Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Physics 561

Radiation Biophysics, Lecture 9:
Radiation Biology of Normal Tissues

Andrew Howard

Plans For This Class

- Discuss homework for 3/9 and 3/23
- *In vivo* assays of normal tissue
- Acute lethal response
- Teratogenesis

} ch 10

- Nonstochastic effects (chapter 10)

Homework problem 9.1

- See website for details (to be updated with specifics…)
- General point: you don't actually need the MTSH *n* and D_0 values to solve the problem—just the OER values and the recognition that in this situation the OER at high $[O_2]$ values is the m value (see eqn. 9. e5)
- Then if you plot OER against $[O_2]$, find the point where $S/S_N = (m+1)/2 = 1.905$. That point is at $[O_2] = 0.61\%$.
- Ratio of type 1 to type 2 damage = $n_1/n_2 = m-1$.

SUGGESTED ADDITIONAL READING

Dertinger, H., and Jung, H. (1970). *Molecular Radiation Biology*. Springer-Verlag, Berlin.
von Sonntag, C. (1987). *The Chemical Basis of Radiation Biology*. Taylor and Francis, London.
(See particularly Chapters 10 and 11.)

PROBLEMS

1. A mammalian cell line has a D_0 of 120 cGy and an extrapolation number of 12. The OER is found to be of a dose modifying character with a value of 2.81. What is the value of n in the Alper-Howard-

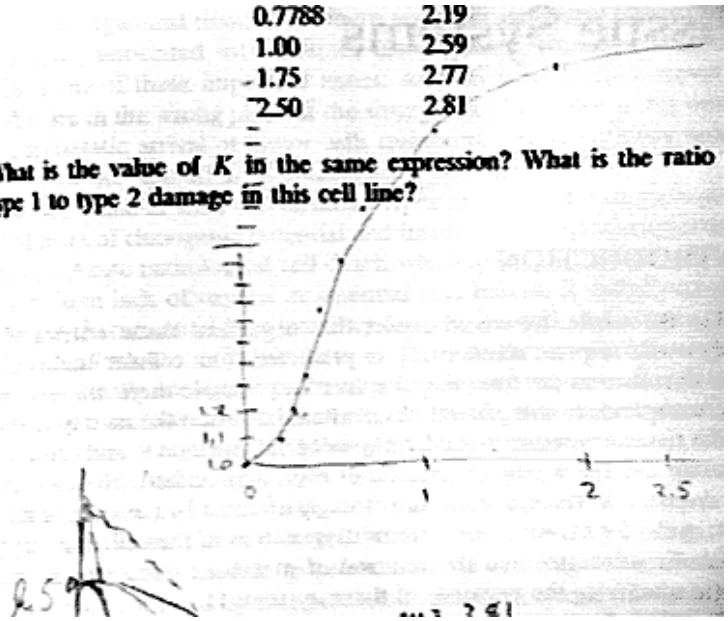
Flanders equation? The following data have been found for this cell line for OER as a function of oxygen partial pressure.

$[O_2]$ (%)	OER
0.1353	1.10
0.223	1.20
0.2865	1.33
0.3679	1.64
0.6065	1.88
0.7788	2.19
1.00	2.59
1.75	2.77
2.50	2.81

What is the value of K in the same expression? What is the ratio of type 1 to type 2 damage in this cell line?

0.7788	2.19
1.00	2.59
1.75	2.77
2.50	2.81

What is the value of K in the same expression? What is the ratio type 1 to type 2 damage in this cell line?



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When $[O_2]$ is very much larger than K,

$$\frac{S}{S_N} = \frac{m[O_2]}{[O_2]} = m.$$

The conditions of Eq. (9.5) are met for the region of the concentration–sensitization curve where S/S_N is the maximum. I words, the constant m is equal to the maximum relative sensitivity

The constant K can be determined by observing that when K i to $[O_2]$, the following derivation is possible:

$$\frac{S_K}{S_N} = \frac{m[K] + K}{K + K} = \frac{K(m+1)}{2K} = \frac{(m+1)}{2}.$$

