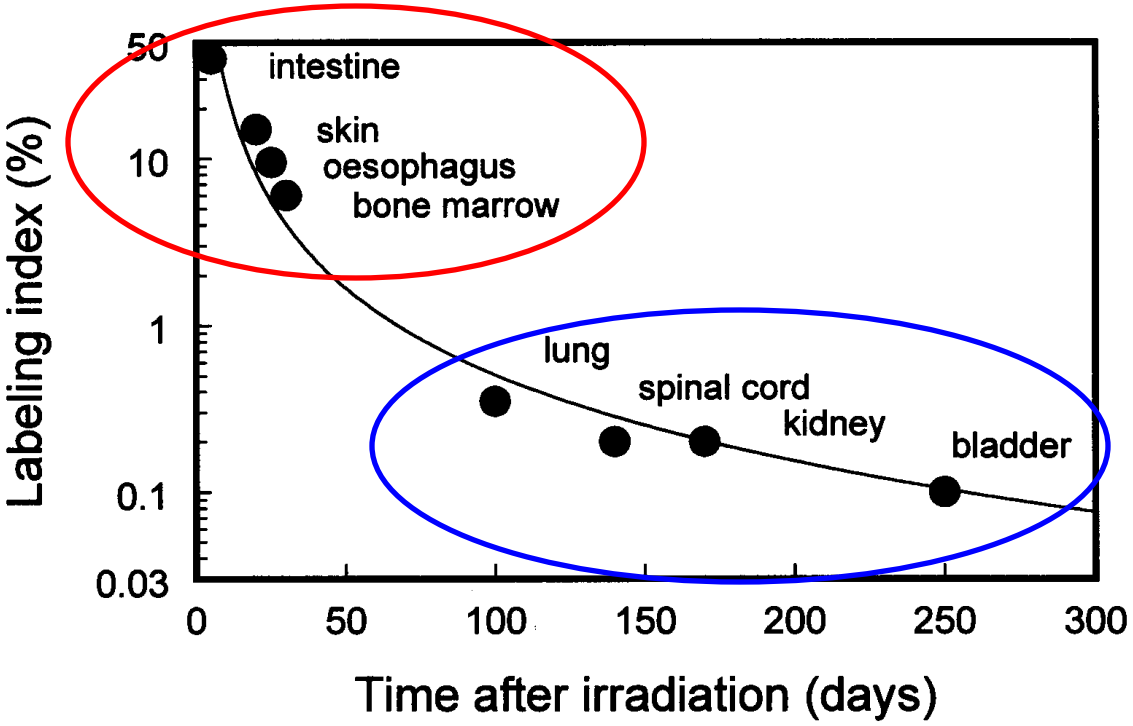
- ICRP 41 (1984): *non-stochastic* injury in populations of cells
- ICRP 60 (1991): *deterministic effects*, causally determined by preceding events i.e. the dose
- ICRP 103 (2007): *tissue reactions (deterministic effects),* subject to biological response modifiers (dose modifying factors 1.1 to 2)


Volume 14 No. 3 1984
Annals of the ICRP
ICRP PUBLICATION 41
Nonstochastic Effects of Ionizing Radiation
Pergamon Press OXFORD · NEW YORK · FRANKFURT


Volume 36 Nos. 1-2 2006
ISSN 0146-6453
ISBN 008-045-0636
ICRP
Annals of the ICRP
ICRP Publication 10XX
Early and Late Effects of Radiation in Normal Tissues and Organs:
Threshold Doses for Tissue Reactions in a Radiation Protection Context
ELSEVIER

