Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Physics 561

Radiation Biophysics, Lecture 10:
Nonstochastic Effects

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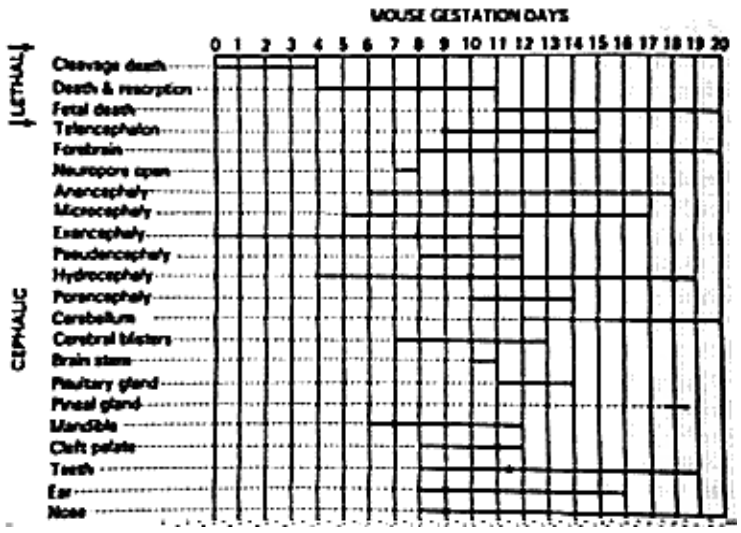
Plans For This Class

- Discuss homework for 3/30
- Review: Vascular Endothelium
- Late Effects where Vascular Endothelium is the primary target
- Exceptions
- Fractionation
- Models for Fractionation
- Role of Repair in Fractionation
- Stochastic effects: Cancer

Homework problem, Chapter 10

- This is an attempt to get you to think about the collected information in fig. 10.10. There is no right answer, but some general conclusions should be evident:
- Most effects on the eye (other than cataracts) occur relatively late
- Most functional disorders are very late
- Cephalic disorders occur all through gestation



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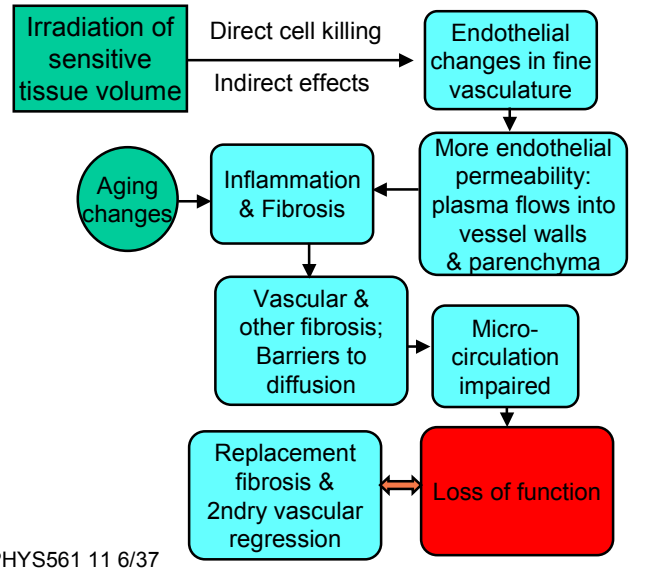
Review of fig. 11.1



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Systems where this mechanism predominates

- Gastrointestinal
  - Esophagus
  - Stomach
  - Small & large intestine
  - Rectum (not the only mechanism)
- Skin (dermal layer) & other epidermoid mucosal organs
- Liver (except for hepatitis)
- Kidneys (many other mechanisms)
- Lung (other mechanisms)
- Brain
- Spinal cord (low-dose effects are of this type)

Non-endothelial late effects

- Rectum: thinning & perforation of rectum
- Epidermal layer of skin: desquamation
- Kidneys: complicated, multi-causal; tubular disfunction in glomerulus unrelated to vascular disorders
- Lung: killing of type 2 alveolar cells
- Spinal cord: fast paralysis involves damage to myelin sheath around cord
- Eye: improper differentiation of lens fiber cells leads to cataracts

Summary of organ-specific effects

See table in website for full summary:

http://icarus.csrri.iit.edu/radbio/nonstochastic.html

Fractionation

- Radiotherapy can't wait for research: people need answers now
- Even in the 30's and 40's it was recognized that there was an advantage in treating tumors to fractionate the dose, i.e. if the total dose you wanted to deliver was 5 Gy, you got a better therapeutic ratio if you delivered it in several small doses rather than all at once.

