Chapter 6

Biological Effects of Radiation

Objectives

- Describe basic cell structures and the cell life cycle
- Describe the differences between the direct and indirect biological effects of radiation
- Discuss the tissues and organ systems that are sensitive to radiation
- Discuss factors that affect the radiosensitivity of cells and tissues

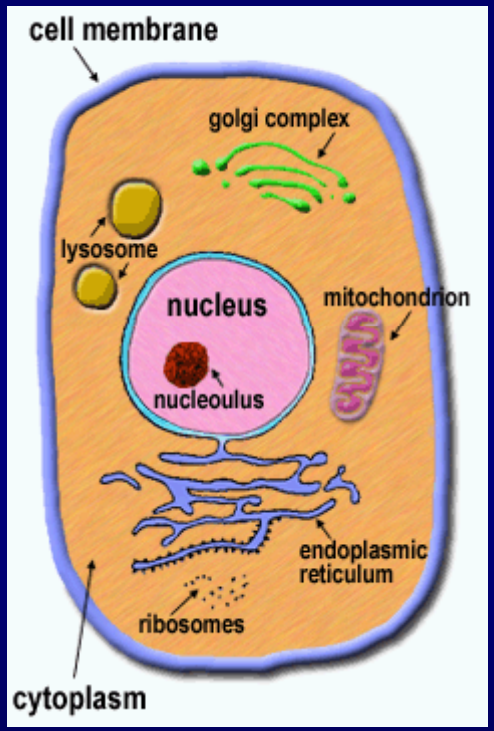
Objectives

- Discuss the biological effects of high doses of radiation
- Describe the acute radiation syndrome
- Discuss the biological effects of low level radiation exposure
- Discuss the linear no threshold theory used to describe risks associated with exposures to low levels of radiation

Biology of the Human Cell and its Genetic Material

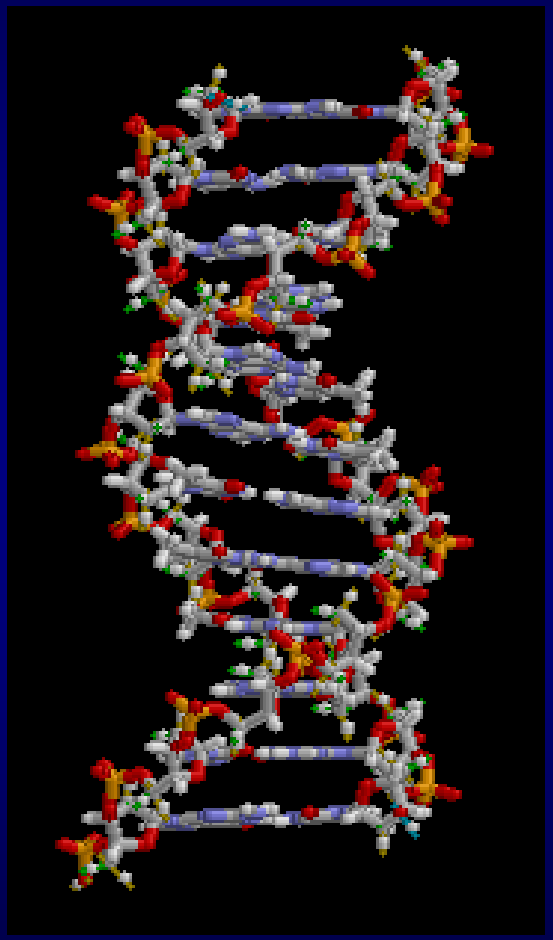
Cell Biology

- Cell is basic building block of life
- Has basic structures that allow cell to function and reproduce
- Cell function is determined by genetic codes contained on chromosomes
- Chromosomes are in the cell nucleus and are made up of DNA



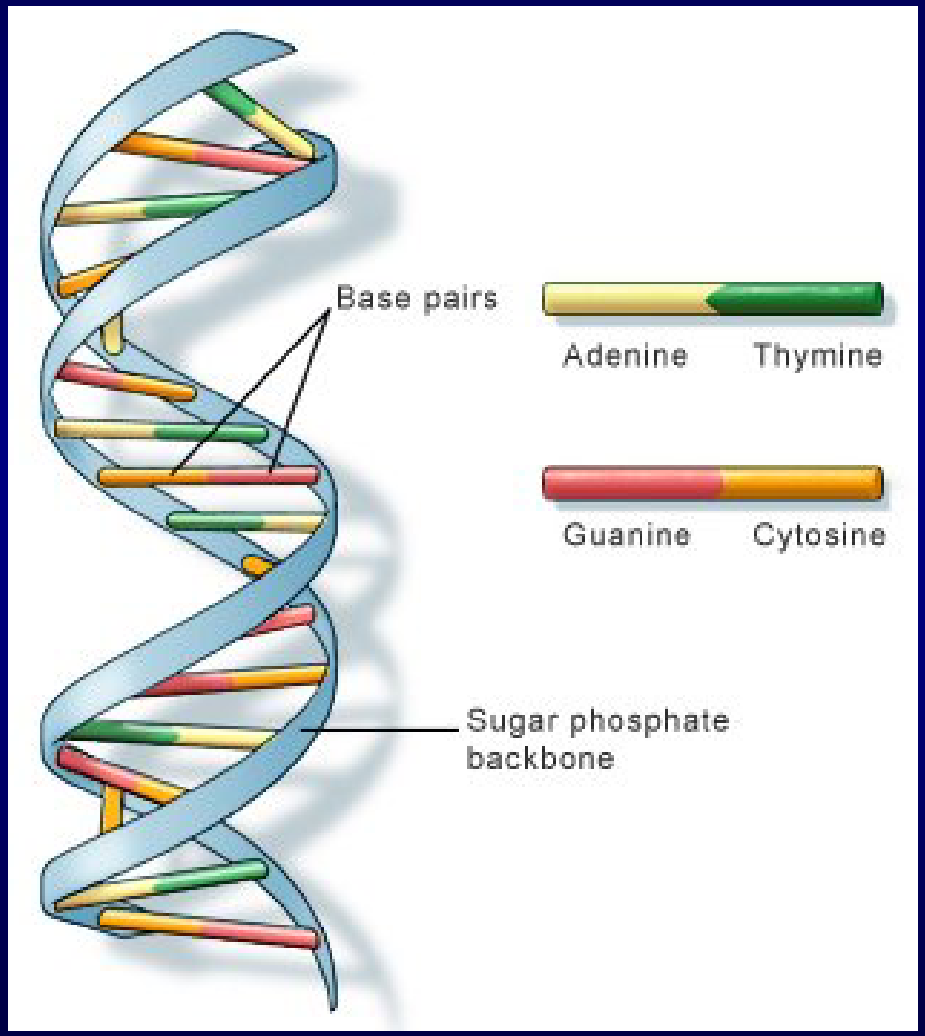
DNA

DNA is a vast chemical database found in the nucleus of each of the body's trillions of cells. It contains the genetic instructions required for cellular development and function.