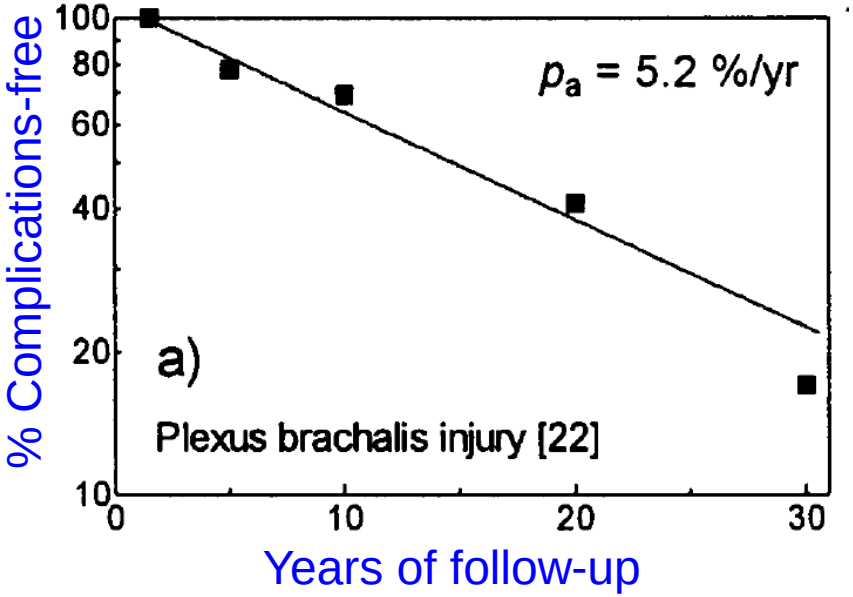
9/4/2011 9:51

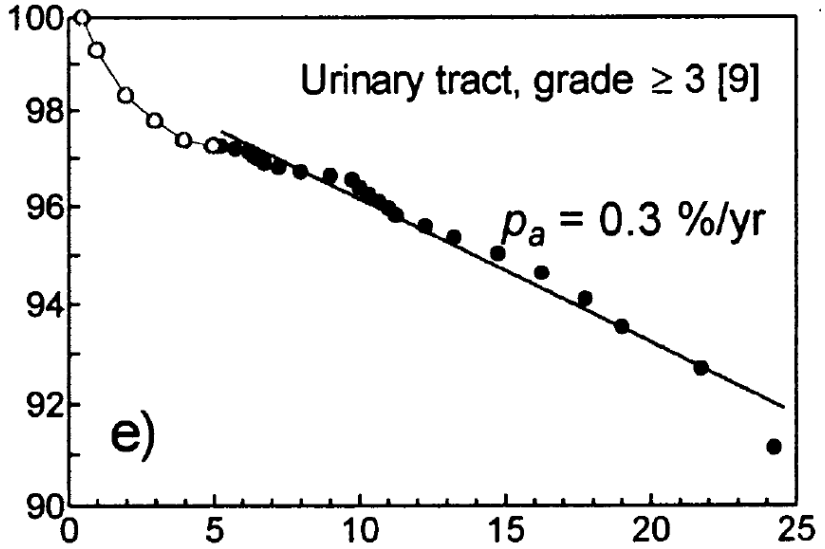
Time of expression of radiation injury in rodents

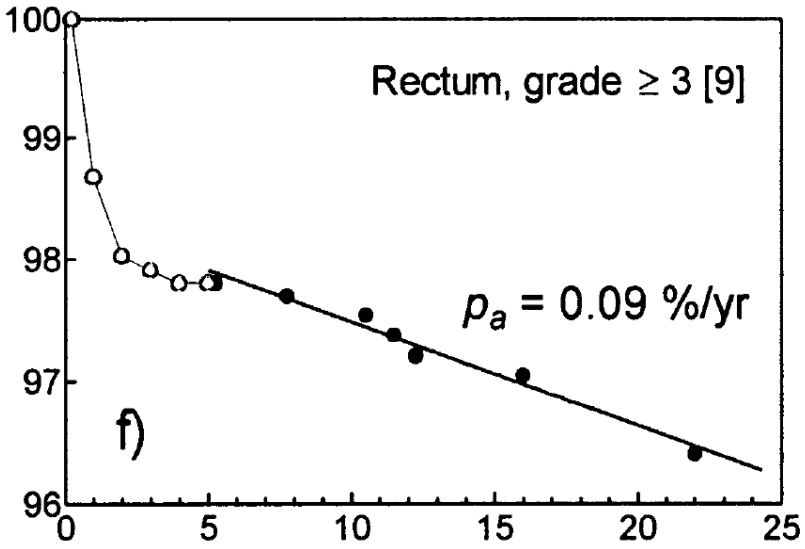


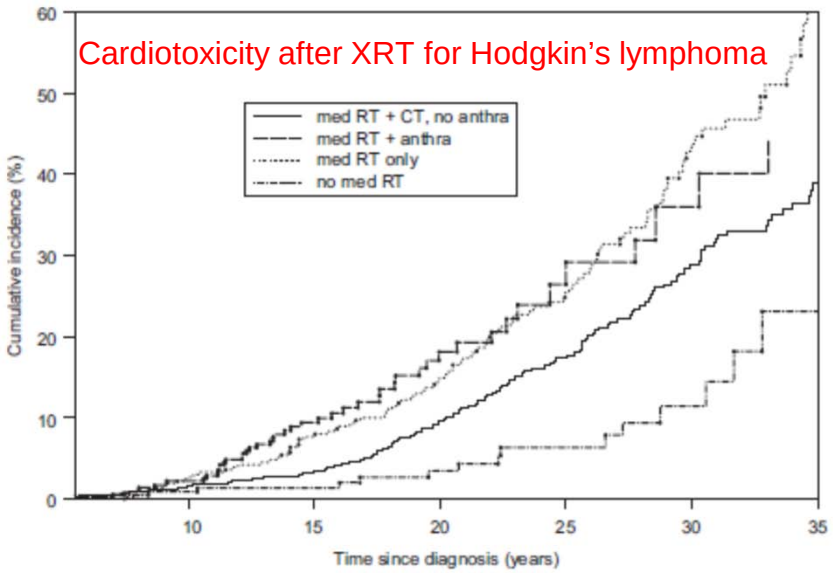
Rapidly proliferating tissues (short turnover time) express radiation injury much earlier than slowly proliferating tissues