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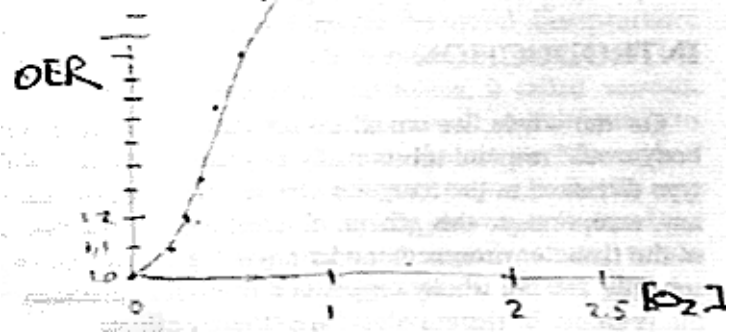
0.6065	1.88 ←
0.7788	2.19
1.00	2.59
1.75	2.77
2.50	2.81

alue of K in the same expression? What is the ratio of 2 damage in this cell line?



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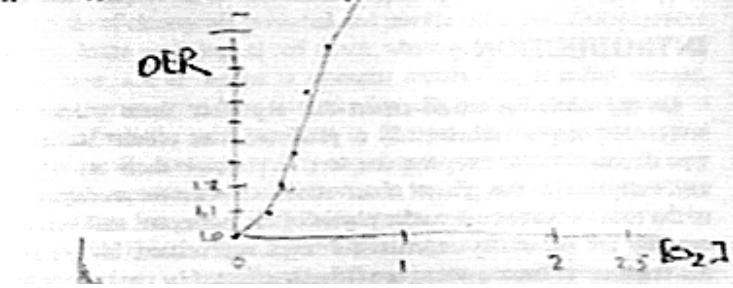
What is the value of K in the same expression? What is the ratio of type 1 to type 2 damage in this cell line?



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taken as always lethal to the target. The type 1 lesion can be chemically restituted by the chemical repair mechanisms discussed earlier. This chemical repair process is competitive with the damage fixation with oxygen. In terms of this model, the constant, m, is related to the relative number of the lesions of types 1 and 2 (n_1 and n_2),

$$\frac{n_1}{n_2} = m - 1, \tag{9.7}$$

and K is the ratio of the rate constants for the two processes, chemical repair (k_{m_2}) and oxygen fixation (k_{f_0}),

$$K = \frac{k_{m_2}}{k_{f_0}}. \tag{9.8}$$

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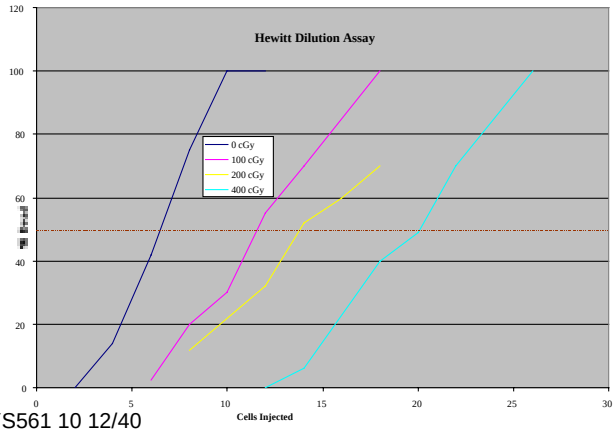
Homework Hints

- 2. Hewitt Dilution Assay: doses 0-4 Gy shown below. Last 3 dose-levels are farther to right. Dotted red line corresponds to LD_{50}.



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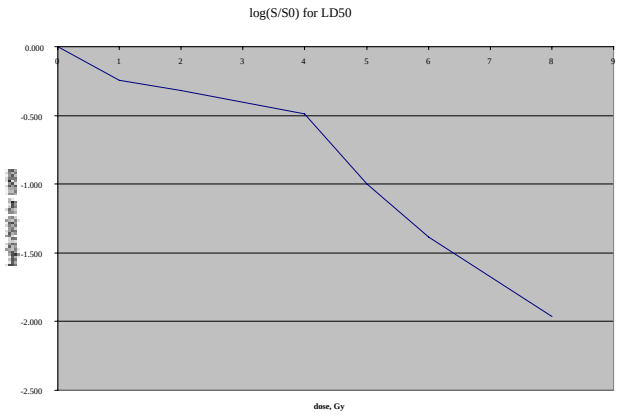
Homework Hints, Continued

2. Hewitt dilution assay:
from curves shown, we can estimate the LD_{50} for each radiation dose:

Dose, Gy	LD_{50}
0	6.4
1	11.8
2	13.8
4	20.2
5	65
6	160
8	597

So S/S_0 = (LD_{50} at a given dose)/ (LD_{50} at Dose=0).