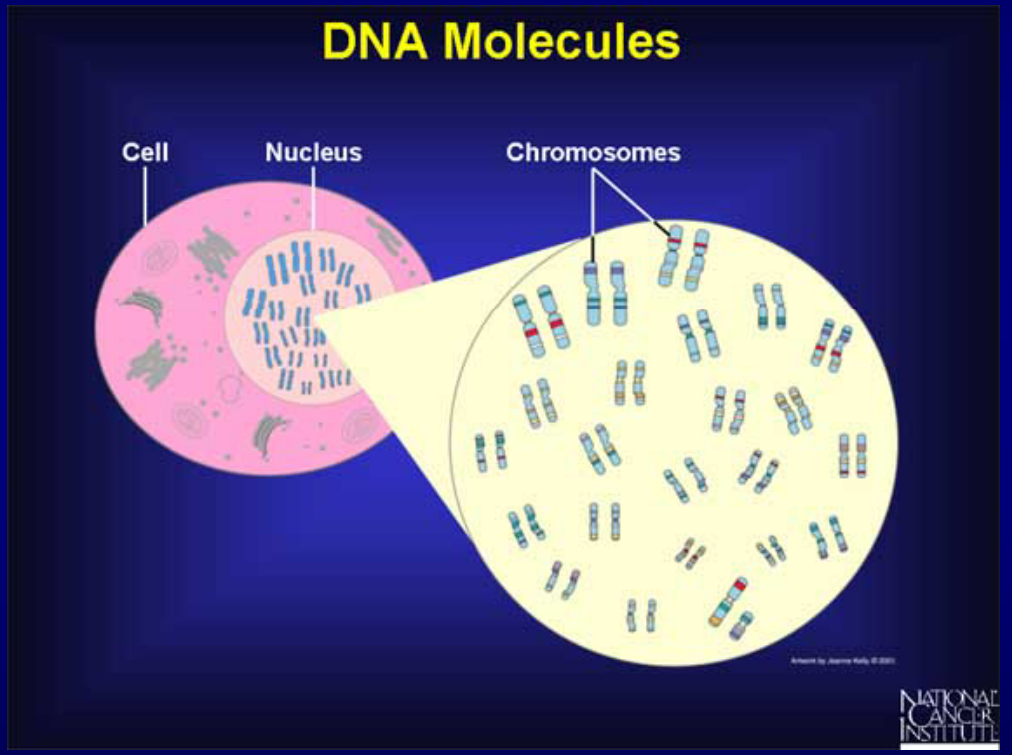
DNA Molecular Structure

- DNA exists as two long, paired strands spiraled into the famous double helix.
- The strands are joined by chemical bases that can be arranged in countless ways. The order of the bases determines the messages to be conveyed, much as specific letters of the alphabet combine to form words and sentences.



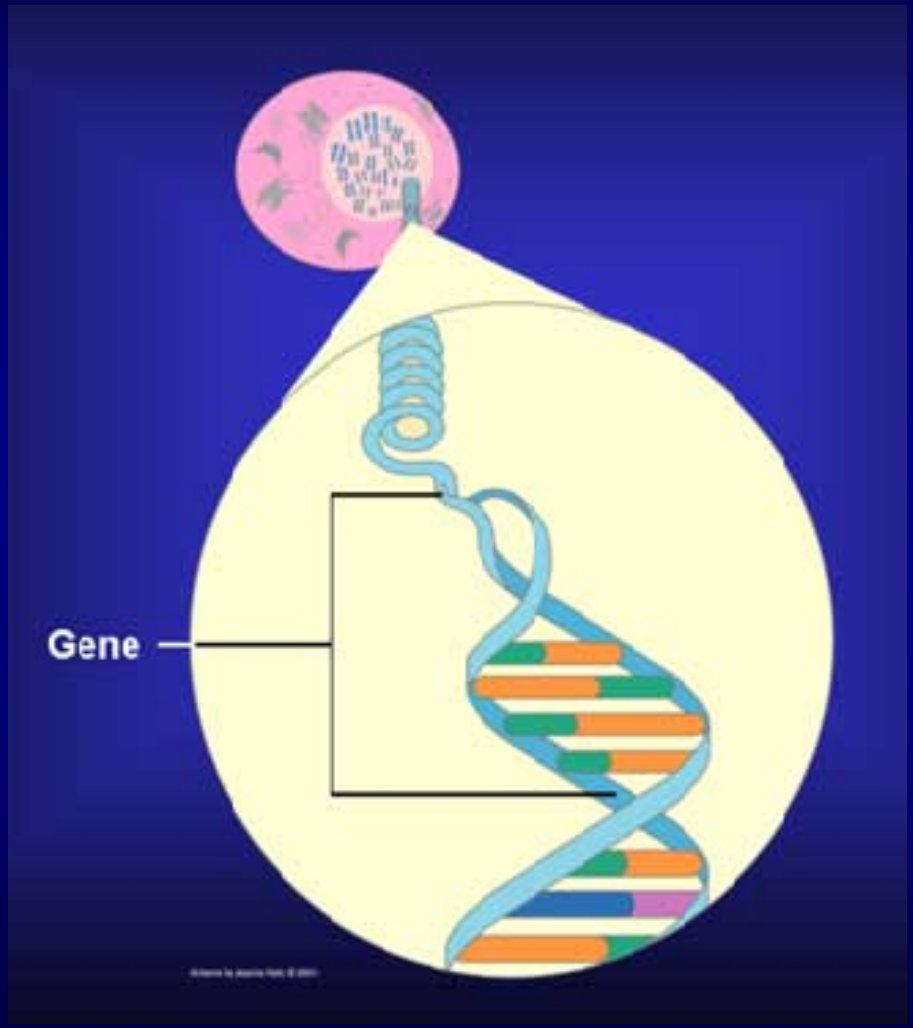
DNA Molecules

- The DNA found in every human cell is identical.
- Each cell has 46 molecules of double-stranded DNA made up of 50 to 250 million bases housed in a chromosome.



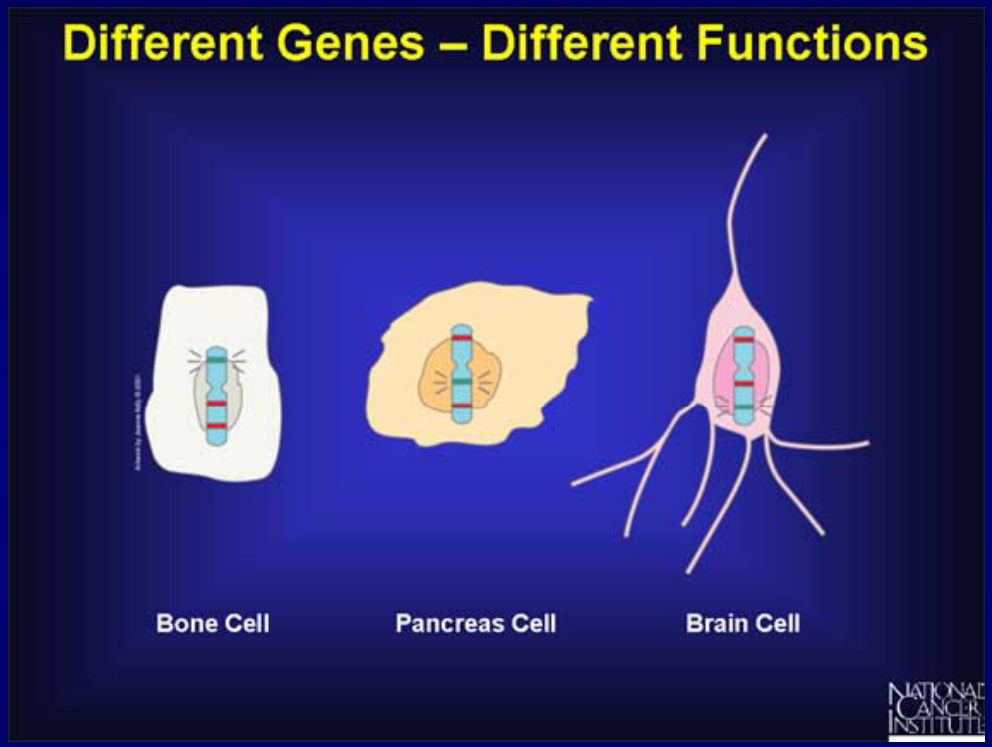
Genes

- A gene is a given segment along the DNA molecule.
- Each gene carries a particular set of instructions for the cell.
- There are about 25,000 genes, and every gene is made up of thousands of chemical bases.