Fiona Stewart and Bert van der Kogel, 2002





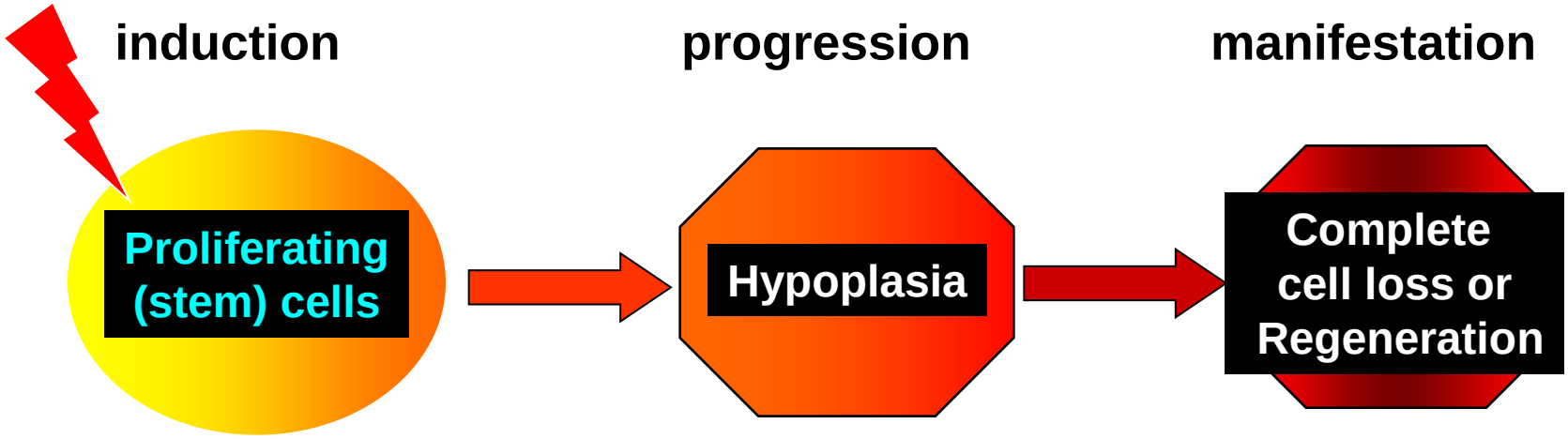




Jung. Rad. Onc. 61, 233 (2001)

Aleman et al. Blood 109, 1878 (2007)

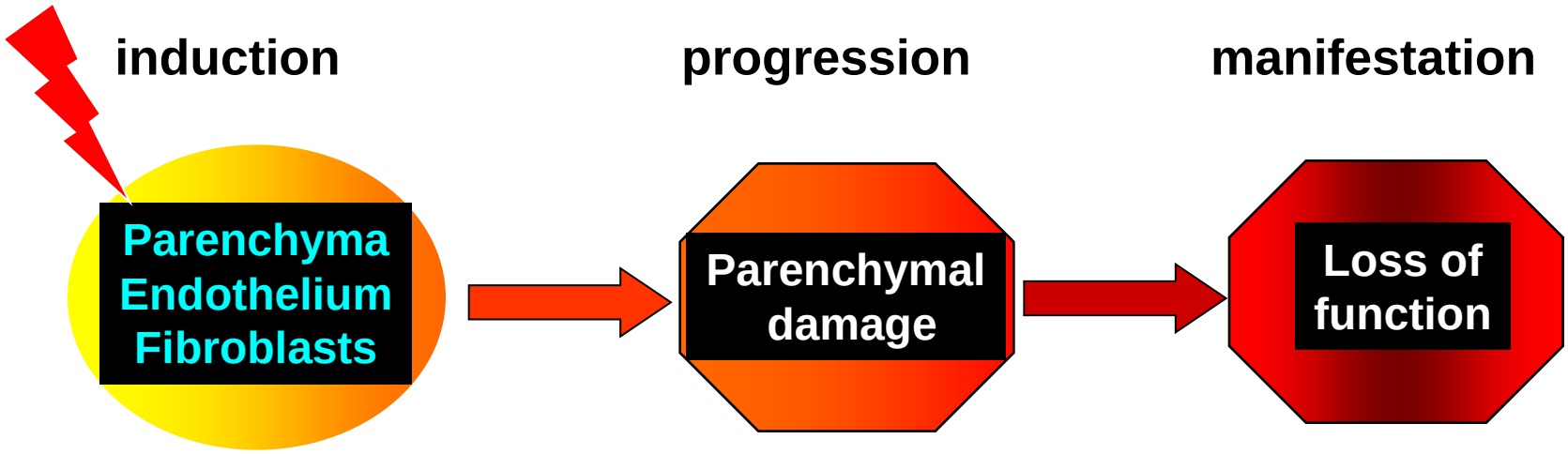
Radiation injury in early-responding tissues with “stem cell” population