Homework Hints, Continued



$$S/S_0 = e^{-K(SD + bD^2)}$$

$$e^{-p(aD + bD^2)}$$

calc p_a, p_b:

$$\ln S/S_0 = -p_a D - p_b D^2$$

$$\frac{\ln S/S_0}{D} = -p_a - p_b D$$

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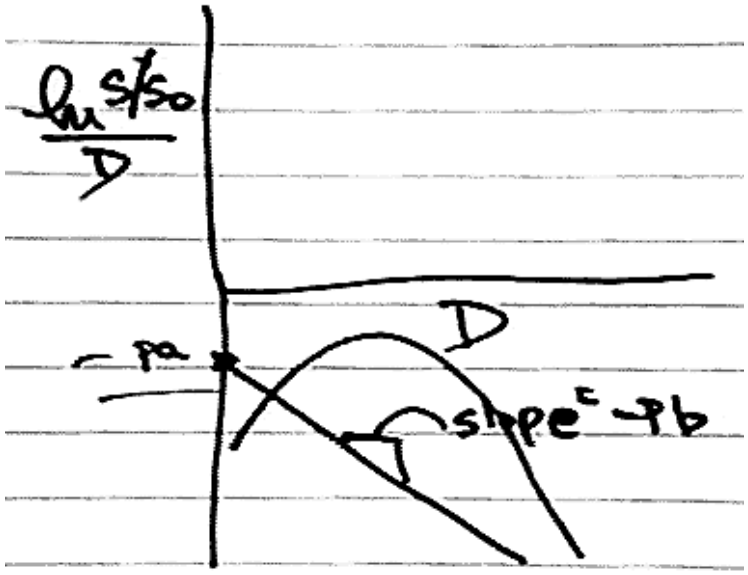

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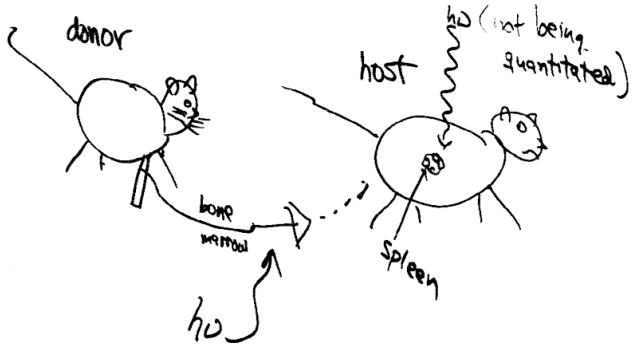
In Vivo Assays of Normal Cells

- CFU-S assay p. 244
  colony-forming unit/spleen



MTSH Model for Colony-Forming Units-Spleen (CFU-S)

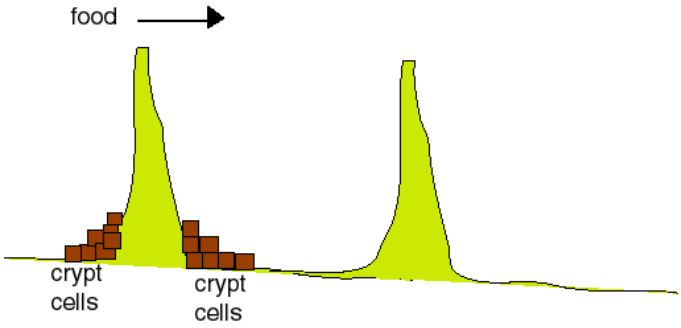
	n	D_o, cGy
in vitro irradiation	2.5	105
in vivo	1.5	95

Thus, this is a system with moderate inherent radiation sensitivity and virtually no capability of repair. Why is the in vivo repair capability smaller? Unclear.

