Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Physics 561

Radiation Biophysics:
Radiation Biology of Tumor Cells

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Class Plan

- Cell Death
- Cell population kinetics and cell survival
- Definition of Tumor
- How Tumors respond to Radiation
- Break
- Tools for studying tumor response
- Radiobiological Responses
- Hypoxia and radiosensitivity
- Dose fractionation and tumor therapy

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Cell Death

- Clonogenic cell death:
  inability to produce several generations' worth of progeny
- Acute pathological cell death: necrosis
  - Cells typically swell, then lyse
  - Accompanied by inflammation
- Apoptosis
  - Programmed cell death
  - Shrinkage, fragmentation, phagocytosis
  - P53 is activator of genes that regulate it

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Cell populations in Tissue

- A. Simple transit population
  - Cells in, cells out
  - Spermatozoa, blood cells
- B. Decaying population (e.g. oocytes)
- C. Closed, static population (neurons?)
- D. Dividing, transit population
  - Some cell division, so more leave than enter
  - Differentiating blood cells
- E. Stem cell population (many kinds)
- F. Closed, dividing population
  - No cells in or out--just a lot of division
  - Tumors, eye-lens epithelial cells

Cell population kinetics

- Cell types that divide are the most sensitive.
- Cells are most sensitive during G2 and M, so cells that spend a lot of time in G2 and M are more sensitive
- If a cell population is exposed to radiation, the outcome depends on there being an adequate number of (clonogenically) surviving cells.

Growth Fraction

- Lathja (1963): described “G0” phase in cell cycle: cell is not engaged in proliferation but could later re-enter proliferative statge
- Growth fraction is defined as fraction of total cellular population that is clonogenically competent and actually *in* the process of DNA replication and cell division.
- Measurement: uses ^{3}H-thymidine uptake
- Significance: cells in G0 have time to repair DNA damage (it works even if the concentration of repair enzymes is low during G0)

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What is a Tumor?

- A *tumor* is an mass of undifferentiated or poorly differentiated tissue growing amidst differentiated tissue.
- A tumor may be *malignant*, i.e. growing uncontrollably and with a propensity for spreading to other tissues.
- Or it may be benign, i.e. growing slowly or not at all and without a propensity for spreading
- The phenomenon of spreading is called *metastatis*.

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Cancer

Cancer is the growth of one or more malignant tumors. The process by which cancer develops is called *carcinogenesis*.

The causes, rapidity of onset, course of disease, treatment possibilities, and likely outcomes of cancer depend enormously on what tissue is being attacked, i.e. on the kind of cells from which grew.

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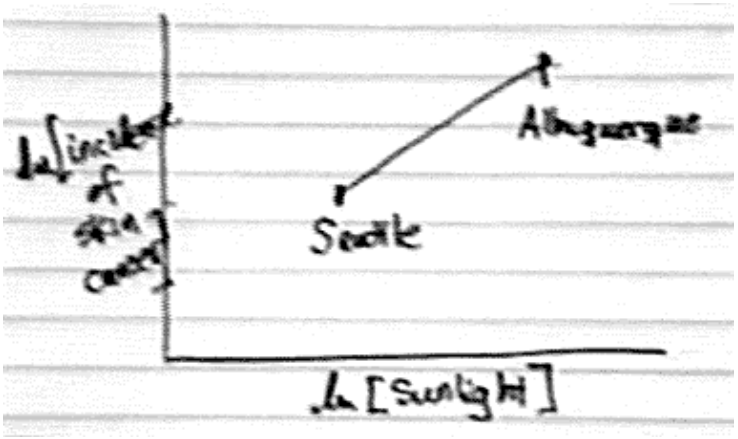

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Characteristics of Cancer Cells

- Cancer cells lack differentiation
- Cancer cells have abnormal nuclei
  - May have an abnormal number of chromosomes
  - Gene amplification (abormal # of copies of specific genes) is common
  - Not subject to apoptotic controls
- Cancer cells form tumors
- Cancer cells metastasize

Cell types and cancer

- Epithelial cells (skin, digestive tract, tracheal lining, glands, . . .) give rise to *carcinomas*.
- Connective tissue cells (bone, cartilage) give rise to *sarcomas*.
- Blood cells give rise to *leukemia*.
- Lymphatic tissue gives rise to *lymphomas*.