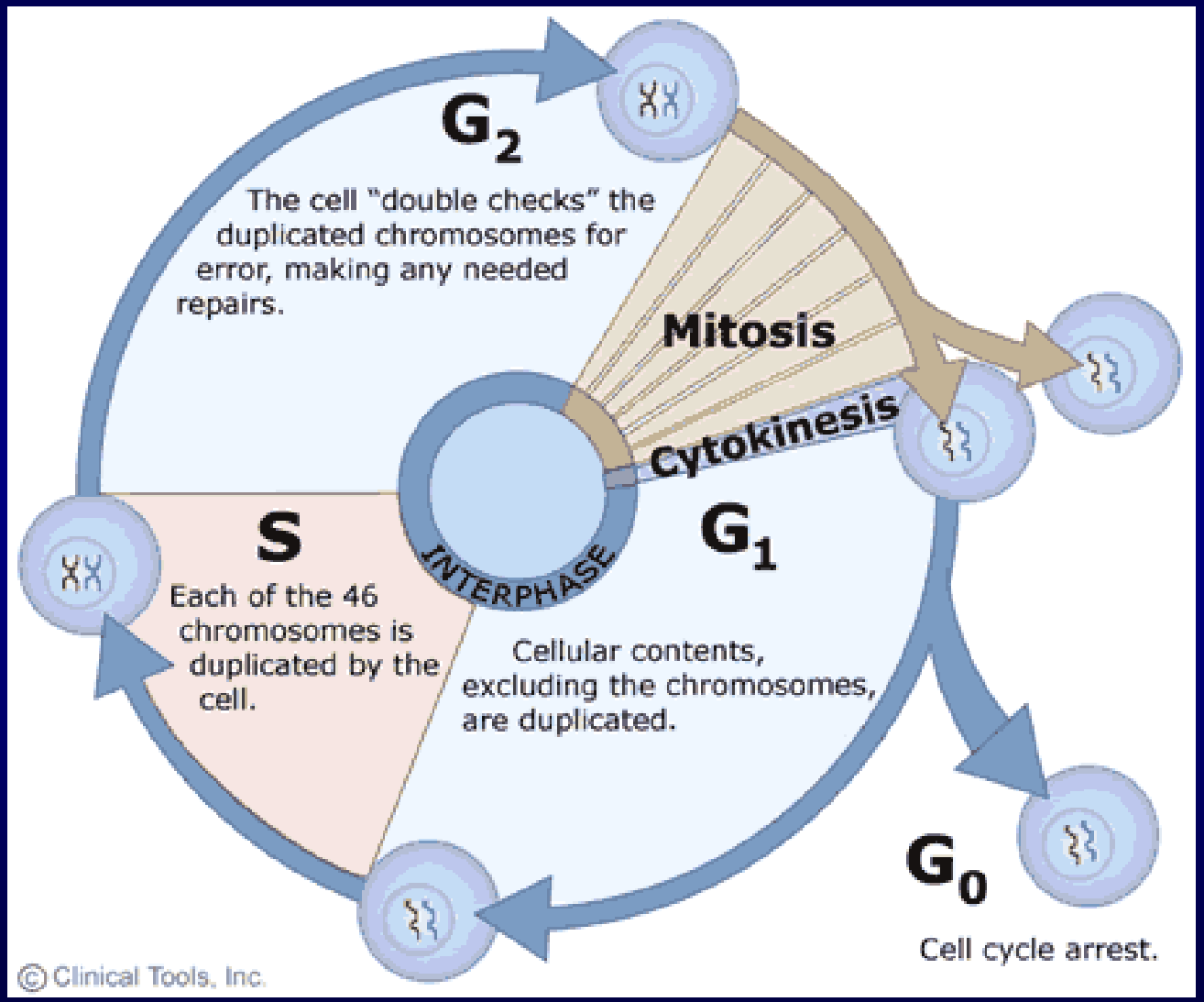


Genes and Cellular Function

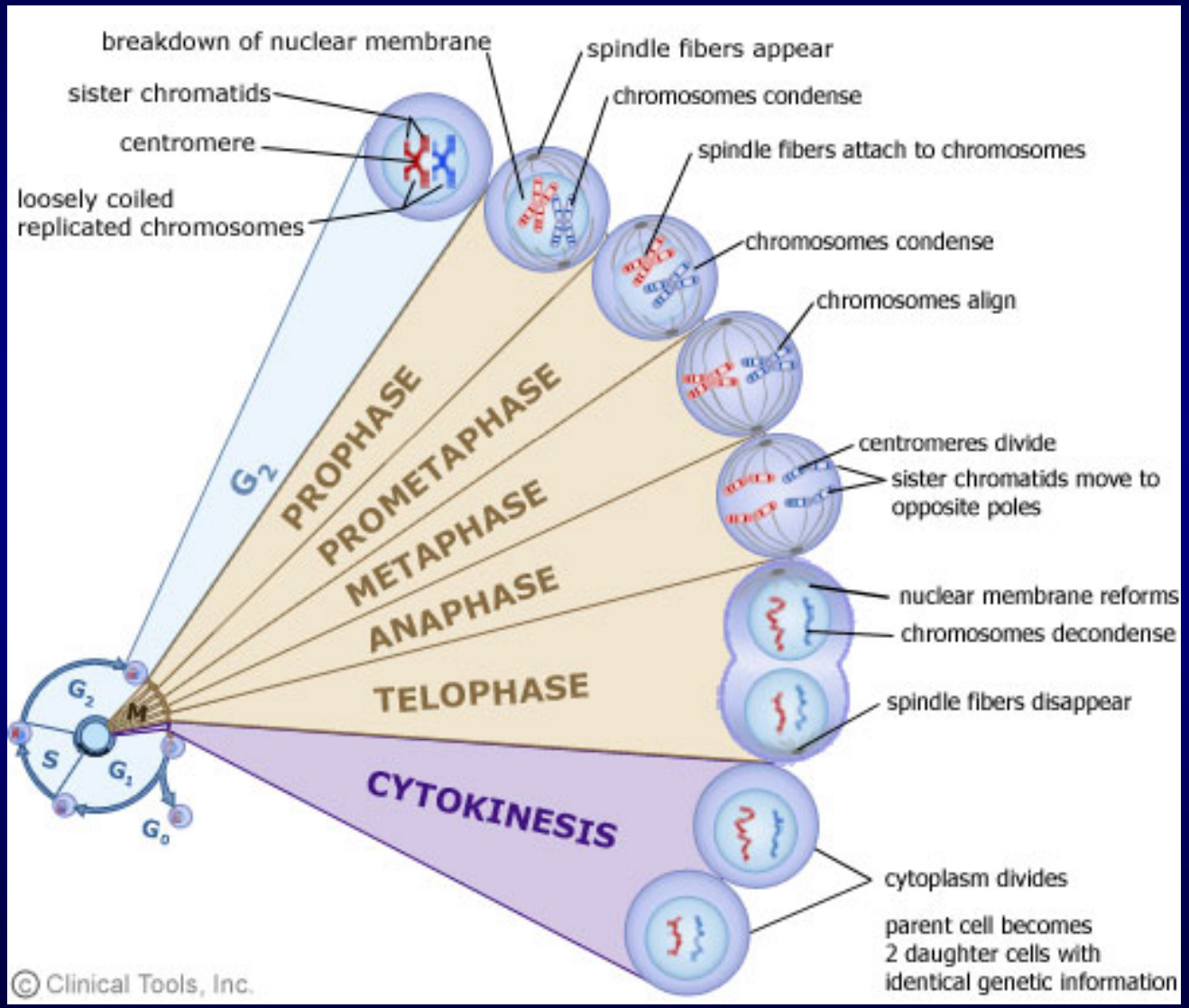
- Cells use genes selectively.
- Cells activate only the genes needed and suppress the rest. The unique selection of genes used by a cell gives that cell its character – making a brain cell different from a bone cell.
- Genes also guide the cell life cycle including cell division.



