Illinois Institute of Technology

Radiation Biophysics
High-LET Radiation
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Class Overview

- High-LET Radiation
  - Review of definitions
  - Physics of energy deposition
  - Impact on DNA
  - Resistance to repair

High LET Radiation

- Review definition of LET: Rate of change of energy with distance along a track
- Caveat I: Local Deposition
- Caveat II: LET only associated with charged particles

LET Equation: Bethe-Block Formulation

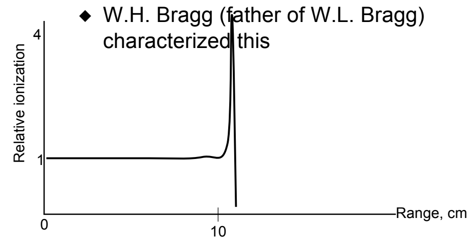
- If we let:
  - z^* = Effective charge of projectile particle
  - Z = Atomic number of atoms in medium
  - A = Atomic weight of atoms in medium
  - C = sum of electron shell corrections
  - $\delta/2$ = condensed medium correction
  - β = v/c for particle
  - I = <ionization potential for absorbing medium>
- $-dE/dx = (0.307 z^{*2} Z/A\beta^2) \bullet \{[\ln((2m_0c^2\beta^2)/(1-\beta^2)I)] - \beta^2 - C/Z - \delta/2\}$

Where is Energy Deposited?

- Most of the energy is deposited just before the particle stops moving
- We're interested in *average* LET over a region or track

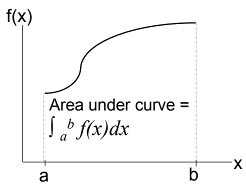
Depositions with heavy particles

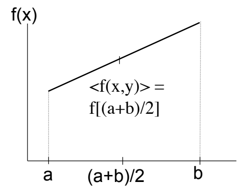
- "Bragg peak": most of the energy is deposited over a narrow linear track.
- W.H. Bragg (father of W.L. Bragg) characterized this



Calculating Averages of Continuous Variables

We wish to calculate the mean of a continuous function $f(x)$ over a range of x from a to b,
Then $\langle f(x)\rangle_{a,b} = [\int_a^b f(x)dx] / (b-a)$



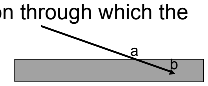


Applying this to LET

- Average LET over energies:
  $(LET_{av})_S = (1/(E_2-E_1)) \int_{E_1}^{E_2} [LET(E)]dE$
- So for a slowly varying LET function we assume that it is close to linear, i.e.
  $(LET_{av})_S = [(LET)_1 + (LET)_2] / 2$
- These are instances of *track segment averages,* $(LET_{av})_{TS}$;
  they're somewhat different from *energy averages*, for which we average over energy deposited.

Alternative averages

- Energy-averaged LET
  (see previous slide; energy range from E_1 to E_2):
  $\langle LET\rangle_S = [1/(E_2-E_1)] \int_{E_1}^{E_2} LET(E)\, dE$
  where E is the energy that we're averaging over.
- Track-averaged LET
  (track from position a to position b):
  $\langle LET\rangle_{TS} = [1/(b-a)] \int_a^b LET(x)dx$
  where x is the linear dimension through which the energy is being deposited



Average LET, keV μm^{-1}

Table 14.1:

Radiation type	$(LETav)_T$	$(LETav)_E$
^{60}Co γ-rays	0.27	19.6
250 kVp x-rays	2.6	25.8
3 MeV neutrons	31	44
Radon α rays	118	83
14 MeV neutrons	11.8	125
Recoil protons	8.5	25
Heavy recoils	142	362

•Looks like the $(LETav)_{TS}$ is more in accord with our intuitive notion of what constitutes LET!

Direct & Indirect Effects

◆High LET means that many ionizations occur in a small neighborhood

	LET Kev/μm	Spur energy eV	Events/μm	Spacing nm
60Co γ	0.25	60	4	250
Radon α	118	60	2000	0.5

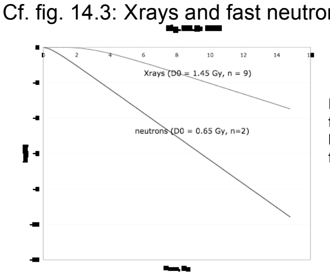
◆This fact by itself accounts for much of the difference in biological consequence of high LET radiation

Biological Effects of High-LET Radiation

- RBE = relative biological effectiveness
- analogous to OER in its definitional form:
  RBE = (dose for given end point for reference radiation) / (dose for given end point for test radiation)
- Problem with this formulation:
  - assumes that dose-response curves are described by identical functions, i.e.
  - RBE is independent of the response level at which it is estimated. Often not true!