- Time of expression of injury depends on lifespan of differentiated (non-proliferating) cells; *independent of dose.*
- Maximum injury and rate of recovery depend on level of cell killing in stem cell compartment; *dose dependent.*

Adapted from Wolfgang Dörr/ Fiona Stewart

Pathogenesis of late radiation injury



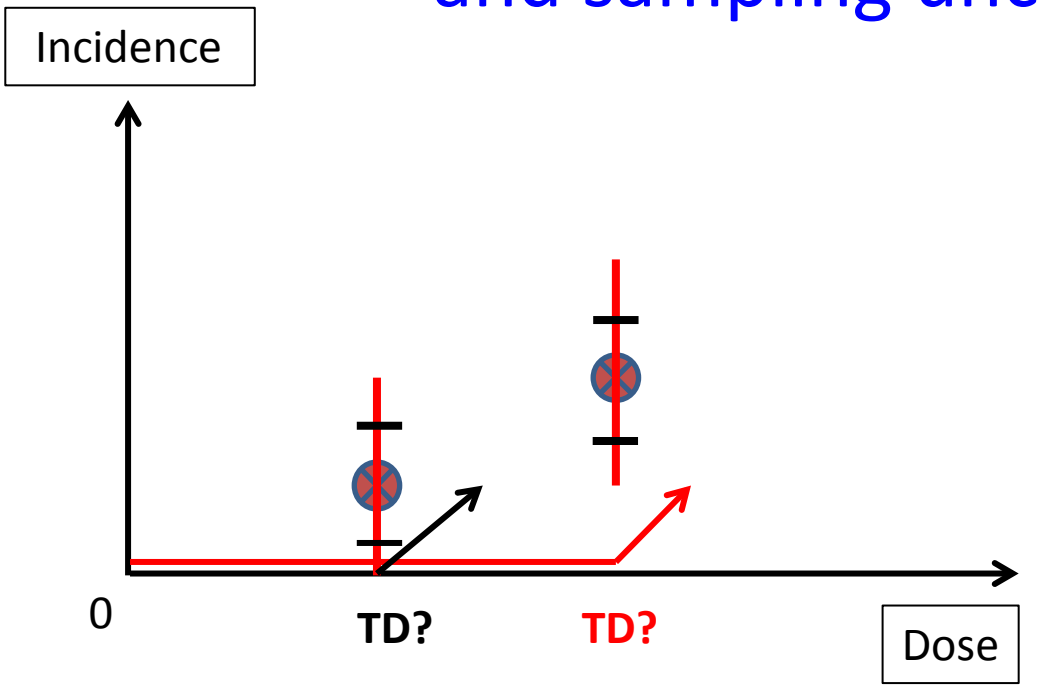
- Time of expression of injury depends on level of cell kill; *dose & time dependent.*
- Numerous cytokine responses contribute to, & modify, extent of radiation injury.
- "Consequential" late effects in mucosal tissues after severe early injury.
- "Functional" radiosensitivity depends on tissue architecture and reserve capacity.

Adapted from Wolfgang Dörr/ Fiona Stewart

Threshold dose

- Maximum dose at which the effect does not occur (ICRP principle).
- The lowest dose at which a statistically-significant positive dose-response can be detected (Epidemiology).