Power Law

- Witte:
  measured dose D required to reach the threshold for skin erythema as a function of dose rate or number of fractions n:
- Power law:
  $\ln D = a + b \ln n$, i.e.
  $D = e^{a+b\ln n} = e^{a}\, e^{b\ln n} = e^{a}\, e^{\ln n^{b}}$
  $D = Q n^{b}$, where $Q = e^{a}$.
- Strandqvist: total time of treatment T:
  $D = UT^{1-p}$; 1-p for skin was about 0.2.
- Cohen: $1-p$ is tissue specific (0.30 normal, 0.22 for carcinomas); this enables radiotherapy!

Normalized Standard Dose

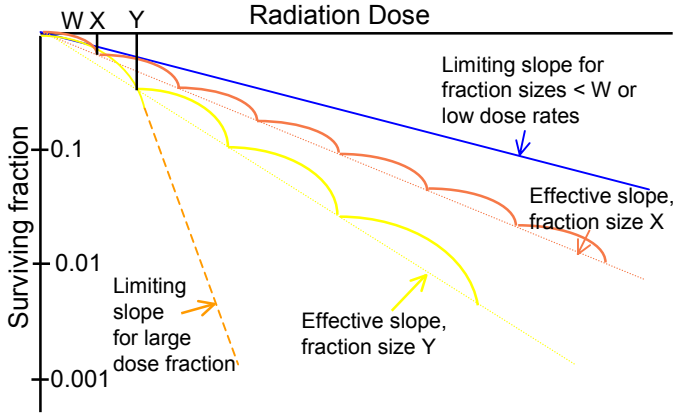
- Ellis: tolerance dose D for normal tissue is related to the number of fractions N and the overall treatment time in days, T:
- $D = \rho T^{0.11} N^{0.24}$
- The value of ρ is called the Normalized Standard Dose or NSD; it can be determined separately for each tissue and each treatment modality.

Can we do better than this?

- Explicit accounting for damage in terms of repairability:
  - Sublethal
  - Potentially lethal
  - Nonreparable
- Model suggests that the limiting slope of ln*S* vs *D* as you fractionate a lot is determined by the single-hit (nonrepairable) mechanism

Effect of Fractionation

Fig. 11.3: Repair capability; limiting slope determined by fraction sizes < W



Douglas & Fowler

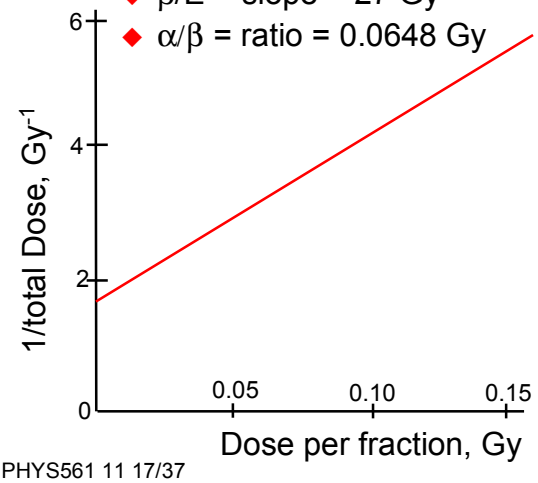
- Used mouse-foot skin reaction to fractionated doses: ≤ 64 fractions , constant overall time
- For an isoeffect, the following equation held:
  $n(\alpha\Delta + \beta\Delta^2) = \gamma$
  where n = # of fractions, Δ = dose per fraction
  note: I'm using Δ where Alpen uses D.
- Assumptions:
  - Repair occurs after single doses
  - Biological outcome depends on surviving fraction of critical clonogenic cells
  - Every equal fraction will have same biological effect

