Illinois Institute of Technology

Physics 561
Radiation Biophysics

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Lecture 11: Carcinogenesis

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Class Overview

- Tumors
  - Definitions
  - Prevalence and significance
  - Clonal theory
  - Multistage model
  - systems for study
- Break
- Midterm

Tumors: Definitions

- Tumor: abnormal, de-differentiated cellular proliferation
  - Benign: small mass reaches a certain size and then stops growing
  - Malignant: those capable of uncontrolled growth metastasis
- Cancer: a malignant tumor
- Carcinogen: a chemical or physical agent that increases the likelihood of cancer

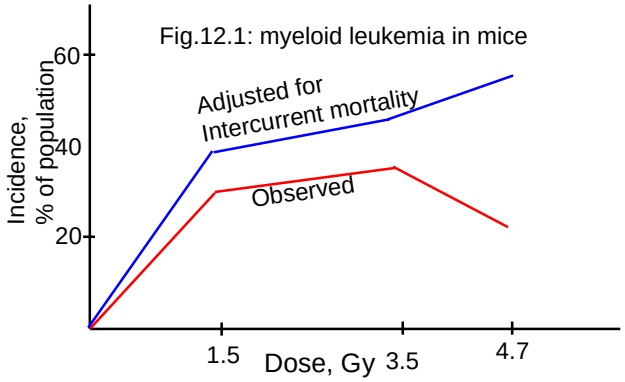
Cancer: Prevalence and Significance

- 550,000 cancer deaths per year in the US
- 20-40% caused by environmental and workplace pollutants
- Others caused by smoking, diet, and natural causes
- Teasing apart these statistics is tricky:
  - Probability of any individual getting cancer under a particular set of circumstances is small
  - Multistage model makes multiple causes likely

Tumors and Radiation

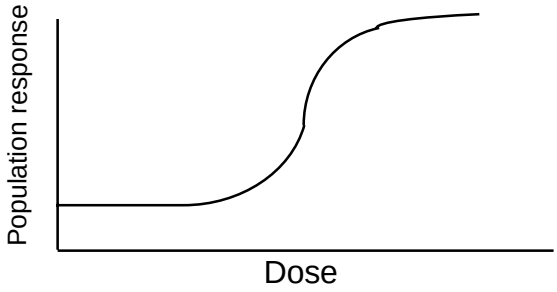
- Stochastic late effects (cf. end of last lecture)
  - Are these effects truly stochastic?
  - Even with cancer, there exists some dose-response effects in the individual

Fig.12.1: myeloid leukemia in mice



Tumors and Radiation (Cont'd)

- Is there a threshold?
  - Probably not (but is this a red herring?)
  - Not at the population level
- Serious Inquiry: the ED01 experiment
  Brown & Hoel, *Fundamental & Applied Toxicology* **3**: 458 (1983)



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How do Cancers Begin?: The Clonal Theory

- In general, mutational events in a single cell are sufficient to begin the process of tumorigenesis
- Often several mutations must arise in order for cancer to be a likely outcome
- Generally the mutation must be in one of the 50 or so genes that control cell replication and differentiation
- The mutagenic events are *never* enough to guarantee development of cancer
- Mutations must be followed by promotional events, which stimulate uncontrolled cell division

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Modifying Factors

- Immune system ↑↓
- Hormonal effects
- Oncogenes
- Oncogenic viruses
- Environmental factors

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How Cancers Develop: The Multistage Theory

- Initiation
  - DNA damage
  - e.g. Intercalators
- Promotion
  - Not necessarily mutational
  - Involves changes in control systems, e.g. arachidonic acid cascade
  - Tumors are present and capable of metastasis but haven't necessarily metastisized
- Progression
  - Development of metastatic tumors

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Potentiation of Effect of Radiation by Smoking

- Inquiry into lung-cancer incidence among uranium miners and nearby office workers. Smokers and nonsmokers were surveyed.

Smoking \ Uranium Exposure	Yes	No
Yes	+++	+
No	—	—

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What Constitutes a Cancer?

- Morphological change
- Cell immortality (escape from apoptosis)
- Tumorigenicity, i.e. spread of undifferentiated cells

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Oncogenes

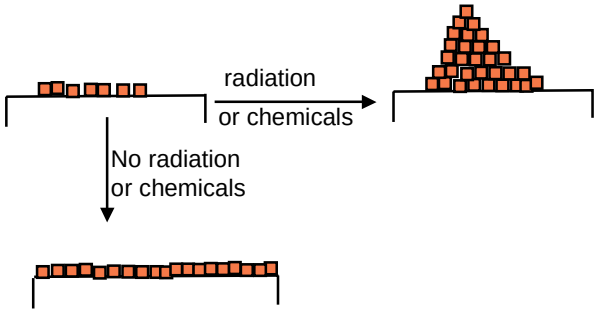
- Genes that are activated or show enhanced expression in tumors
- Limited data showing connection between human radiation-induced tumors and activation of oncogenes

Experimental Systems for Studying Rad-induced Tumors

- We need these because we can't deliberately do high-dose experiments on humans!
- CHO cells
  - Chinese Hamster Ovary
  - Good for looking at early effects--Initiation
  - Difficult to model the promotional events.
  - Transformation results in loss of contact inhibition
- Mouse embryo fibroblasts
  - Immortalized
  - Still display contact inhibition

CHO Cells (Cont'd)

- Key assay: resistance to contact inhibition



Mouse Embryo Cells:

- Experiment: growing total confluence
- Lose contact inhibition?
- Can induce tumors in syngeneic animals

- Limitation in both systems:
  - Fibroblasts (mesenchymals)
  - Most human tumors are epithelial

Mutagenesis

- Many chemicals, as well as radiation, can be shown to cause mutations.
- It's therefore logical to test for mutagenicity as a first-stage inquiry into the likelihood that a compound or a radiation treatment might be carcinogenic
- Standard mutagenic test:
  The Ames test (developed by Bruce Ames), in which *Salmonella* cells are exposed to a chemical and mutation rates in the cells are measured.

Is an Ames Test a Good Substitute for These Complex Systems?

- No!
- 1,3-dinitropyrene is the most mutagenic substance known in the Ames test; yet it is only weakly tumorigenic in rats.