Threshold doses (TD) and sampling uncertainties



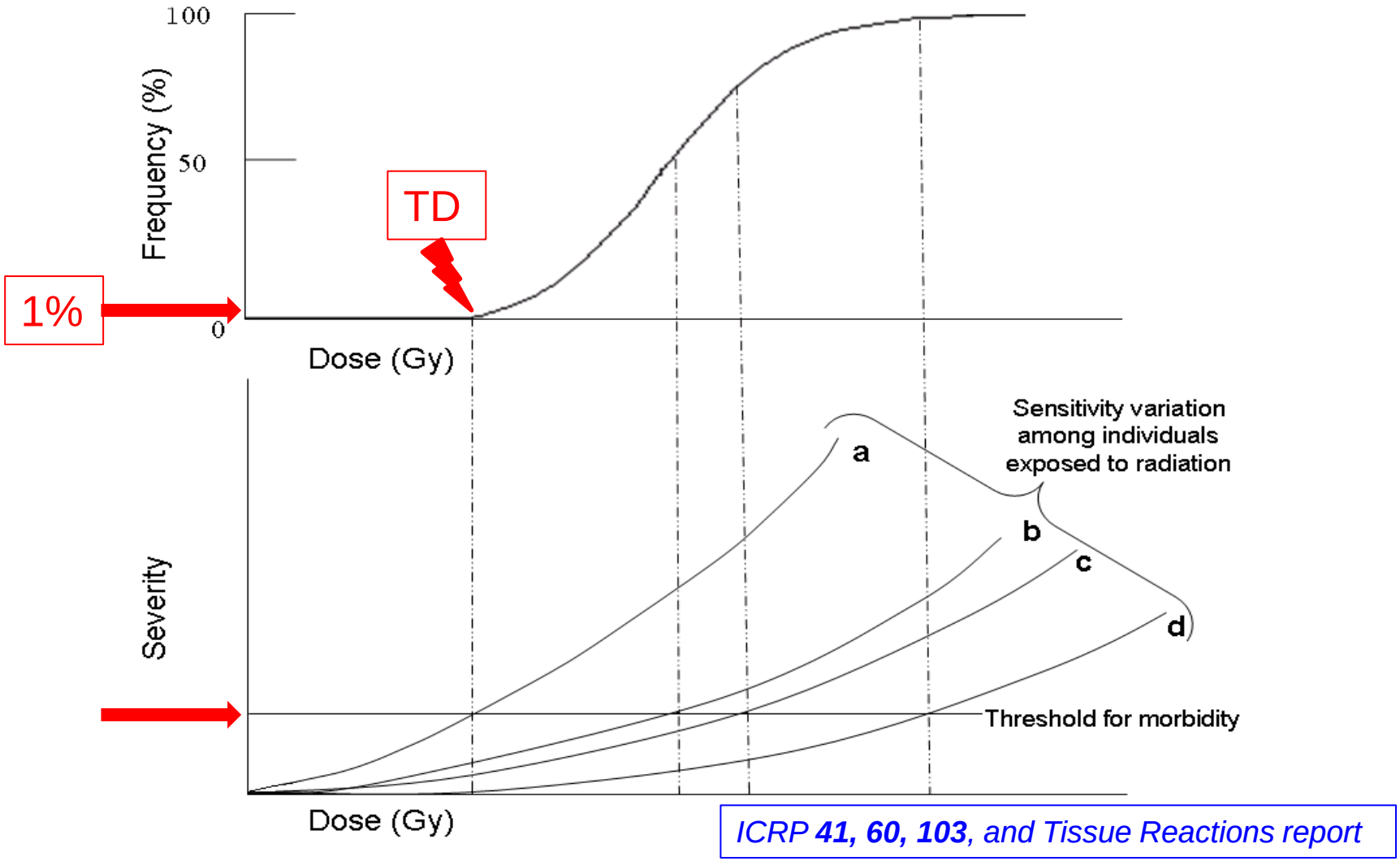
…..a linear dose-response relationship will not suddenly dive to zero immediately below the lowest level at which a statistically significant excess is observed.

Professor Sir Richard Doll, 1997

Threshold dose choices

- Maximum dose at which the effect does not occur (ICRP principle).
- The lowest dose at which a statistically-significant positive dose-response can be detected (Epidemiology).
- Dose resulting in only 1% incidence of defined tissue reactions, chosen for 'practical' purposes (ICRP, 2007).
  - Less than 1% : greater extrapolation, less accurate.
  - More than 1% : less extrapolation, more accurate, but unacceptable.
  - Context needs to be considered i.e. public, workers, medical practice.

Threshold dose (TD)



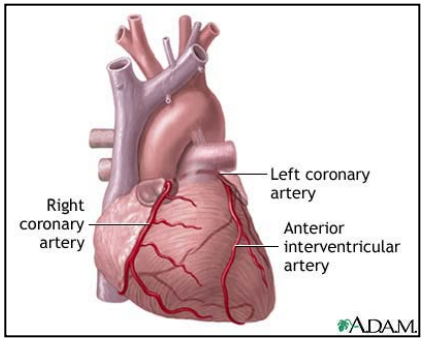
*ICRP **41, 60, 103**, and Tissue Reactions report*

Effect	Organ/tissue	Time to develop effect	Absorbed dose[b] resulting in about 1% incidence		
Mortality: Mortality			Acute exposure (Gy)	[c]Highly fractionated (2 Gy per fraction) or equivalent protracted exposures (Gy)	Annual (chronic) dose rate for many years (Gy y^{-1})
Bone marrow syndrome:					
- without medical care	Bone marrow	30-60 days	~1	10	NA
- with good medical care	Bone marrow	30-60 days	2-3	? >10	NA
Gastro-intestinal syndrome:					
- without medical care	Small intestine	6-9 days	~6	NA	NA
- with conventional medical care	Small intestine	6-9 days	>6	40	NA
Pneumonitis –mean lung dose	Lung	1-7 months	6.5	15	NA
Cardiovascular disease – whole body exposure	Heart	>10-15 years	~0.5	~0.5	~0.5 divided by years duration
Cerebrovascular disease	Carotid artery	>10 years	~0.5	~0.5	~0.5 divided by years duration

Mortality

Threshold doses (ED_1):

Acute, Fractionated, Chronic exposures



? ? ?