Survival fraction, Douglas&Fowler formulation

- $\ln S = n(F_e/a)\Delta$
- Note that a is not α.
- For an appropriate choice of a, $F_e = 1/(n\Delta)$
- Single-dose cell survival is $S = exp(F_e/a)\Delta$
- So we do an isoeffect plot of F_e vs. Δ:
  $F_e = b + c\Delta$
- Thus $\ln S = n(b\Delta/a + c\Delta^2/a)$
- cf. Standard LQ model, assuming constant effect per fraction: $\ln S = -n(\alpha\Delta + \beta\Delta^2)$
- Defining $E = -\ln S$, $E/(n\Delta) = \alpha + \beta\Delta$
  $1/(n\Delta) = \alpha/E + \beta\Delta/E$
- plot Δ vs $F_e = 1/(n\Delta)$ to get α/E, β/E.

Fig. 11.4: finding α/E, β/E

- α/E = intercept = 1.75 Gy^{-1}
- β/E = slope = 27 Gy^{-2}
- α/β = ratio = 0.0648 Gy



Applicability

- We don't have to be using an LQ model to work with the Douglas-Fowler formulation; we just need a nonzero slope of lnS vs. D at low dose.
- Thus MTSH doesn't work:
  With MTSH, $S= 1 - (1 - \exp(-D/D_0))^n$
- For n > 1,
  $dS/dD = -n(1-\exp(-D/D_0))^{n-1}$
  at D = 0, $dS/dD = -n(1-e0)^{n-1}= -n(0)^{n-1} = 0$.
- For n = 1, $S = \exp(-D/D_0)$
  $dS/dD = -1/D_0\exp(-D/D_0)$
  at D = 0, $dS/dD = -1/D_0e-0 = -1/D_0 \neq 0$.

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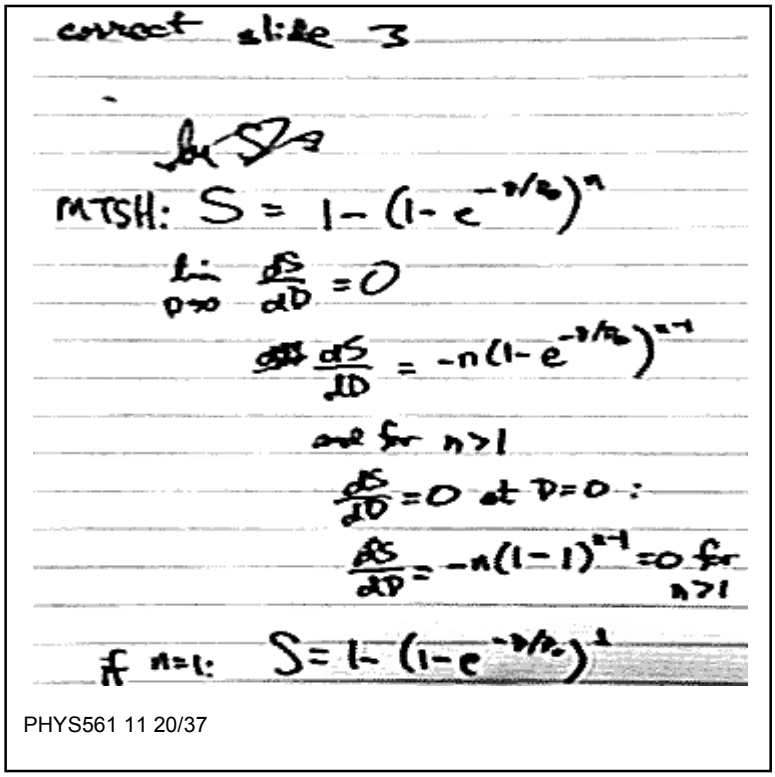
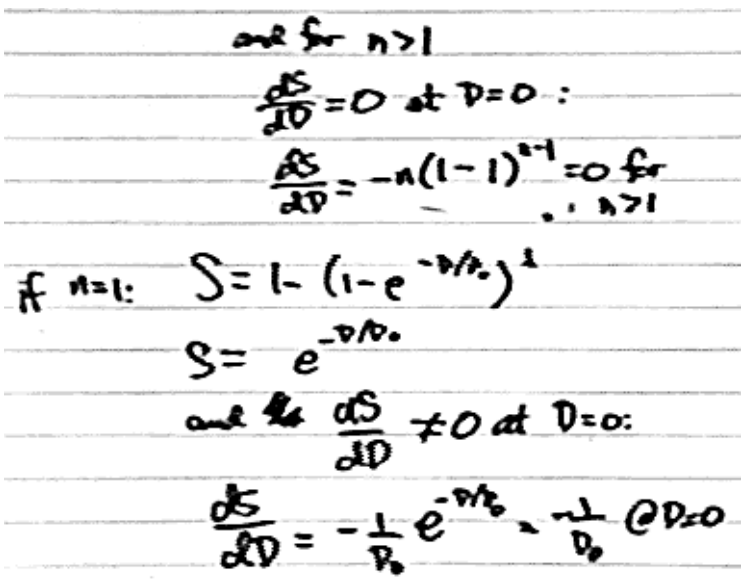