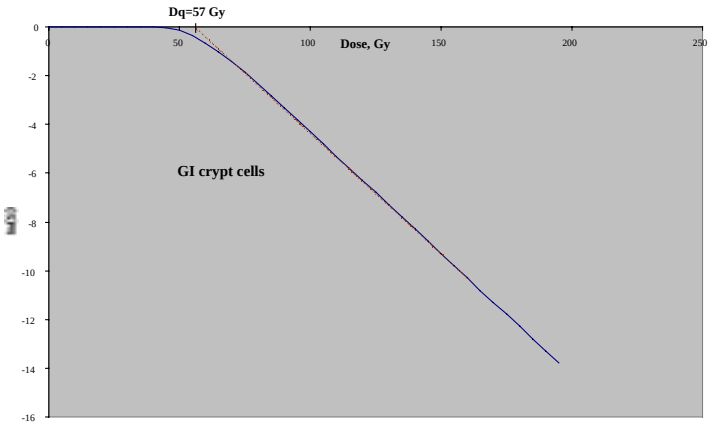
Gastrointestinal Crypt Cells

4 day turnover from base to tip.

Results: D_o ~ 10 Gy, n = 300 = exp(D_q/D_o)
large n value => rapid repair of sublethal damage

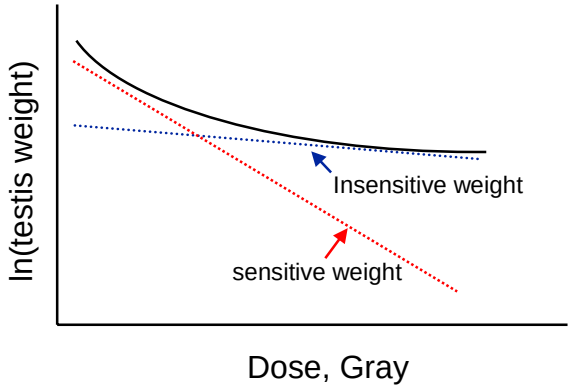


MTSH Model for GI crypt cells



Spermatogenesis

- Analyze radiation's effects via changes in weight of testes



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Developmental Stages in Spermatogenesis in the Mouse

Cell type	Days to mature spermatozoon	LD_{50} (cGy)
Type A spermatogonia (types A_s, A_1, A_2, A_3, A_4)	35–45	200 +
Intermediate spermatogonia	32–35	20
Type B spermatogonia	30–35	100
Primary spermatocytes[a]	20–35	
Resting (preleptotene)		200
Leptotene		500
Zygotene		500
Pachytene		Unknown
Diplotene		800
Diakinesis		900
Secondary spermatocytes	20–22	1,000
Spermatids	7–20	1,500
Spermatozoa	0–7	50,000

[a] Meiotic stages

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Testis Weight Loss Assay

Very early in the development of radiation biology it was observed by several investigators that there was a dramatic weight loss in the testes after irradiation. A number of approaches to developing a quantitative tool for the use of this observation were briefly reviewed by Alpen and Powers-Risius (1981). Kohn and Kallman (1954) were the pioneers in this effort, but it remained for J. S. Krebs to appreciate that a true survival curve could be developed from this weight loss data. Unfortunately, Krebs died before publishing this method, but it has been documented by Alpen and Powers-Risius (1981).

This version of the testes weight loss assay is based on the assumption that the loss of weight in the organ after irradiation is made up of two parts. There is a radiosensitive portion of the mass of the testis that is rapidly reduced after irradiation, and the logarithm of this weight loss is related linearly to dose. The remaining fraction of the weight of the testis (somewhat less than half) is taken to be radioresistant, but again it falls as an exponential function with dose.

The change in weight is described by

$$W_D = W_S e^{-k_S D} + W_R e^{-k_R D}, \qquad (10.3)$$

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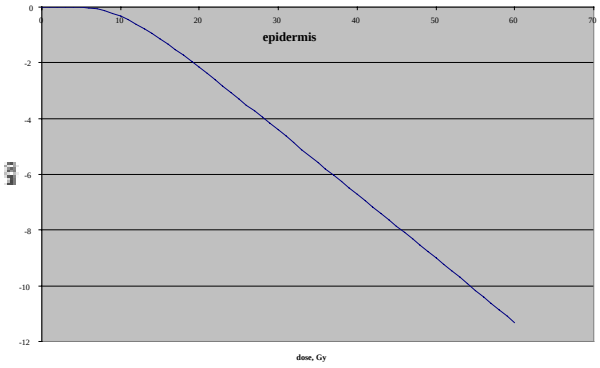
Skin

Exposure of epidermis can be modeled with MTSH kinetics. We find D_o ~ 4.35 Gy, n = 12. Note $D_q = D_0 \ln n = 10.81$.