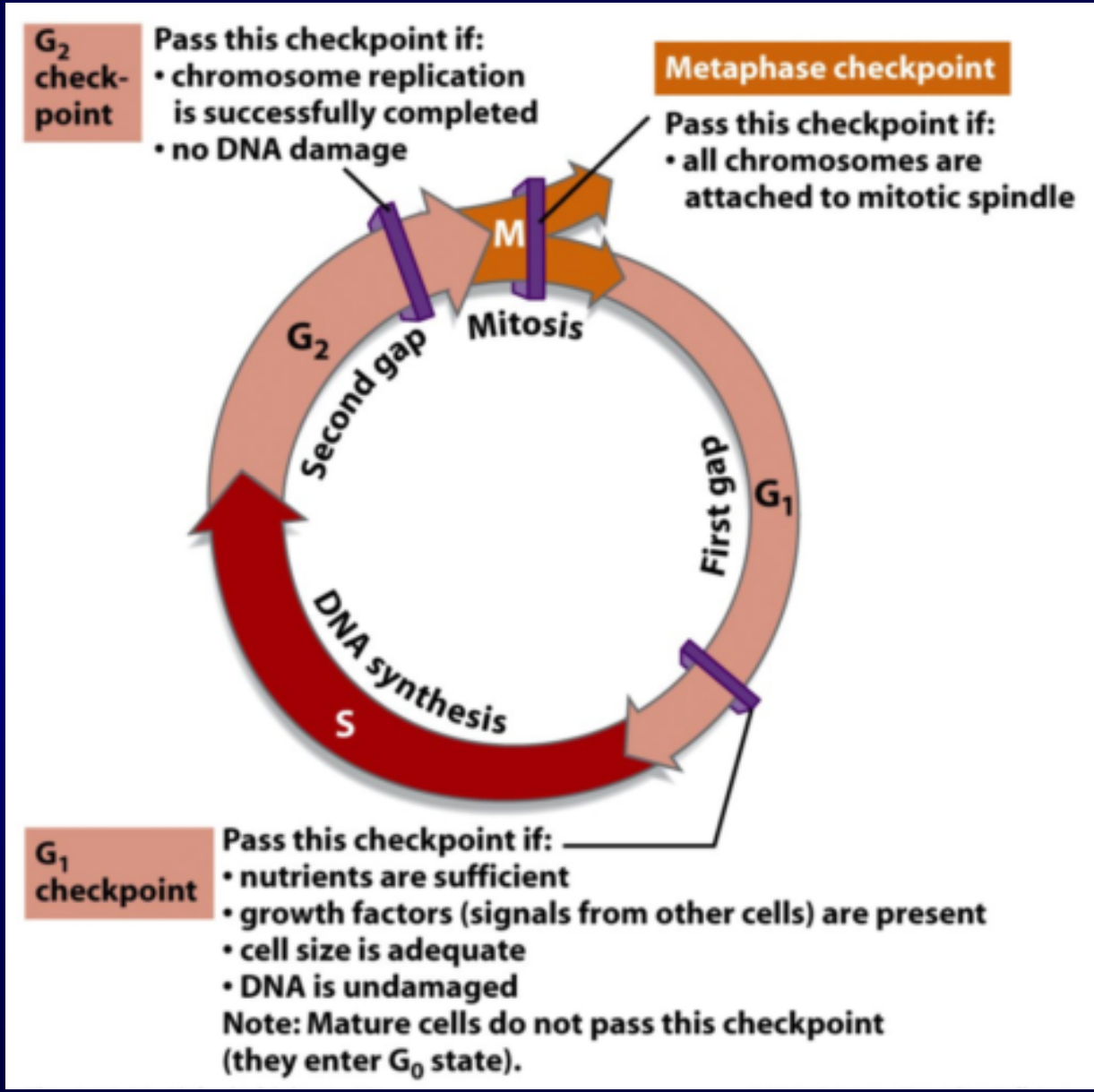
The Cell Cycle



Cell Division (Mitosis)



Cell Cycle Checkpoints



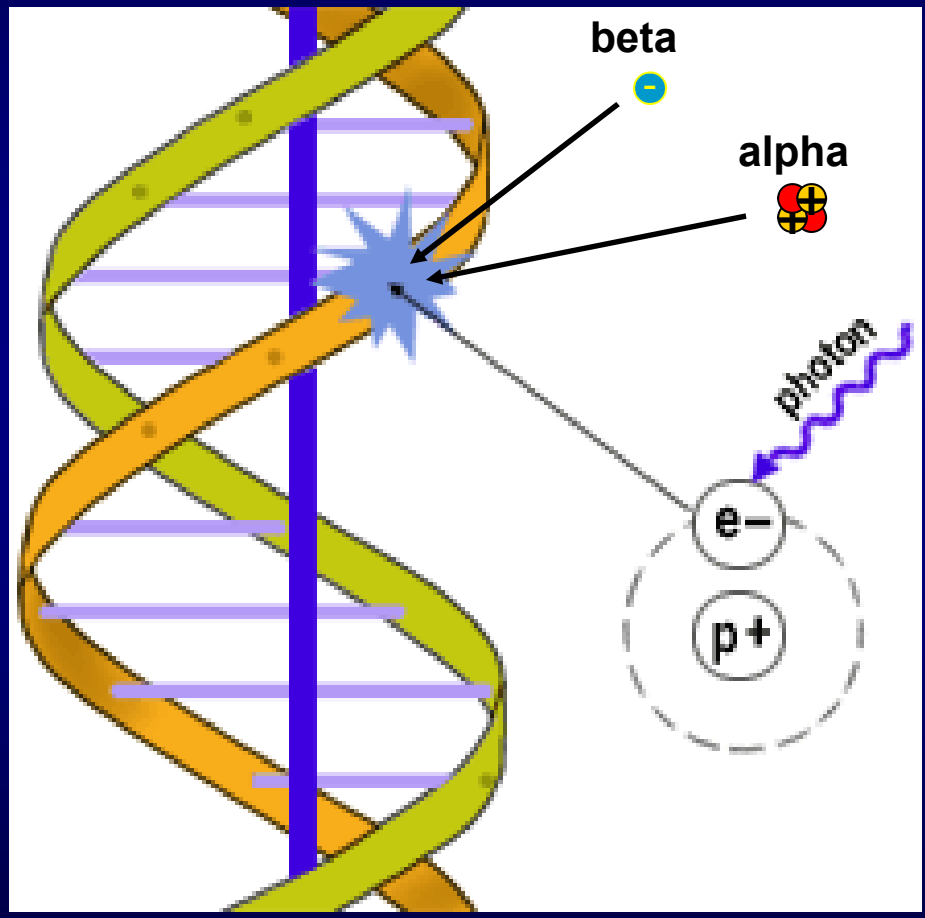
Cellular Damage from Radiation

Radiation Damage

- Biological effects on the cell result from both direct and indirect action of radiation.
- Direct effects are produced by the initial action of the radiation itself.
- Indirect effects are caused by the later chemical action of free radicals and other radiation products.

Direct Biological Effect

- When radiation or secondary ions directly damage critical biological molecules in human cells
- DNA within the cell nucleus is believed to be the critical biological target for radiation damage

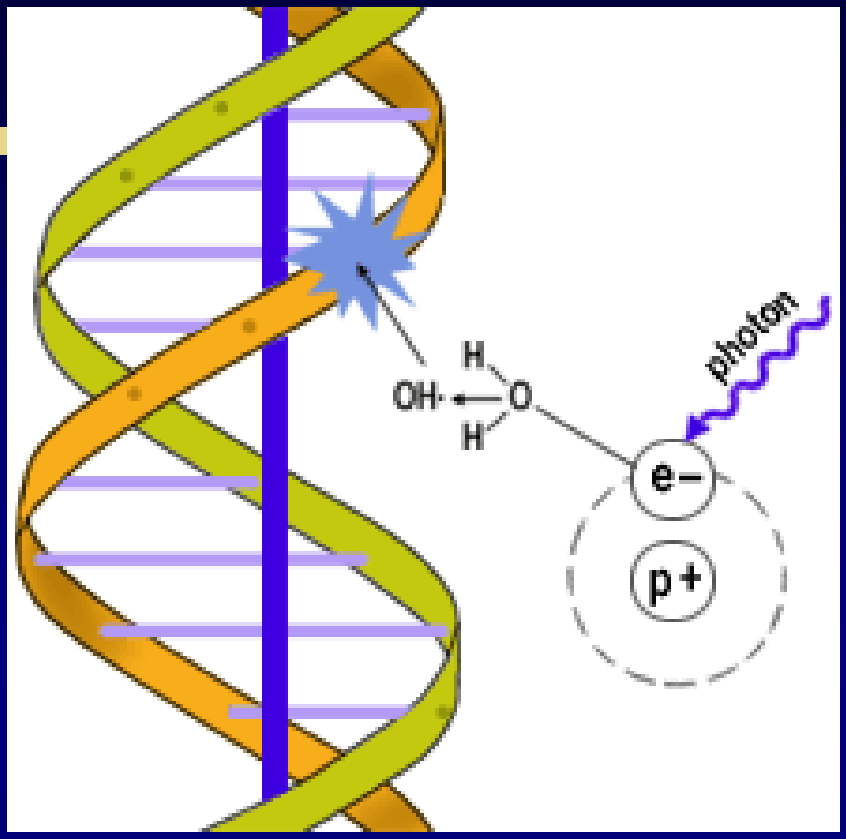


Indirect Effect

Radiation interacts with cellular water to produce free radicals and other reactants.

Free radicals are reactive agents that can damage DNA.