Withers extension of F_e model

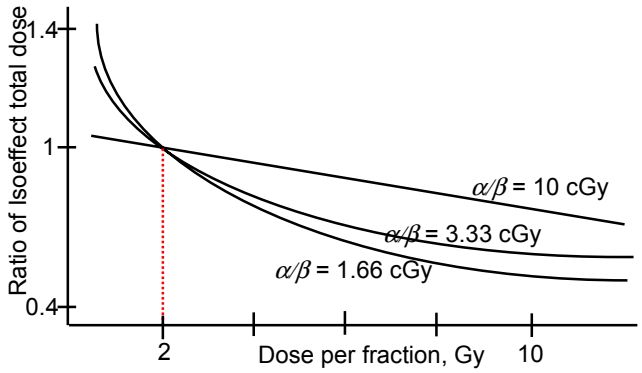
- Define *flexure dose* as the dose per fraction below which no further protection is provided by interfraction repair.
- It turns out the flexure dose is a multiple of α/β (units are correct: α/β is in Gy)
- Let's pick a reference total dose D_{ref} and a reference dose per fraction Δ_{ref}. Then $-\ln S_{ref} = N_{ref}(\alpha\Delta_{ref} + \beta\Delta_{ref}^2)$, where N_{ref} is the reference number of doses ($D_{ref} = N_{ref}\Delta_{ref}$)
- Then for a different total dose D and different dose per fraction Δ, $D = N\Delta$, $-\ln S = N(\alpha\Delta + \beta\Delta^2)$

Withers result

- In order for the reference regimen to have the same effect as the test regimen,
- $S = S_{ref}$, or $-\ln S = -\ln S_{ref}$
- Therefore
  $N_{ref}(\alpha\Delta_{ref} + \beta\Delta_{ref}^2) = N(\alpha\Delta + \beta\Delta^2)$, i.e.
  $\alpha N_{ref}\Delta_{ref} + \beta N_{ref}\Delta_{ref}^2 = \alpha N\Delta + \beta N\Delta^2$
- But $N_{ref}\Delta_{ref} = D_{ref}$ and $N\Delta = D$, so
- $N_{ref}\Delta_{ref}^2 = D_{ref}\Delta_{ref}$ and $N\Delta^2 = D\Delta$
- Thus $D_{ref}(\alpha + \beta\Delta_{ref}) = D(\alpha+\beta\Delta)$
  $D/D_{ref} = (\alpha + \beta\Delta_{ref})/(\alpha+\beta\Delta) = (\alpha/\beta + \Delta_{ref})/(\alpha/\beta+\Delta)$

Withers plot

Comparison of three different Isoeffect curves, depending on α/β:



Homework for Friday 6 April

- *[This is a variation on problem 1 of chapter 11 in the book. I don't understand the wording of Alpen's problem, so I made up my own version]*
- Suppose that the Ellis power law equation (11.2) is valid in a particular tissue. A typical tumor dosing regimen consists of twenty treatments over four weeks using weekdays only, i.e. 25 days from the first Monday through the last Friday. Thus if the total dose delivered is 60 Gy, we deliver 3 Gy in each of the 20 treatments.