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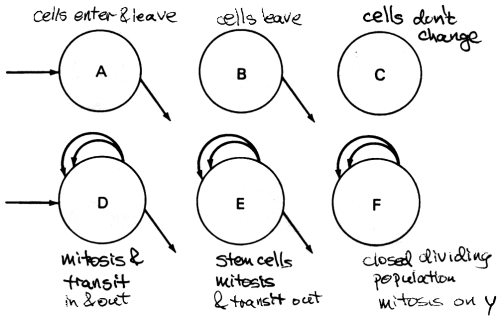
Acute Lethal Effects (< 1 Month)



- Fig. 10.1 ⇒ Populations of cells
- D & E categories are responsible for most acute effects:
  - D: mitotic, translatable in & out
  - E: mitotic, translatable out (stem cells…)

How do humans die of acute radiation exposure?

- Acute lethal dose typically above 5 Gy
- Organ systems affected:
  - Blood-forming organs:
    sensitivity mostly dependent on cycle time

Cell type	*cycle time*	*sensitivity*
Granulocyte	4 days	very high
Platelet	12 days	moderate
Erythrocyte	40 days	low

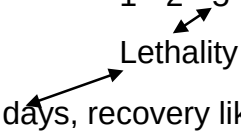
  - GI organs
  - CNS
  - Lymphocytes

Acute Lethal Effects (< 1 Month)

- Blood-forming effects
  - 3 weeks
  - Not very repairable
- GI - If not fatal within 10 days, recovery likely
- CNS
  - 1 Gy
    - Vomiting
    - Direct stimulation
  - 100 Gy
    - Massive disorientation
    - Death

1 - 2 - 5 Gy

Lethality

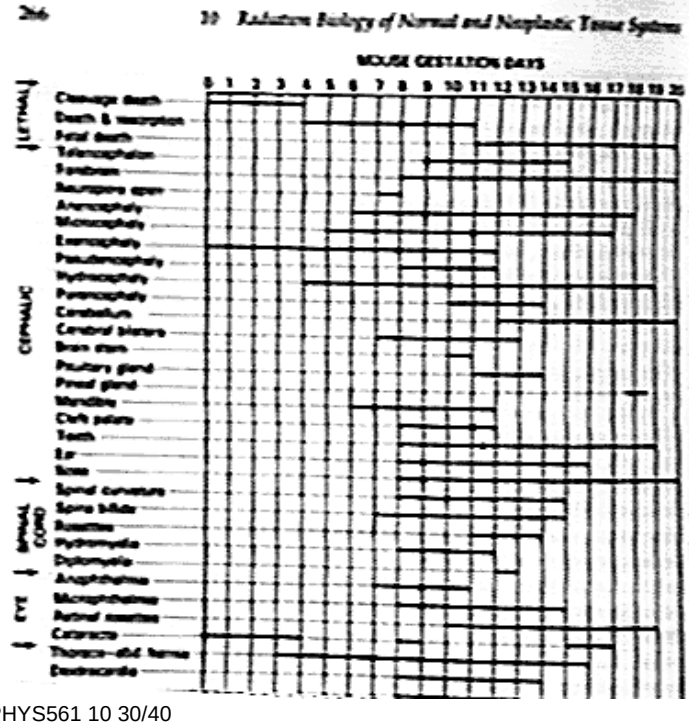


Lymphocytes: a special case

- Mature lymphocytes are fairly radiosensitive
- This is unusual for a nondividing, terminal cell type
- Some kind of “interphase death”
- There’s a lot of p53 gene product produced in lymphocytes: maybe they’re being stimulated into dying with moderate radiation exposure

Homework for 30 March

- Using, in part, the information in fig. 10.10, summarize which systems in a mammal are radiosensitive at various stages of fetal development.