Time-Course of Cancer

- Steps in causation:
  - Initiation
  - Promotion
  - Progression
- Steps in clinical outcome:
  - Exposure
  - Latency
  - Onset
  - Disease

Initiation

- Initiation is typically a series of mutational events, often single-base changes in DNA in a single cell.
- The clonal hypothesis states that cancer typically arises from clonal growth out of a single damaged cell.
- In most cases it does appear that the number of mutations that have to occur in order for a tumor to grow out of a single cell is more than one.
- Initiation events can arise over a short time span if the exposure to the mutagen is intense and short (or if only one event is required).

Promotion

- Promotion is a process in which metabolic and then morphological changes in the mutated cell occur.
- It does not typically involve mutations in the affected cell, but rather interference with some of the surveillance mechanisms by which these metabolic and morphological changes are controlled.
- Among the systems involves are the arachidonic acid cascade, by which the cell's differentiation capacity is regulated; and apoptosis factors like P53.

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Cell Kinetics

Attribute	Tumor	Growing cells
Total cycle time	~20 hrs	~20 hrs
Time spent in S	~8hrs	~8hrs
Vascularization	chaotic	orderly
G0<->cycling transitions	nutrient-dependent	regulated

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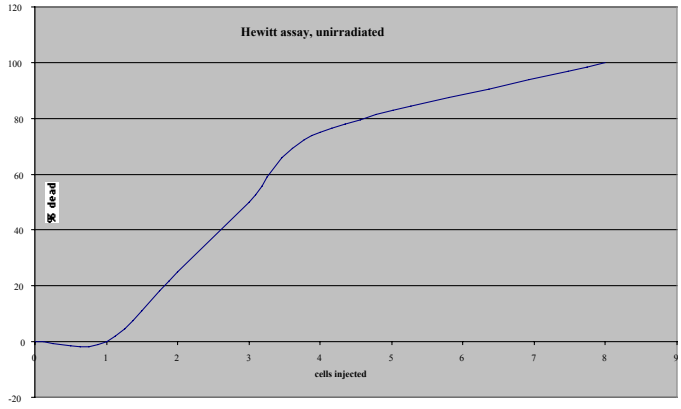
Modeling Sensitivity in Tumors

- Why?
  Because it enables us to optimize treatment regimens when exposing patients to radiation
  - Maximize cell killing in the tumor
  - Minimize damage to normal tissues
- Also provides test-bed for understanding interactions between tissues and radiation in general

Hewitt Dilution Assay

- Tumor cells grown in peritoneal (gut) cavity of mouse--"ascites" tumor
- Tumor cells can be harvested and injected into recipient mice
- Inject varying number of tumor cells and fraction killed against number of cells injected
- Result: if you pre-irradiate the tumor cells, they don't kill as many hosts.

Hewitt assay



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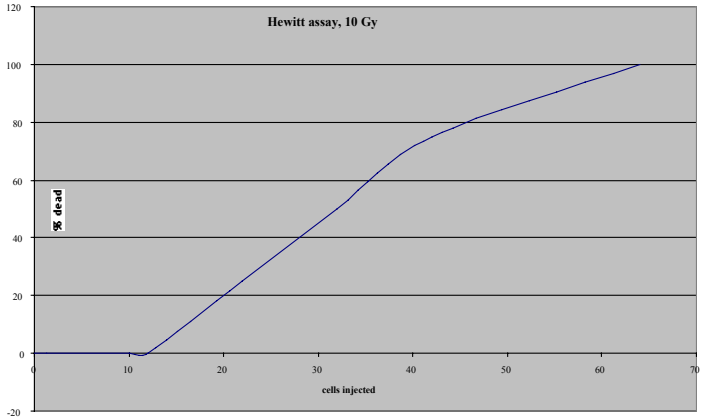
Hewitt assay, continued