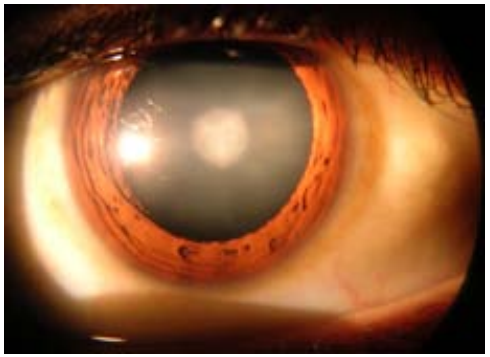
Effect	Organ/tissue	Time to develop effect	Absorbed dose[a] resulting in about 1% incidence		
Morbidity: Morbidity			Acute exposure (Gy)	[b]Highly fractionated (2 Gy per fraction) or equivalent protracted exposures (Gy)	Annual (chronic) dose rate for many years (Gy y^{-1})
Temporary sterility	Testes	3-9 weeks	~0.1	NA	0.4
Permanent sterility	Testes	3 weeks	~6	<6	2.0
Permanent sterility	Ovaries	< 1week	~3	6.0	>0.2
Depression of haemopoiesis	Bone marrow	3-7 days	~0.5	10-14Gy	>0.4
Digestive system					
	Salivary glands	1 week	NA	<20	NA
	Oesophagus	3-8 months	NA	55	NA
	Stomach	2 years	NA	50	NA
	Small intestine	1.5 years	NA	45	NA
	Colon	2 yaers	NA	50	NA
	Rectum	1 year	NA	60	NA
	Liver	2 weeks	NA	<30-32	NA
Main phase of skin reddening	Skin (large areas)	1-4 weeks	<3-6	30	NA
Skin burns	Skin (large areas)	2-3 weeks	5-10	35	NA
Temporary hair loss	Skin	2-3 weeks	~4	NA	NA
Late atrophy	Skin (large areas)	> 1 year	10	40	NA
Telangiectasia @ 5 years	Skin (large areas)	> 1 year	10	40	NA
Cataract (visual impairment)	Eye	>20 years	~0.5	~0.5	~0.5 divided by years duration[c]
Urinary Tract	Kidney	> 1 year	7-8	18	NA
	Bladder	> 6 months	15	55	NA
	Ureters	>6 months	NA	55-60	NA
Musculoskeletal system	Adult bone	> 1 year	NA	50	NA
	Growing bone	< 1 year	NA	25	NA
	Muscle	Several years	NA	55	NA
Endocrine system	Thyroid	?	NA	>18	NA

Morbidity

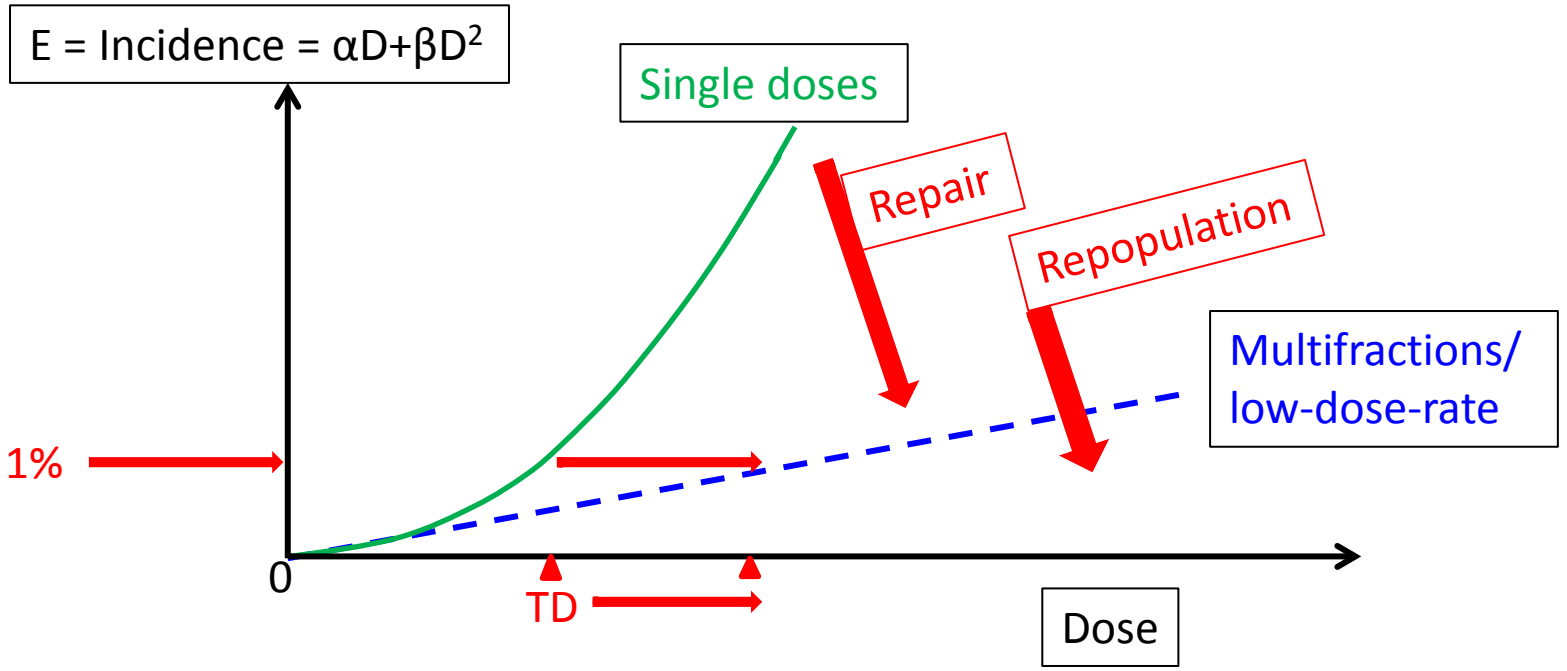
Threshold doses (ED_1):

Acute, Fractionated, Chronic exposures

? ? ?