MTSH comparisons

- Cf. fig. 14.3: Xrays and fast neutrons

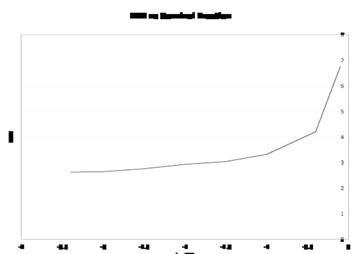


Results from hamster fibroblasts

Can we define a single RBE?

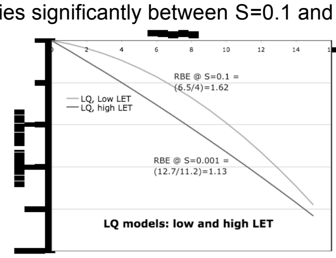
- Not really, unless our survival curves are really just rescalings of one another (“dose-modifying effect”)
- For MTSH data RBE will be close to constant if the extrapolation numbers aren’t too high
- For LQ we’re definitely going to have to pick a survival ratio

Survival Level Matters!



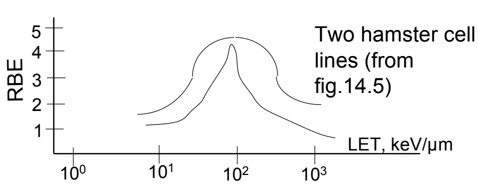
LQ case

- RBE varies significantly between S=0.1 and S=0.001:



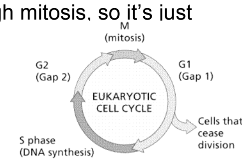
Relationship between RBE and LET

- RBE vs LET:
- Generally higher LET radiations have higher RBE, up to a certain point.
- With some systems the curve turns over.



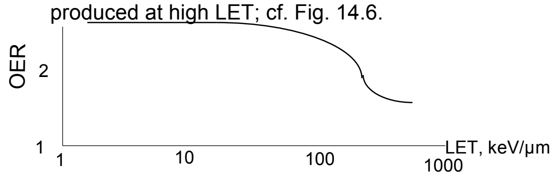
Cell-Cycle Dependence for RBE

- Low LET radiations exert much more effect in late G2 & M than elsewhere
- High LET radiation exerts approximately equal effects throughout the cell cycle
- Reason: irreparable damage early in the cycle will persist through mitosis, so it’s just as bad!



OER vs LET

- OER for High-LET Radiation is generally smaller than for low-LET radiation because the damage is less dependent on oxygen fixation of radical species.
- This plot shows OER going not to 1 but to ~1.5-- because water-derived radicals are still produced at high LET; cf. Fig. 14.6.



LET vs Fractionation

- Recall that repair-competent systems respond less to fractionated doses than to single doses whereas repair-deficient systems are fractionation-independent
- For high-LET radiation fractionation does not decrease biological effects

Contrarian results for fractionation

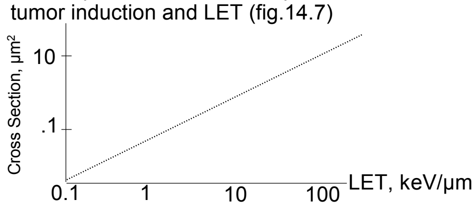
- Sometimes in tumors fractionation *increases* biological effect!
  - Why? - no explanation in Alpen
  - 2-stage model for cancer: (Ullrich)
  - Also: high dose rate is more likely to simply kill the cell rather than producing clonogenically competent but mutated cells (remember the concept of correcting for mortality in epidemiology)

Late Effects of High LET Radiation

- You can induce cancer with neutrons
- Ignores fractionation or (!) damage is more likely with fractionation
- Tumors also arise from heavy-ion irradiation

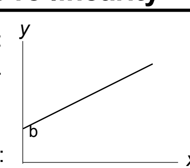
LET vs. Cross Section

- Alpen looked at particle fluence as a dose parameter-- requires constant LET over volume
- Result: power-law relationship between cross section for tumor induction and LET (fig.14.7)

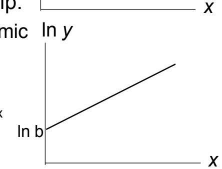


General note re linearity

- Ordinary linear relationship:
  - Both axes on linear scales.
  - $y = ax + b$,
  - a = slope, b = Y intercept