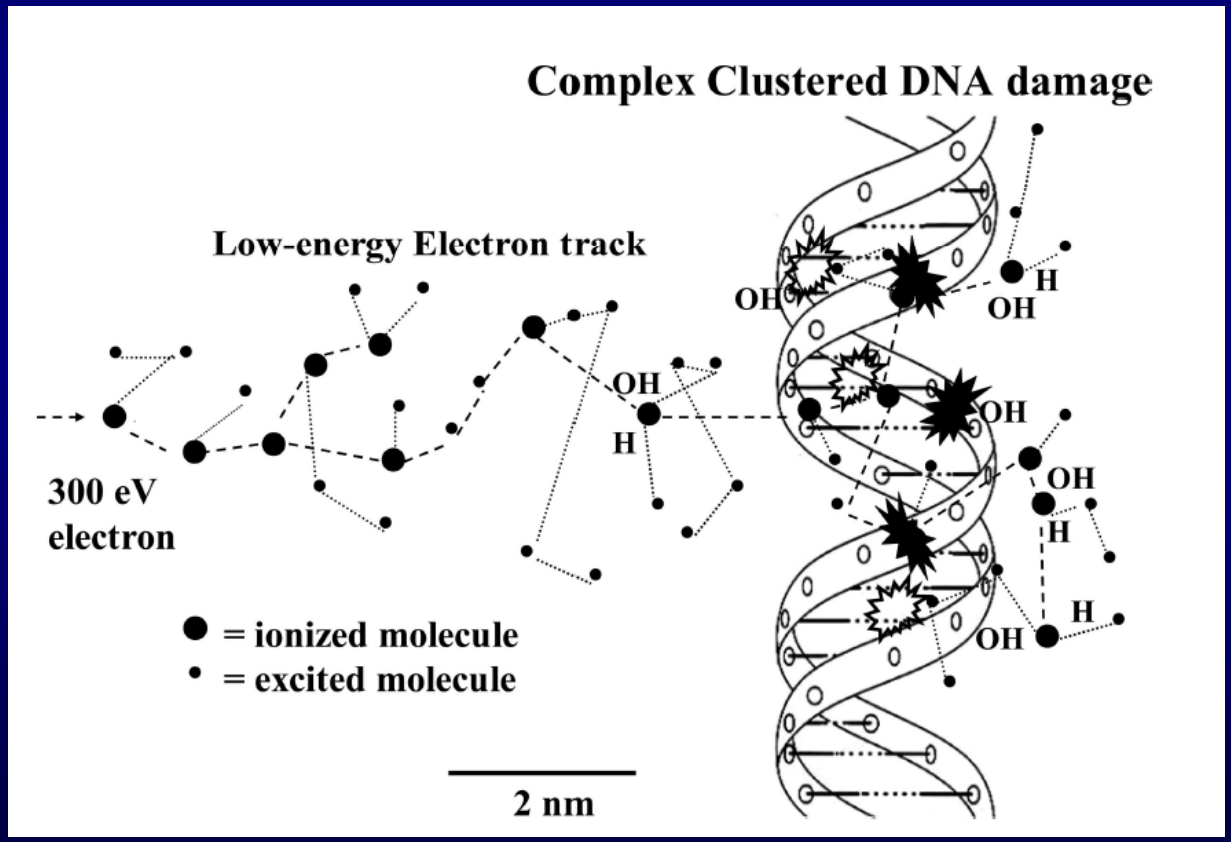
One important free radical is the hydroxyl ion (OH). Two of these radicals combine to form hydrogen peroxide ($OH + OH \rightarrow H_2O_2$) a powerful oxidizing agent that can attack and damage DNA by breaking its chemical bonds.



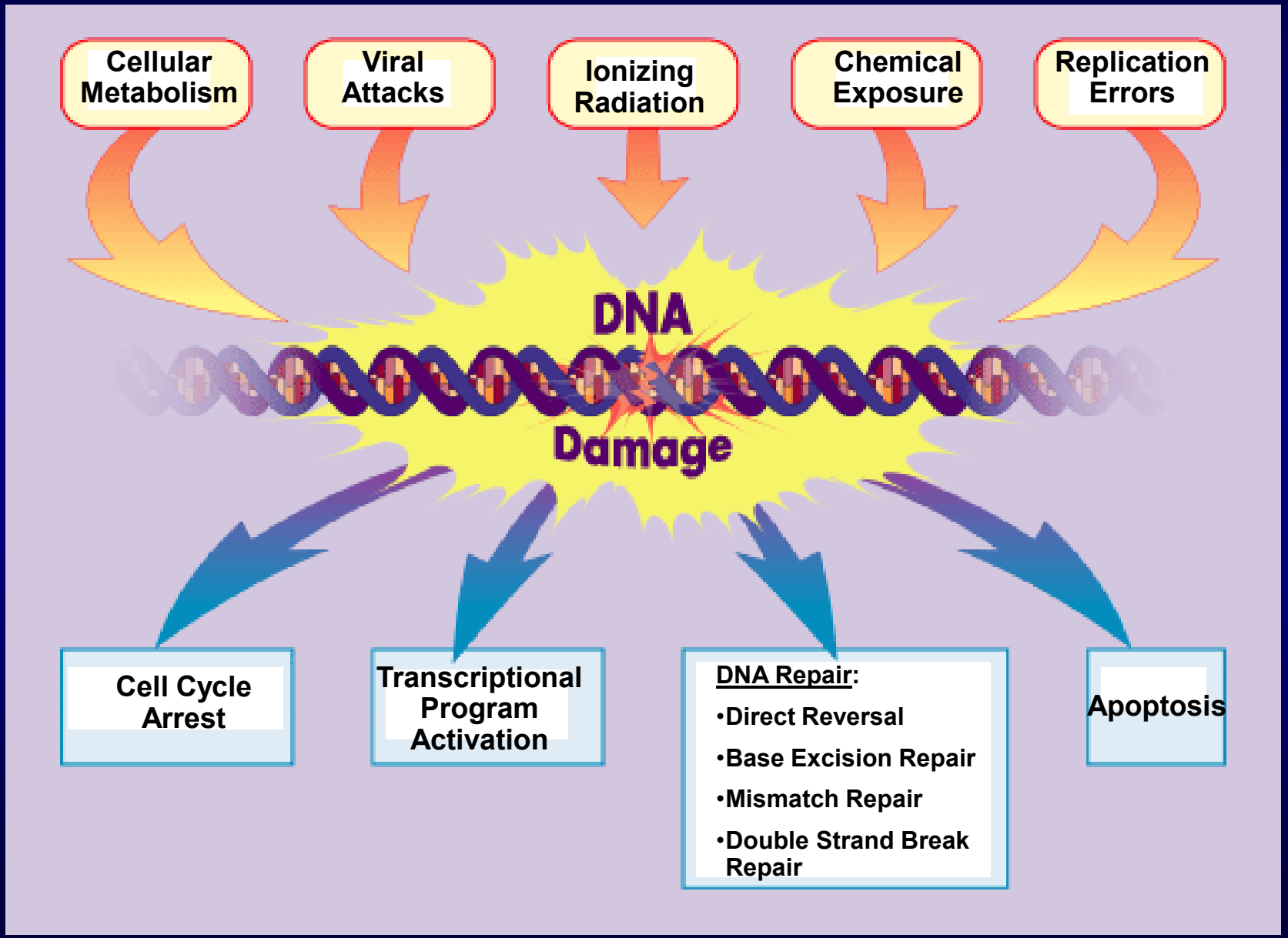
Since the human body is mainly water, the indirect effect is believed to be more likely to occur than the direct effect.