Homework for 6 April, concluded

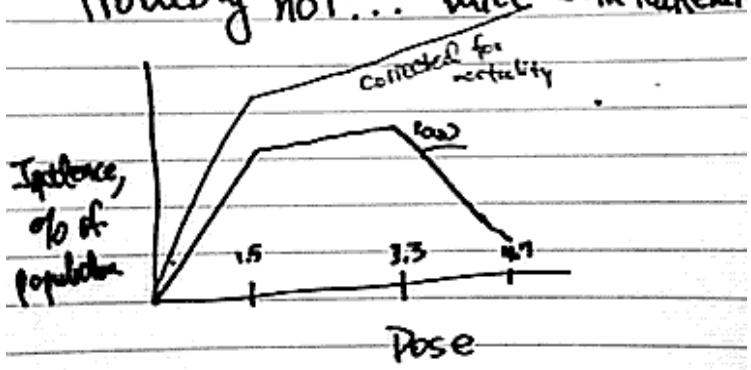
- (a) Assuming NSD=17Gy, calculate the tolerance dose associated with this regimen. Will we be able to deliver this treatment regimen without damage to the normal tissue?
- (b) If we wish to shorten the treatment time to three weeks (18 days from the first Monday to the last Friday) we will have to deliver larger doses per day, e.g. 60/18 = 3.33 Gy/day if we include weekends. If we allow more than one dose delivery per day we can reduce the dose delivered in each treatment back to lower levels, though. Calculate the number of doses we will have to deliver over the 18-day period if we wish to ensure that the full 60 Gy will be tolerated. Determine the dose per treatment.

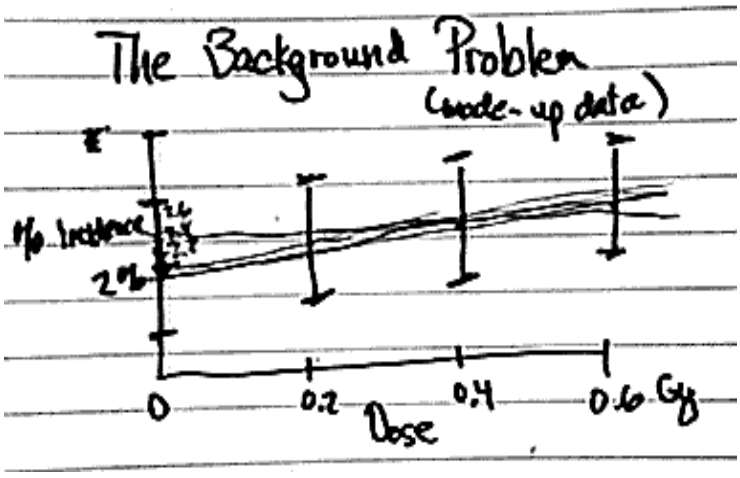
Stochastic:

% of population affected
is dependent on dose
— but —
severity of condition in an individual
is independent of dose -

Does that really describe cancer?

Probably not... mice with leukemia





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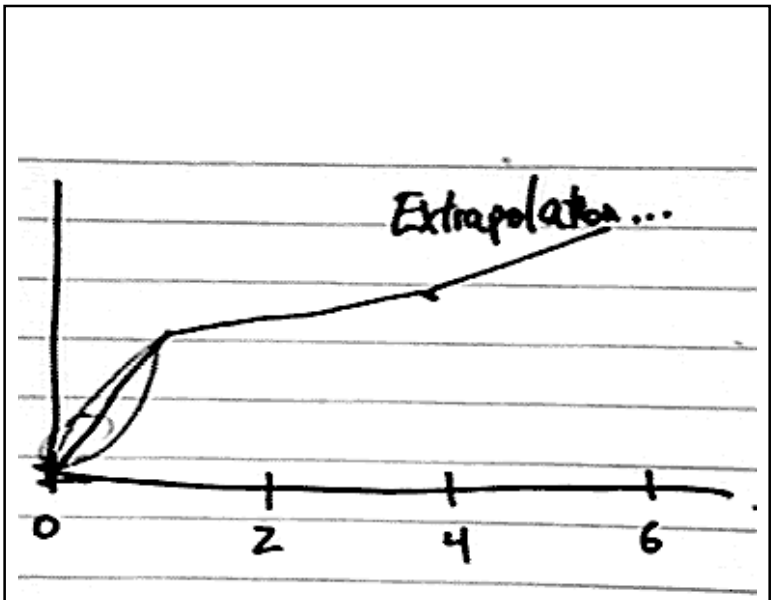