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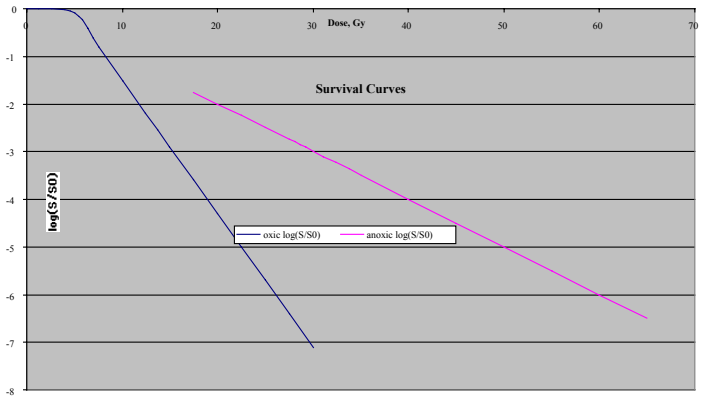
Hewitt assay: analysis

- LD50 is used to construct survival curve
- In our example, 3 cells are enough to kill the host if no radiation is used; 32 are required if 10 Gy are used
- Evidently $S/S_0 = 3/32 = 0.094$ of the initial cells were functional enough to kill the host.
- We can calculate similar numbers for each dose level and calculate a dose-response curve (dose vs. $\log(S/S_0)$, perhaps under multiple conditions.

Hewitt survival curves

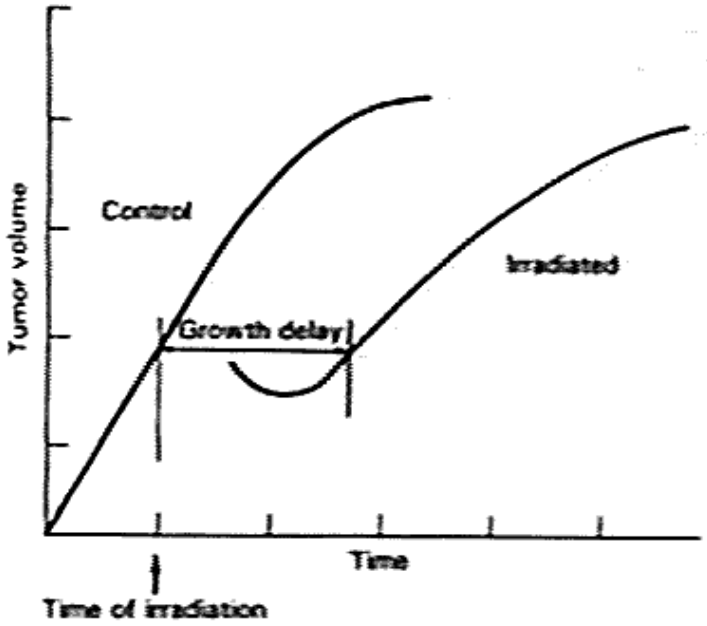


Lung Colony Assay

- Tumor is injected into a recipient mouse's lung
- Number of tumor colonies in lung is counted
- Tumor may be irradiated:
- In vivo
- After dissection and cell dissociation
- Linear relationship between number of cells injected and number of colonies counted.
- 10-50X enhancement in # colonies if heavily irradiated, nonclonogenic cells are injected
- Irradiation increases # cells required to produce a given number of colonies

OER in Hewitt Assay

- Remember that OER is defined as ratio of dose required to get a given effect in the absence of oxygen to the dose required in the presence of oxygen. Since you need more dose to get the same effect if oxygen is absent, the OER is greater than one. For the data in fig. 10.3, the OER is about 2.2, since we need about 40 Gy of dose to damage anoxic cells the same amount as would require only 18 Gy with oxic cells.



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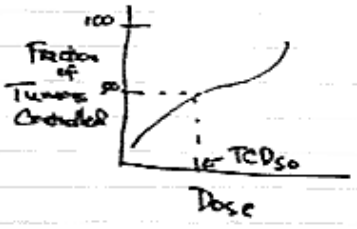
TCD_{50}:

1. Inoculate many animals with tumors.
2. Irradiate them with a given dose.
3. If this dose controls the growth of half the tumors, that dose is the 50% tumor cure dose, TCD