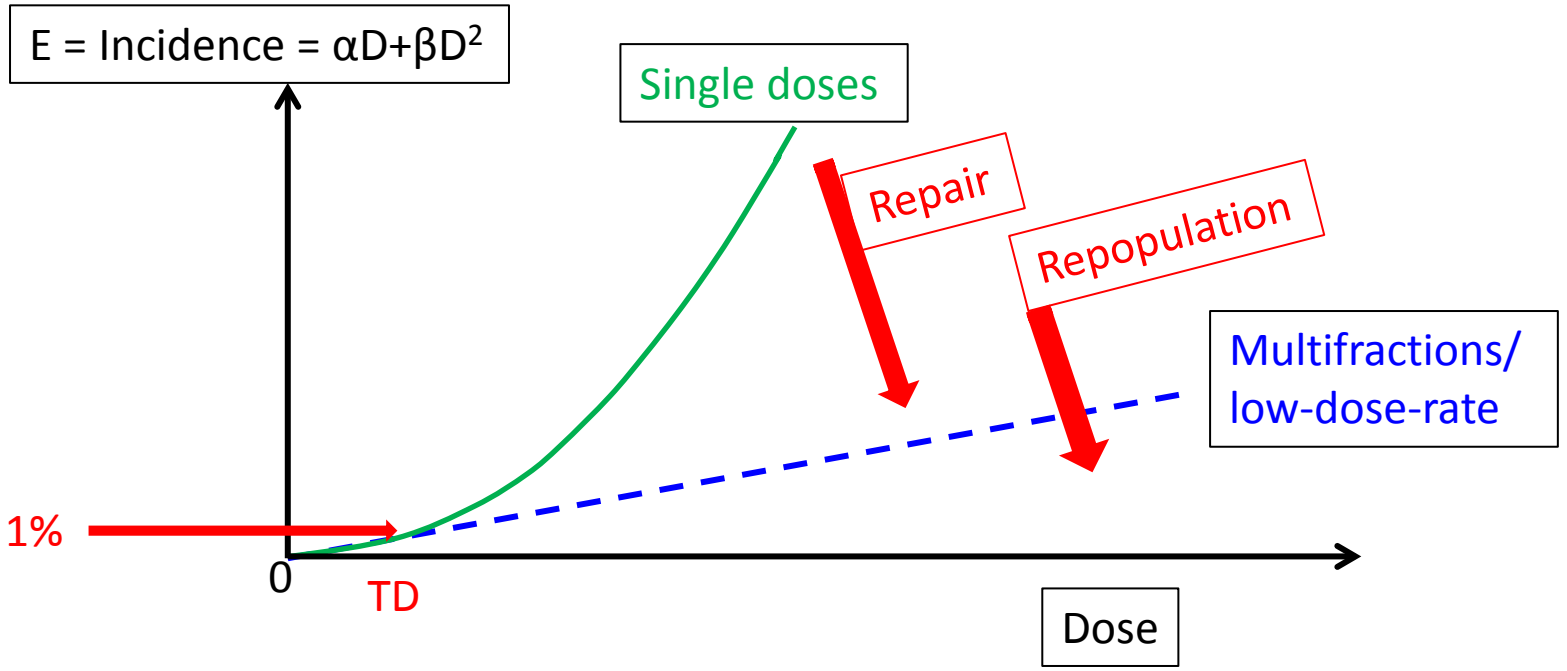
Multi-fractionated doses or low-dose-rate



Threshold Dose dependent on Fractionation/ Dose-rate because:

- Gradual reduction in the quadratic component
- Repair, Repopulation, Adaptation
- If short follow-up time, not all injury expressed and threshold dose high

Multi-fractionated doses or low-dose-rate



Why would the Threshold Dose be independent of Fractionation/ Dose-rate?