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Differential Sensitivity:

some individuals in a population are more susceptible (to tumors) than others

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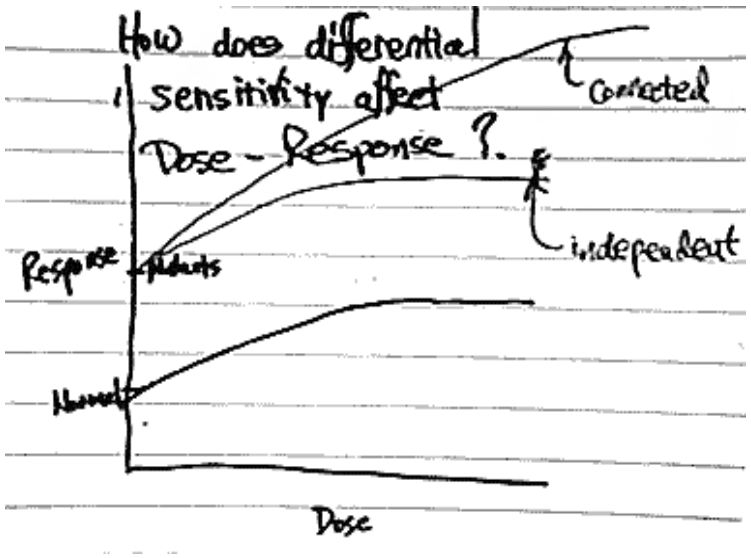

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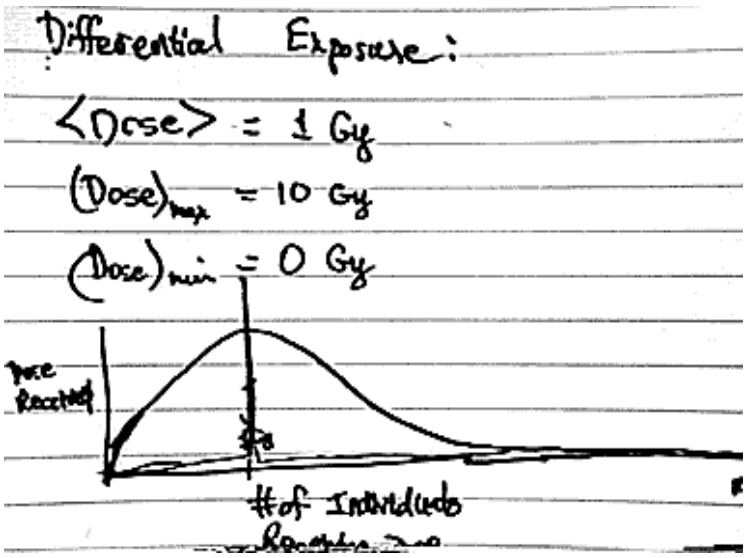

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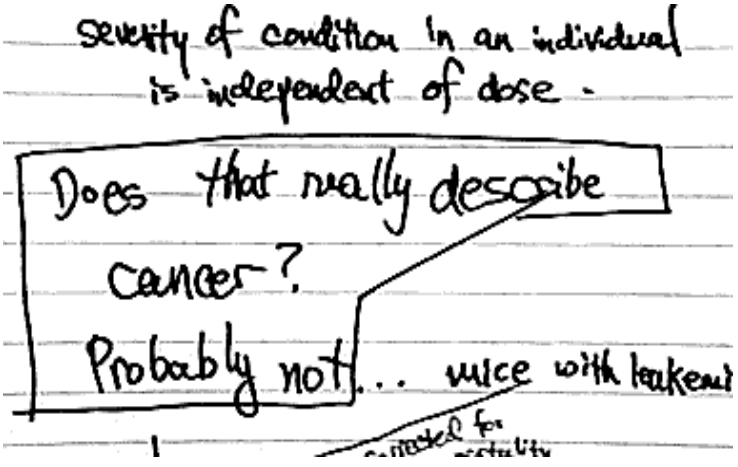