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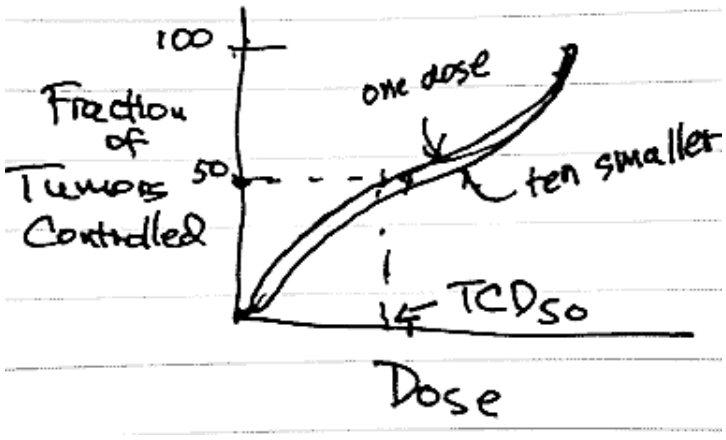

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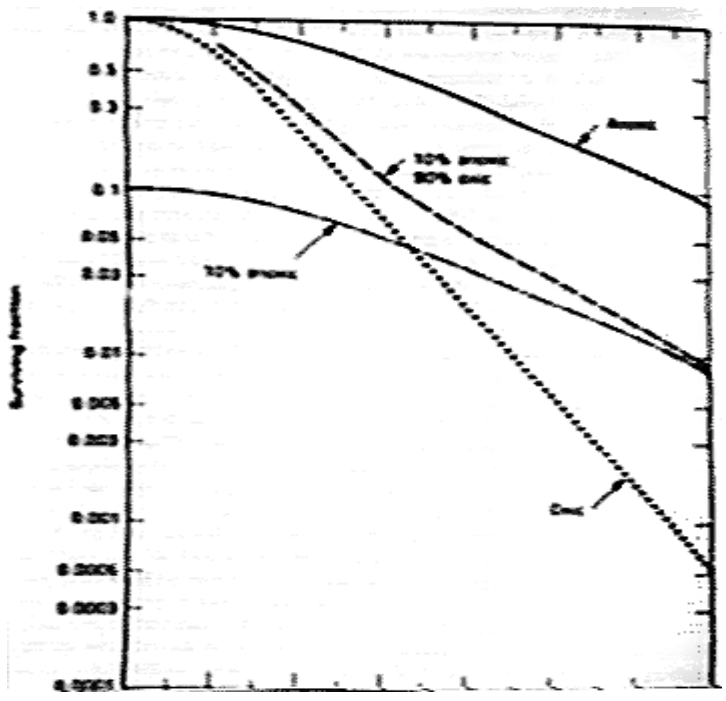

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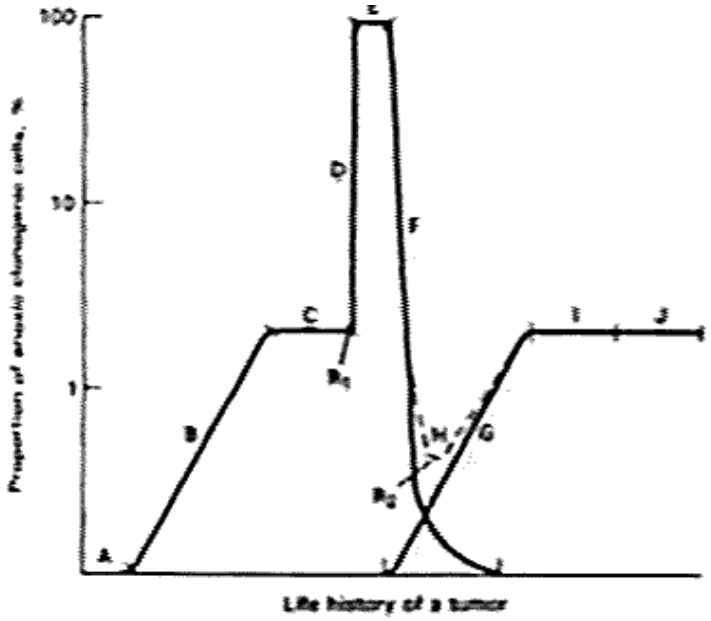

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Assignment for Friday 23 March

- Alpen, chapter 10, problem 1.
- Assume that ionizing radiation exerts its tumorigenic effects primarily through mutational events. Assume further that cigarette tar contains large numbers of cancer promoters. Which scenario would you expect would cause a higher incidence of cancer, and why?:
  - Irradiation followed by ten years of smoking
  - Ten years of smoking followed by irradiation

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