- Greater statistical uncertainties below 0.5 Gy
- Response at low doses due to irrepairable and persistent radiation lesions
- Different target cell populations at risk for low doses versus higher doses

Organ	Agent	DMF[a]
Bone marrow:		
Early reactions	Antibiotics	1.2–1.8 (rodents
	Granulocyte-macrophage	and monkeys)
	Colony-stimulating-factor	
Intestine:		
Early reactions	Antibiotics	1.1–1.4 (rats)
	Interleukin–1	1.1
	Angiogenic growth factors	1.1 (mice)[b]
	Interleukin–11, Transforming growth factor-β3	>1.0
Late reactions	Low molecular weight diet	>1.0 (rats)
	Antiplatelet Clopidogrel	>1.0 (rats)[c]
Skin:		
Alopecia	Prostaglandin E2	1.2–1.5
Early reactions	γ-linolenic acid	1.1–1.2 (pigs)
Late reactions	γ-linolenic acid	1.1–1.2 (pigs)
	Blood-cell modifiers	1.4
	Cu/Zn/Mn-SOD	>1.0 (pigs)[d]
Oral mucosa:		
Early reactions	Keratinocyte growth factor	about 2.0
Lung:		
Pneumonitis	Interleukin–1,	>1.0
	Tumour necrosis factor-α	>1.0
Spinal cord:		
Late reactions	Vasoactive agents	1.1 (rats)
Kidney:		
Late reactions	Captopril, angiotensin II blockers	>1.0 (rats)

Dose modifying factors (DMF) in mice and other species (updated from Hendry, 1994)

[a] DMF = ratio of radiation doses with or without the protective agent, causing the same level of effect.

>1.0 indicates that the observed protection could not be quantified in terms of a DMF value, because dose-response relationships were not available. Reactions were assessed as less severe for combined radiation and agent.

[b] Okunieff et al. (1998).

[c] Wang et al. (2002).

[d] Lefaix et al. (1996).

Breaking News:
Biological Response Modifiers

LITTLE ROCK – The University of Arkansas for Medical Sciences (UAMS) has signed a contract with the federal Biomedical Advanced Research and Development Authority (BARDA) to proceed with *"advanced development of a promising treatment for use in radiological or nuclear emergency situations."*

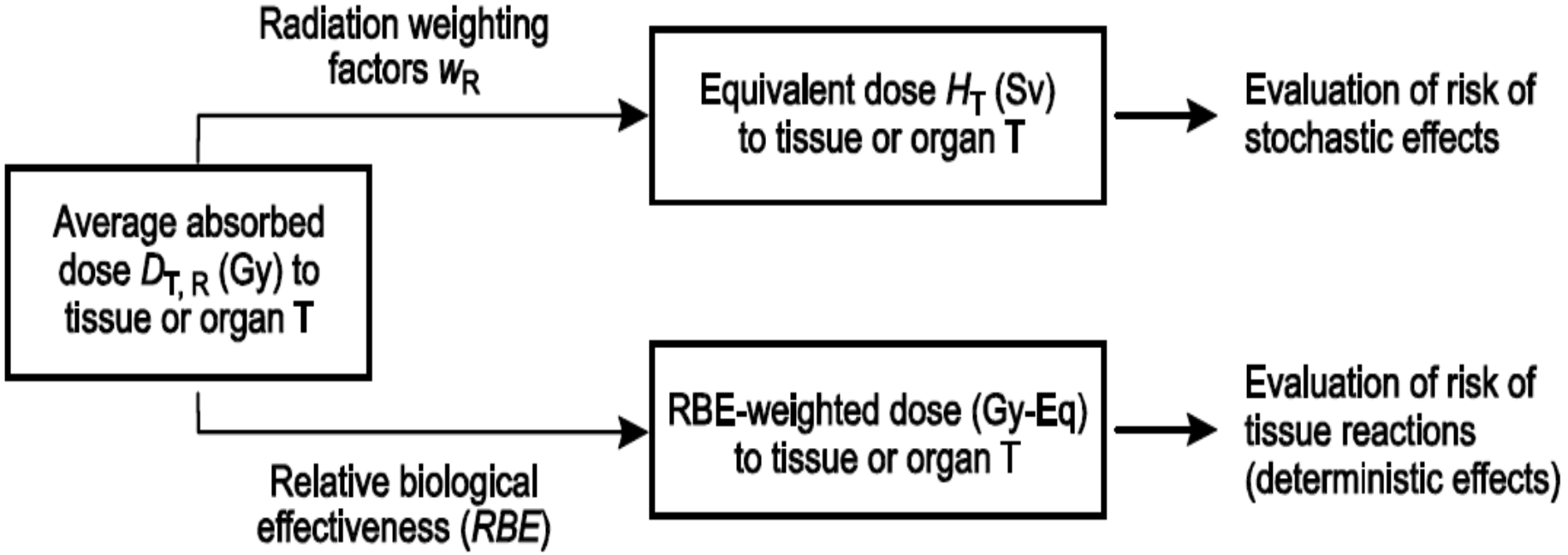
The initial award is for $4.5 million over two years rising to nearly $13 million.

UAMS' Martin Hauer-Jensen, M.D., Ph.D., an internationally renowned radiation researcher, will lead the evaluation of *the drug, SOM230, or pasireotide, to treat gastrointestinal injuries* after radiological or nuclear accidents or terrorist attacks.

The intestine and bone marrow are most susceptible to radiation because of their rapidly proliferating cells. *Treatments exist for irradiated bone marrow but not for the intestine.*

Gray and Sievert Units

Stochastic effects: Sv



Tissue reactions: Gy or RBE.Gy