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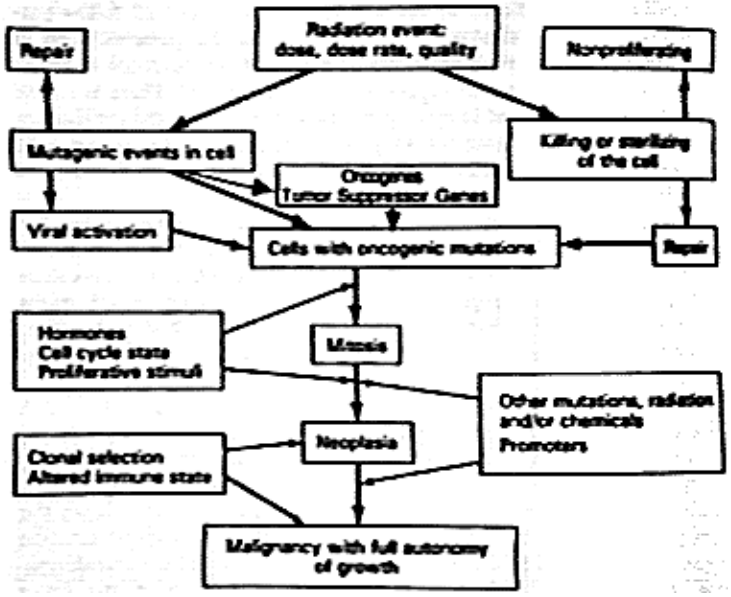
at very high doses. This explanation is not entirely satisfactory to explain the continuous plateau in the dose–response curve seen for many tumors. Literally hundreds of studies have been done on animal models for radiation carcinogenesis, but it would be unproductive to review these reports in detail. Upton (1986) has, however, provided a very concise summary of the findings of all of these experiments:

1. Neoplasms of almost any type can be induced by irradiation of an animal of suitable susceptibility, given appropriate conditions of exposure.
2. Not every type of neoplasm is increased in frequency by irradiation of animals of any one species or strain.
3. The carcinogenic effects of irradiation are interconnected through a variety of mechanisms, depending on the type of tumor and the conditions of exposure.
4. Some mechanisms of carcinogenesis involve direct effects on the tumor forming cells themselves, but others may involve indirect effects on distant cells or organs.
5. Although the dose–incidence curve has not been defined precisely for any neoplasm over a wide range of doses, dose rates, and radiation qualities, the incidence generally rises more steeply as a function of dose and is less dependent on dose rates with radiations of high linear energy transfer (LET)—such as alpha particles or fast neutrons—than with radiations of low LET—such as X-rays and gamma rays.
6. The development of neoplasia appears to be a multicausal and

8. At high dose levels the expression of carcinogenic effect often tends to be suppressed by sterilization of the potentially transformed cells or by other forms of radiation injury, resulting in saturation of the dose–incidence curve.
9. The distribution in time of appearance of radiation induced tumors characteristically varies with the type of tumor, the genetic background and age of the exposed animal, the conditions of irradiation, and other variables.
10. Because of the diversity of ways in which irradiation can influence the probability of neoplasia, the dose–incidence relationship may vary accordingly.

The foregoing conclusions are quoted directly from Upton (1986), and, as for nearly all matters related to radiation carcinogenesis, there are disputes among specialists as to the precise tone of each quote. The "bending-over" of the dose–response curve is easily explained by the cell killing hypothesis, but as we will see shortly, when the cell transformation model is used, even after correction for cell killing, the curve of transformants per surviving cell still shows a saturation-type curve in some in-



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