Midterm

- 4 April 7:55 - 9:05
- Covering half of ch. 7
- 8,9,10,11
- Open book & notes
- No other books

Teratogenesis & Fetal Development

- Teratogenesis - Embryological abnormality
  monster
- It's traditional to argue that the fetus is highly radiosensitive, but it actually isn't, compared to other rapidly dividing cell systems.
- We need to distinguish among:
  - Damage to gametes before fertilization
  - Somatic damage to growing organism
  - Damage to mother that influences development

Measurement Problems associated with Teratogenesis

- Confounding effects (how can one tell these phenomena apart?)
  - Damage to embryo/fetus
  - Genetic damage before fertilization
  - Damage to placental system
- High background
  - High incidence of birth defects in unexposed subjects
  - 5% of all births involve some significant abnormality

Stages of Development

- Single cell $\rightarrow$ rather sensitive
- Conceptus
  - 2 cell: Rather resistant:
    both cells are totipotent, i.e. capable of differentiation into all necessary tissue types
  - All cells remain totipotent in the first few cell divisions; differentiation begins just before implantation
  - Severe damage to embryo can prevent implantation
- Early differentiation: Onset of abnormalities

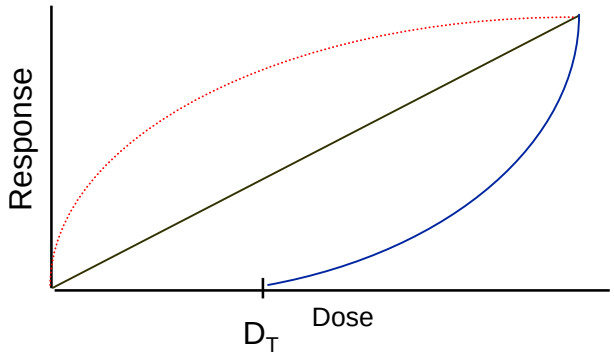
Stochastic Effects of Radiation

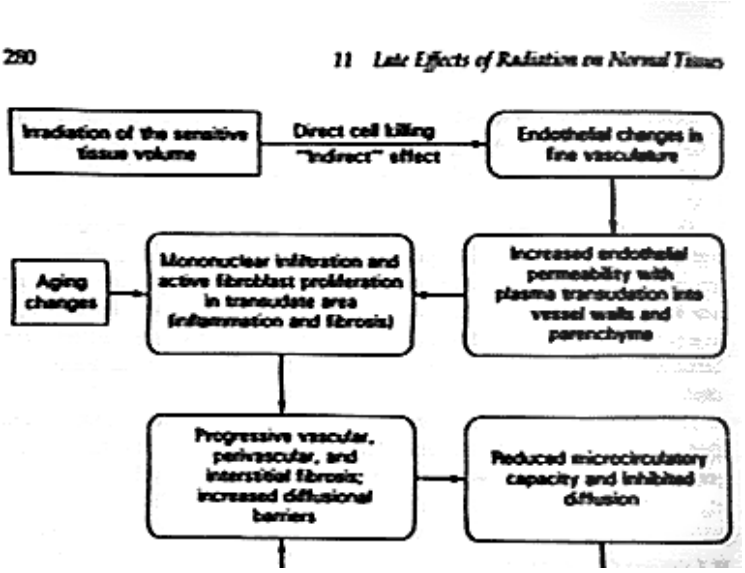
- One of two overarching categories of damage, particularly as it produces long-term effects:
- Percent of population affected by the exposure may be dose-dependent

  -BUT-
- Severity of condition in an affected individual is independent of dose
- Cancer is traditionally regarded as stochastic, but that may be an oversimplification

Nonstochastic Effects on Normal Tissue

- Severity of condition shows dose dependence
- Possible threshold dose (no effect below D_T)
- Most important mechanism: disruption of vascularization (Casarett model, Fig. 11.1)





Other types of late damage

- The assertion: If vascular damage were the whole story for the late effects of radiation, then the time of onset of late damage should be more or less the same for all organs. That's false!
- Stromal and parenchymal damage
  - parenchymal cells are those involved in the actual function of an organ, e.g. the cells in the liver that actually filter out damaging chemicals
  - Stromal cells are the support cells that undergird and provide morphological support for the parenchymal cells

Vascular endothelium as target

- Endothelial cells lining capillaries are a cell-renewal system, so damage there will hurt the organ that those capillaries supply with blood.
- Types of damage:
- Direct: interphase death of cells in wall (DNA damage leading to apoptosis)
- Indirect: interference with cell renewal

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Functional Subunits

- Concept: The fate of an organ depends on individual functional subunits (FSUs).
- When all the stem cells that give rise to the functioning cells in a functional subunit die, then the functional subunit can't continue to operate
- Examples:
  - In the kidney: the nephron
  - In the lung: the alveolus
  - In the pancreas: a single islet of Langerhans
  - In the small intestine: a gastrointestinal crypt
- Can we generalize this to all tissues? Maybe not.

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