Radiation Damage to DNA

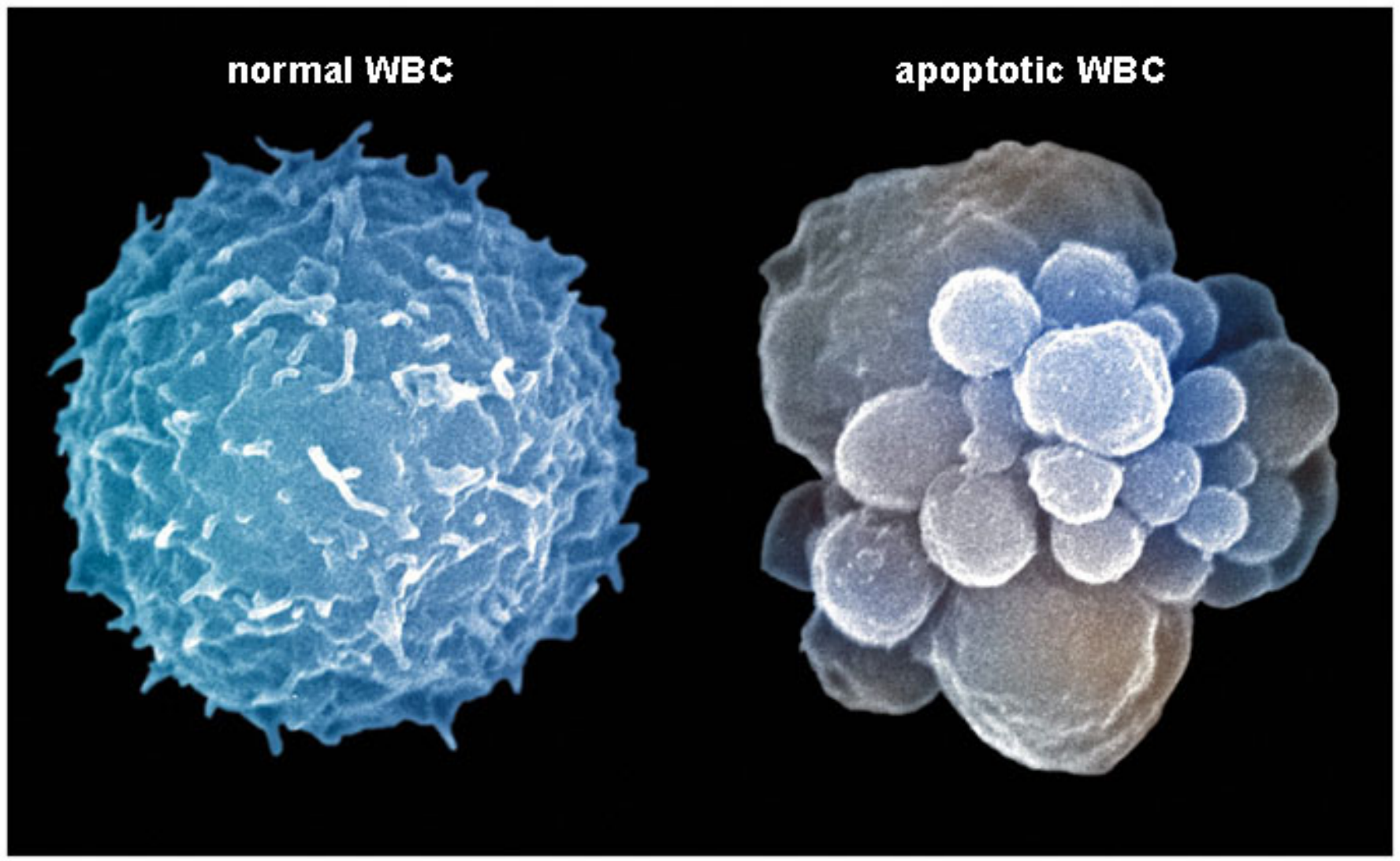
Ionizing radiation causes DNA single strand breaks, double strand breaks, base deletions, etc.



Cell Response to DNA Damage

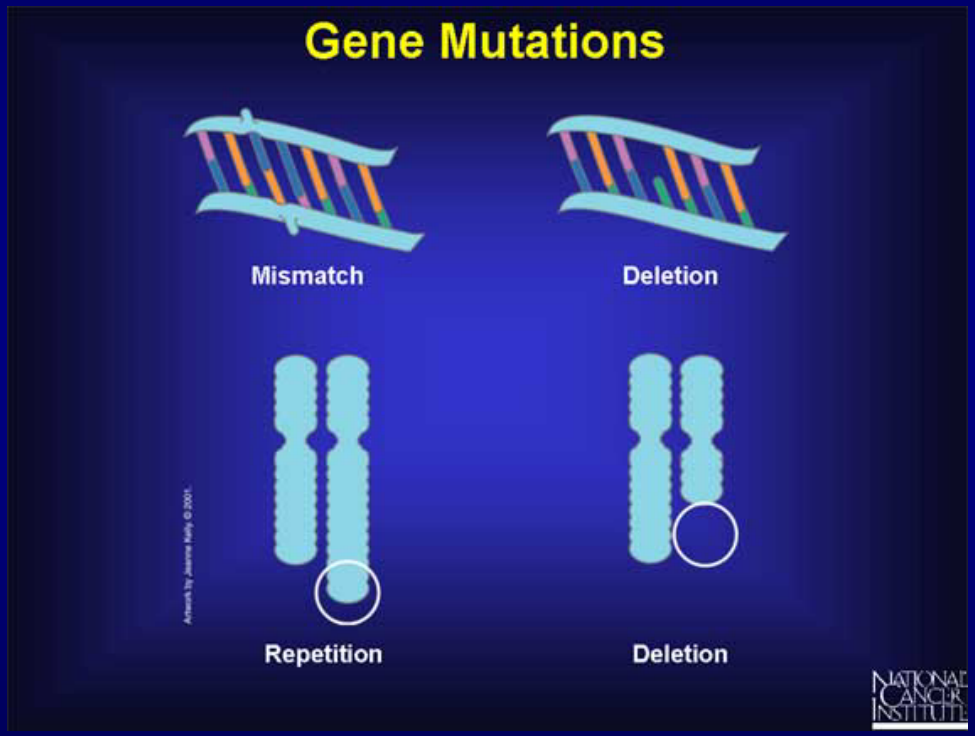


Cell Response to DNA Damage

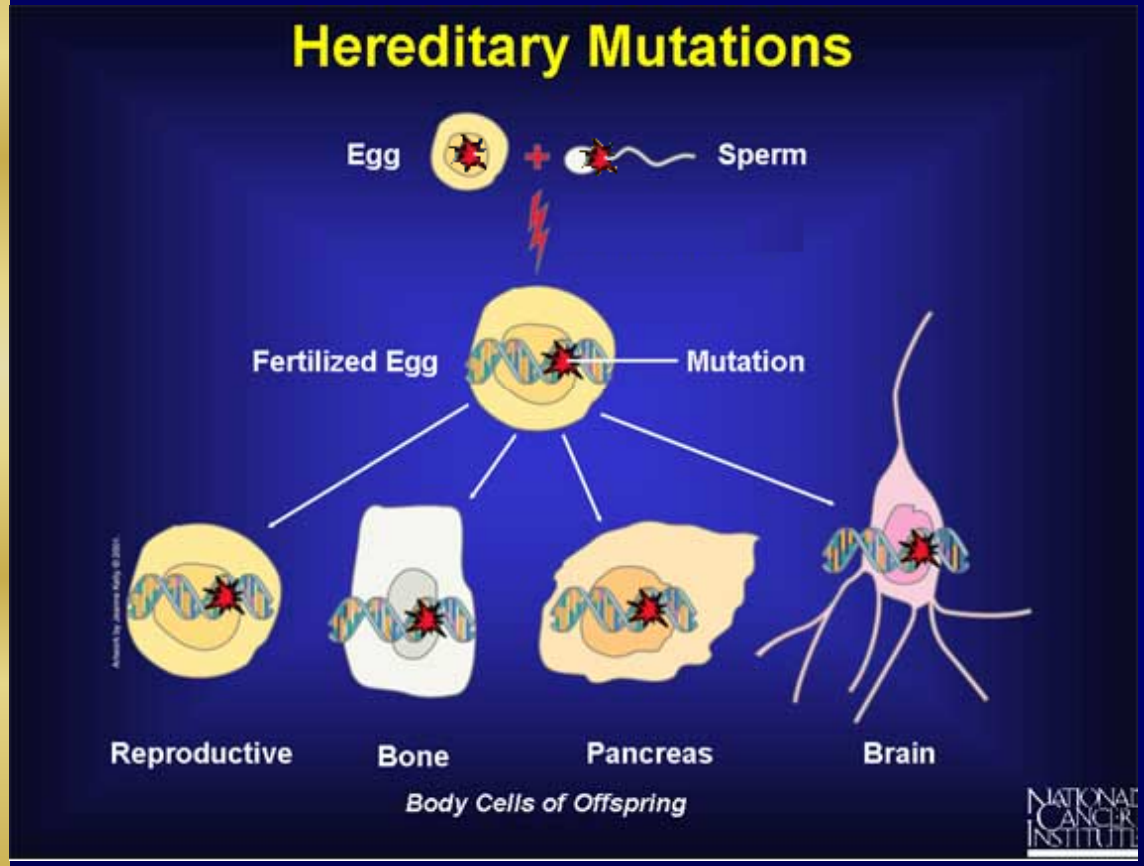


Genetic Mutations

- Although cells have the ability to repair DNA damage and do it continually, misrepair can result in mutations.
- The most common gene mutation involves a single base mismatch-- placing the wrong base in the DNA.
- Not all DNA mutations are manifested as a disease or defect.



