Illinois Institute of Technology

Radiation Biophysics: Nonstochastic Effects

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Lecture 11

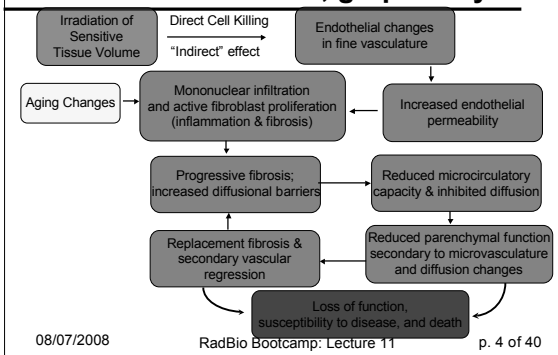
Plans For This Class

- Discuss homework for 7/7
- 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

Casarett model, graphically



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 on website for full summary in the HTML document on nonstochastic effects

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 and Timing

- 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 $Q = e^a$.

Power-law treatments, continued

- 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.

What are we really doing here?

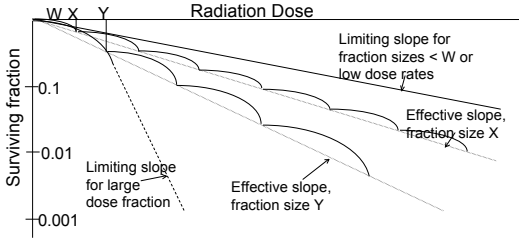
- This is curve-fitting in its most unapologetic form.
- As far as I know there is no attempt to attach physical meanings to the exponent $(1-p)$ in the Strandqvist model.
- Nor is there a reason to think there's anything physically significant about the 0.11 and 0.24 exponents in the Ellis formulation
- Clearly time and number of fractions are (anti-)correlated variables
- BUT this approach can be helpful in treatment planning, at least within the range of conditions for which the formulas are valid.

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, to reduce potential confusion with the overall dose.

Douglas-Fowler 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

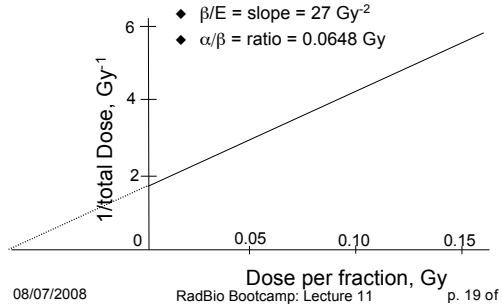
- $\ln S = n(F_e/a)\Delta$
- Note that a is not α.
- For an appropriate choice of a, $F_e = 1/(n\Delta)$
- Single-dose cell survival is $S = \exp[(F_e/a)\Delta]$
- So we do an isoeffect plot of F_e vs. Δ:
  $F_e = b + c\Delta$

Douglas & Fowler Survival Fraction, Continued

- 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 ln*S* 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 $D = 0$, $dS/dD = -n(1-e^0)^{n-1} = -n(0)^{n-1} = 0$.
- For n = 1, $S = \exp(-D/D_0)$
  $dS/dD = -1/D_0 \exp(-D/D_0)$
  at $D = 0$, $dS/dD = -1/D_0 e^{-0} = -1/D_0 \neq 0$.

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)

Withers extension: results

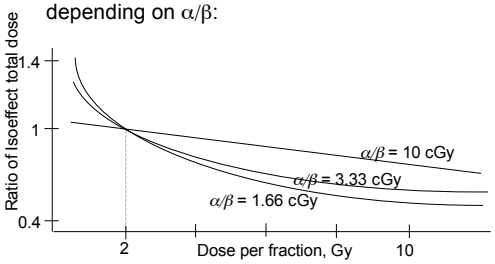
- Let's pick a reference total dose D_{ref} and a reference dose per fraction Δ_{ref}.
- Then
  $-\ln S_{ref} = N_{ref}(\alpha\Delta_{ref} + \beta\Delta_{ref}^2)$,
  where N_{ref} is the reference number of doses
  ($D_{ref} = N_{ref}\Delta_{ref}$)
- Then for a different total dose D and different dose per fraction Δ, D = N Δ,
  $-\ln S = N(\alpha\Delta + \beta\Delta^2)$

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:



An Ellis-law problem

- *[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. 26 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.

Ellis problem, 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 (19 days from the first Monday to the last Friday) we will have to deliver larger doses per day, e.g. 60/19 = 3.16 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 (1.052 Gy/treatment). Calculate the number of doses we will have to deliver over the 19-day period if we wish to ensure that the full 60 Gy will be tolerated. Determine the dose per treatment.

Stochastic Effects

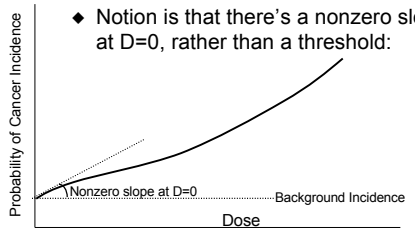
- These are defined as effects for which the percentage of the population affected by the exposure is dependent on dose
- BUT the severity of the [medical] condition in an individual is independent of dose.