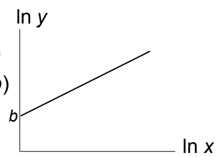


- Semi-log linear relationship:
  - X linear scale, Y logarithmic
  - $\ln y = ax + b$
  - $\exp(\ln y) = \exp(ax+b)$
  - $y = \exp(b)\exp(ax) = ke^{ax}$
  - for $k = \exp(b)$



Third possibility: power law

- Here we have linearity on a log-log plot:
- $\ln(y) = a\ln x + b$
- $\exp(\ln(y)) = \exp(a\ln x)\exp(b)$
- $y = k \exp(a \ln x)$ for $k=\exp(b)$
- But $a\ln x = \ln(x^a)$, so
- $y = k\exp(\ln(x^a)) = k\, x^a$
- So this is a *power law*.



Probability of Traversals

- Table 14.2 shows that multiple traversals of the nucleus are very rare even at high doses
- It also shows a close correspondence between cross section for tumor production and cross-section for traversal

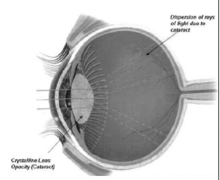
Dose, Gy	<fluence/ cell>	Probability of traversals 0	1	2	>= 1
0.01	0.006	0.993	0.006	$2.1*10^{-5}$	0.006
0.02	0.013	0.987	0.013	$6.8*10^{-5}$	0.013
0.05	0.032	0.968	0.031	$5.0*10^{-4}$	0.032
0.15	0.097	0.907	0.088	$4.0*10^{-3}$	0.092
0.20	0.129	0.878	0.114	$7.0*10^{-3}$	0.121
0.30	0.193	0.823	0.159	$1.5*10^{-2}$	0.176
0.40	0.258	0.772	0.199	$2.5*10^{-2}$	0.227

Cell Transformation in High-LET Irradiation

- Assertion: non local effects on DNA predominate over point mutation events
- Certain assay systems suggest this assertion:
- Kronenberg et al, human TK6 lymphoblasts--entire *hprt* gene is missing after irradiation
- "If large genomic changes are brought about by heavy ion radiation, then a multistep process may be short circuited to a single event."

Cataracts

- The vertebrate eye is a remarkable organ
- All the living components must be completely transparent for maximum fidelity of light transmission.
- Even the lens is made up of living cells!
- A loss of transparency is a *cataract*, either evanescent or permanent.
- A variety of insults can give rise to a loss of transparency.



Cataracts from high-LET radiation

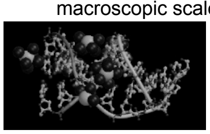
- It's long been known that high-LET radiation can give rise to cataracts, even at low doses.
- Relative biological effectiveness of high-LET radiation (neutrons) is 30 or more for low doses
- RBE goes down for higher doses
- Beams of ions (Z > 20) produce similar effects, again including lowered RBE for higher doses.

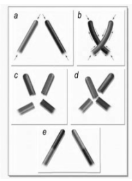
The Ullrich Tumor Experiments

- Ullrich found that with low-doses of neutrons, fractionation never diminished incidence of tumors
- With certain types (lung, mammary) there was an *enhancement* in tumor rate with fractionation
- Dose-response was nonlinear
- Saturation and fall-off of incidence with high doses

Ullrich Experiment: Why?

- Mechanisms of Genetic Damage
- Low vs High LET
  - Low-LET radiation exerts many of its effects at the level of point mutations (single-base substitutions, deletions, or additions)
  - High-LET exerts most of its effects on a more macroscopic scale





Macroscopic Damage to Chromosomes

- First half of chapter 13
- Structural changes in chromosomes
  - Inversions of fragments
  - Multiple hits
  - Isochromatid breaks
  - Dicentrics
  - Minutes
  - Cross over

Cataracts

- Cataracts are common with high-LET radiation
- Reminder: cataracts involve loss of transparency in the lens because problems with differentiation will lead to failure of alignment of the fibers
- Cataracts happened with workers in early accelerator facilities
- RBE values are high, and tend to be higher for lower doses (i.e. low doses cause almost as many cataracts as higher doses)

Cataracts from specific types of radiation

- Neutrons:
  - In animals: cause cataracts with RBE~2 to 100
  - But with humans: cataracts become rare up to 2 Gy, almost universal at D > 11 Gy.
- Argon and iron ions: RBE ~12-40 for low doses (below 0.25 Gy), more like 2-5 for higher doses
- Why does the RBE depend on dose?
  - Can't kill a cell more than once?
  - Mechanistic explanations (see Ullrich discussion)?