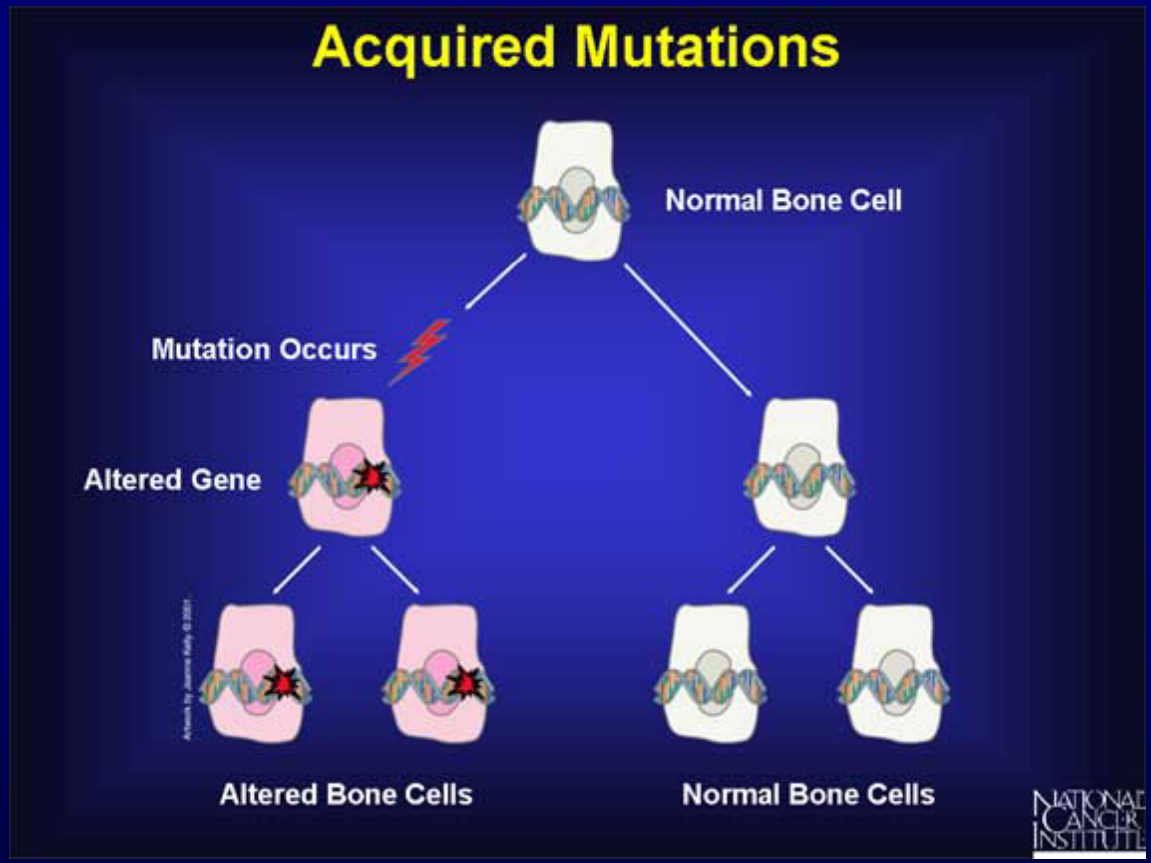
Acquired vs. Inherited Mutations



Hereditary mutations are carried in the DNA of reproductive cells. When the reproductive cells combine to produce offspring, the mutation will be in all of the offspring's body cells.

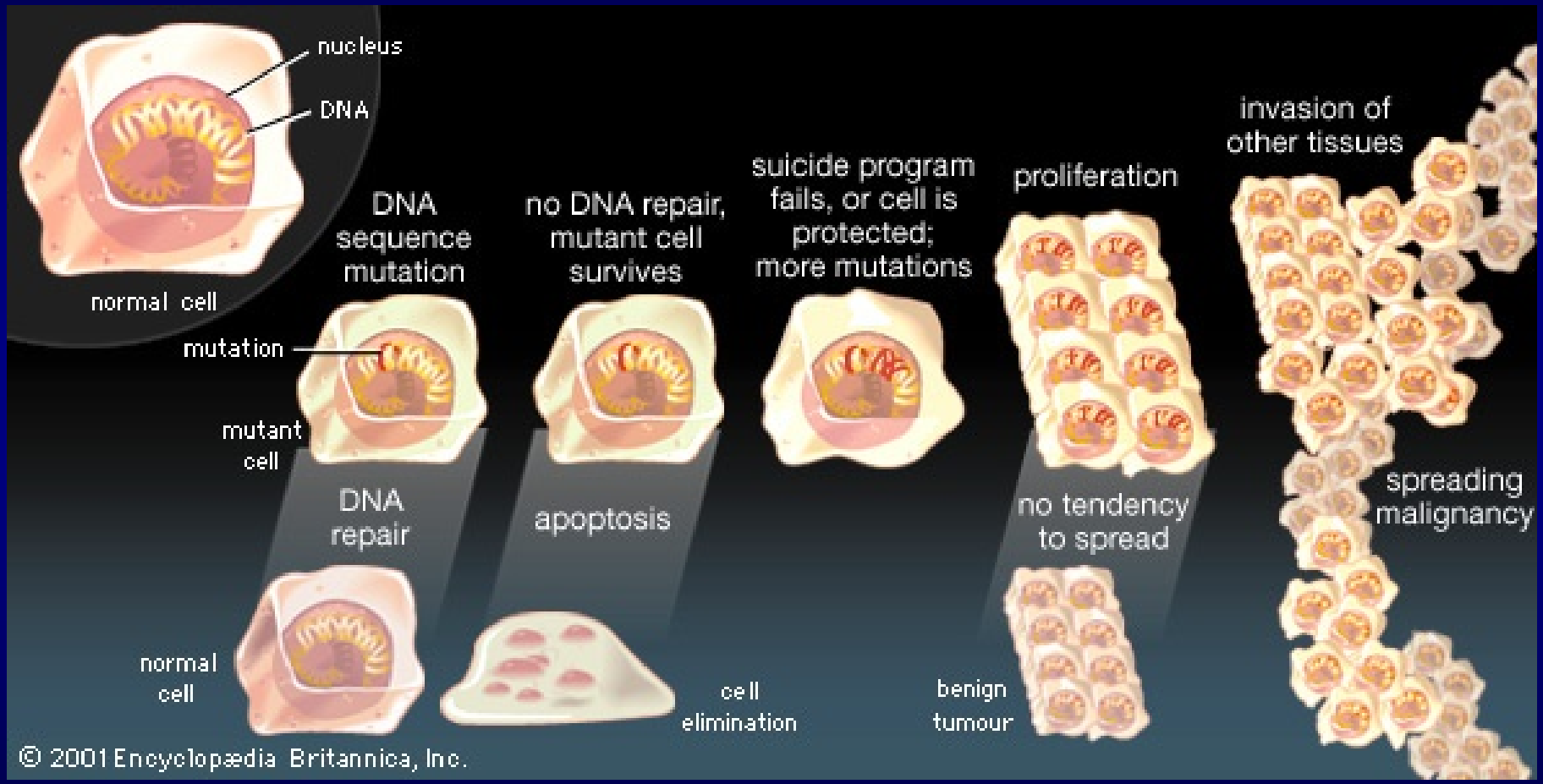
Acquired vs. Inherited Mutations

Acquired mutations are caused by environmental factors such as diet, smoking, and radiation exposure.