Does cancer really work that way?

- Not entirely
- Fry (1976):
  - Harderian gland tumors seldom invasive after low doses of low LET radiation
  - More invasivity and metastasis after higher doses of low LET radiation
- Ullrich & Storer (1979): maybe there's a threshold dose

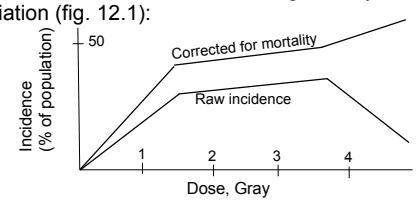
Traditional View of Population Dose-Response Relationships

- Notion is that there's a nonzero slope at D=0, rather than a threshold:



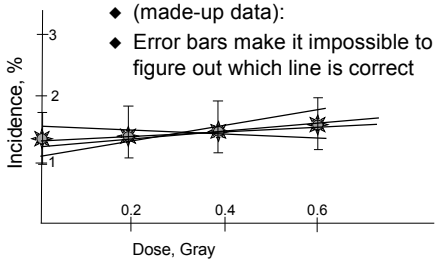
Radiation Carcinogenesis in Animals

- Earliest tool in understanding radiation-induced cancer
- Consider mice with leukemia brought on by ionizing radiation (fig. 12.1):



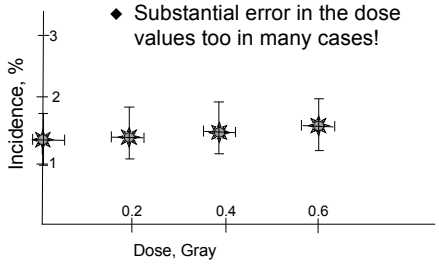
The Background Problem

- (made-up data):
- Error bars make it impossible to figure out which line is correct



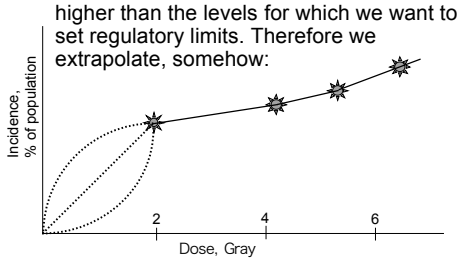
In fact, it's worse!

- Substantial error in the dose values too in many cases!



Extrapolation to low dose

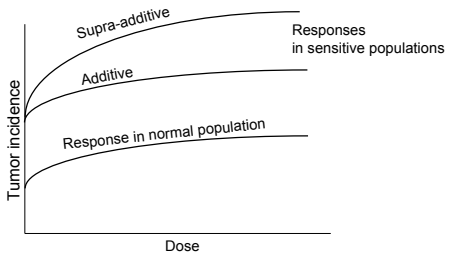
- The only reliable experimental measurements are made at doses much higher than the levels for which we want to set regulatory limits. Therefore we extrapolate, somehow:



Differential Sensitivity

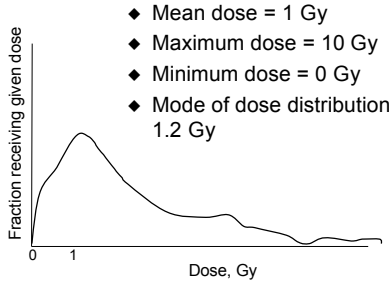
- Some individuals within a population are more susceptible than others
  - To tumors
  - To other conditions
- Why?
  - Defective DNA repair mechanisms
  - Problems in cell signaling
  - Lifestyle agents (smoking, drinking, lack of exercise)
  - Genetic differences among individuals

How does differential sensitivity affect dose-response relationships?



Differential Exposure

- Mean dose = 1 Gy
- Maximum dose = 10 Gy
- Minimum dose = 0 Gy
- Mode of dose distribution = 1.2 Gy



Upton's Summary of the Animal Data

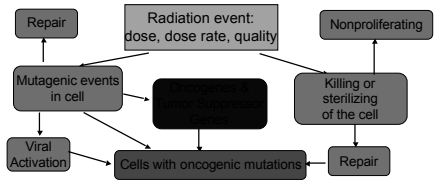
- Neoplasms of almost any type can be induced by irradiation of a suitable animal in a suitable way.
- Not every type of neoplasm is increased in frequency by irradiation of animals of one strain.
- Carcinogenic effects are interconnected through a variety of mechanisms.
- Some mechanisms involve direct effects on the tumor-forming cells; others don't.
- High-LET radiation produces dose-dependent rather than dose-rate-dependent effects

Upton, continued

- Development of tumors is multicausal and multistage; effects of radiation may be modified by other agents.
- Low to intermediate doses produce no tumors unless promoted by other agents.
- At high doses the effect is suppressed by sterilization of potentially transformed cells; this causes saturation.
- Time distribution of appearance of tumors varies with type of tumor, genetics and age, conditions of irradiation.
- Dose-response curves vary significantly.

Events from transformation to mutated cells (fig. 12.2)

- Many factors influence events up through malignancy



Mutations through Malignancy

- Additional influences seen