- **Cancer is uncontrolled cell growth.**
- **All cancer is triggered by gene mutations. Genes that control the orderly replication of cells become damaged, allowing the cells to reproduce without restraint.**
- **Cancer usually arises in a single cell. However, the cell's progression from normal to malignant to metastatic appears to involve a series of mutations or changes.**

Mutations and Cancer



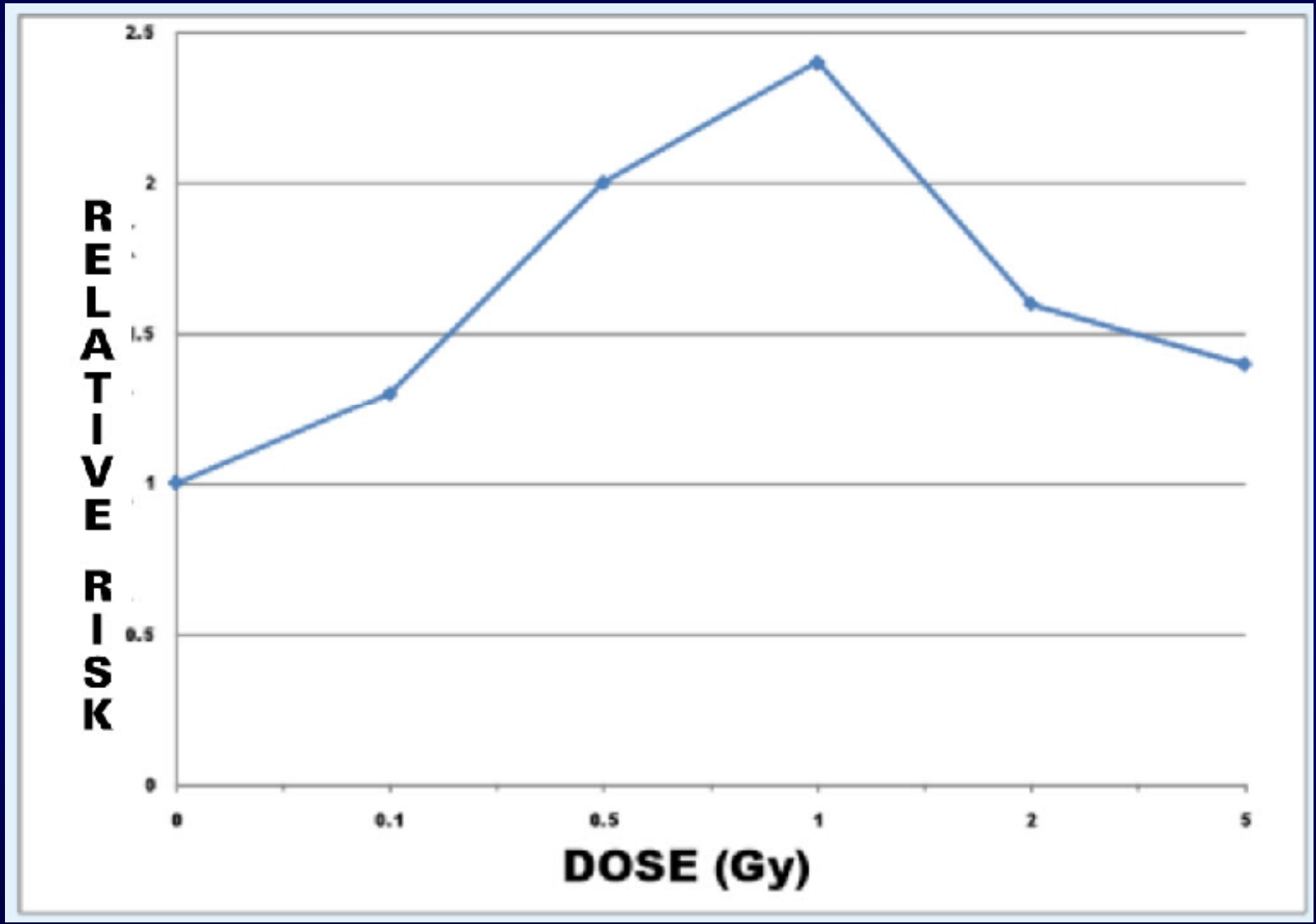
Cancer Induction

- Certain genes along the DNA strand are particularly important for cancer induction. If strand breaks or mutations occur along these genes, it can greatly influence whether the cell will eventually create malignant cancerous cells.
- Cells can be more sensitive to radiation damage during certain times of their lifecycles.
- Bystander effect of adjacent cells.
- According to the ACS, certain types of cancer are more likely to be seen in people exposed to large doses of radiation

Epidemiological Studies

- Radiation is one of the most widely studied carcinogens
- Vast database of epidemiological data – atomic bomb survivors (Life Span Study ~120,000), Chernobyl, medical patients, radium dial painters, animal studies, etc.

Epidemiological Studies

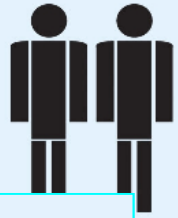


Epidemiological Studies

120,000

THE LIFE SPAN STUDY (LSS) COHORT CONSISTS OF ABOUT 120,000 SURVIVORS OF THE ATOMIC BOMBINGS IN HIROSHIMA AND NAGASAKI, JAPAN, IN 1945 WHO HAVE BEEN STUDIED BY THE RADIATION EFFECTS RESEARCH FOUNDATION.

50%



"TODAY, APPROXIMATELY 50% OF CANCER PATIENTS ARE TREATED USING RADIATION AND SEVERAL MILLION CANCER SURVIVORS ARE ALIVE IN THE UNITED STATES, EMPHASIZING THE IMPORTANCE OF INVESTIGATING THE LONG-TERM CONSEQUENCES OF RADIOTHERAPY AND EXAMINING THE FEATURES OF EPIDEMIOLOGIC STUDIES OF MEDICAL RADIATION." (BEIR VII)

44%

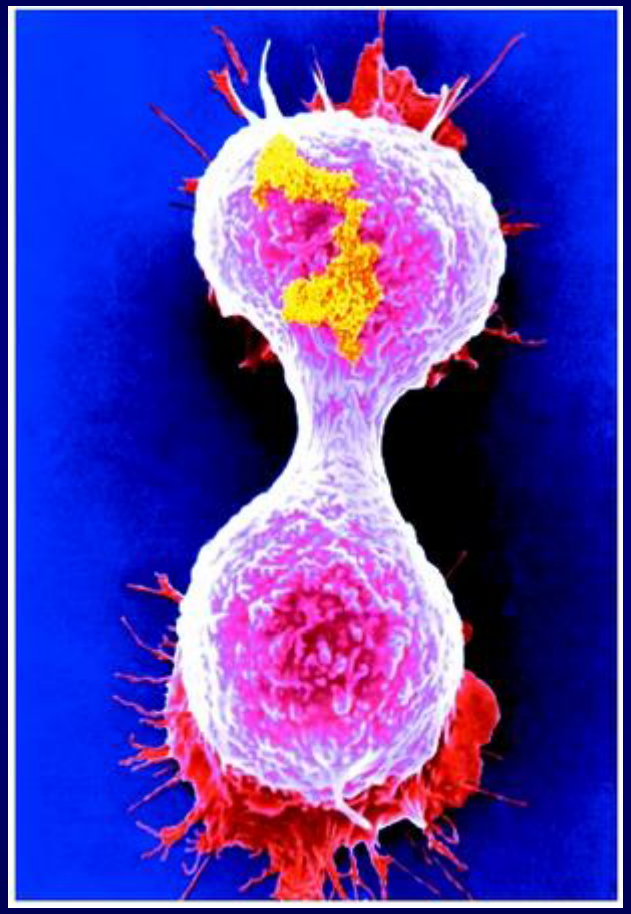
RESEARCHERS ESTIMATE THAT 44% OF LEUKEMIA DEATHS AMONG THE ATOMIC BOMB SURVIVORS WITH DOSES EXCEEDING 500 **mrem (5 mSv)** WERE DUE TO RADIATION EXPOSURE.

Radiosensitivity of Different Cells and Organ Systems

Cell Radiosensitivity

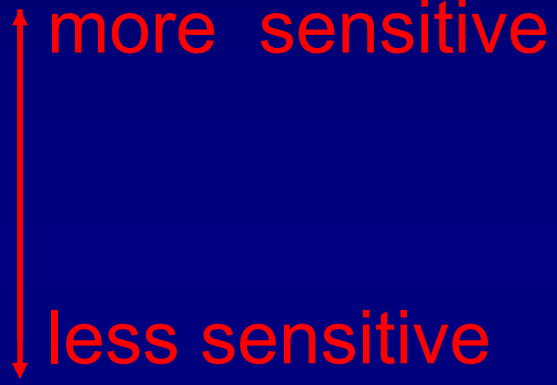
Cells are radiosensitive if they:

- **have high division rate**
- **have a long dividing future**
- **are of an unspecialized type**



Cell Radiosensitivity (cont)

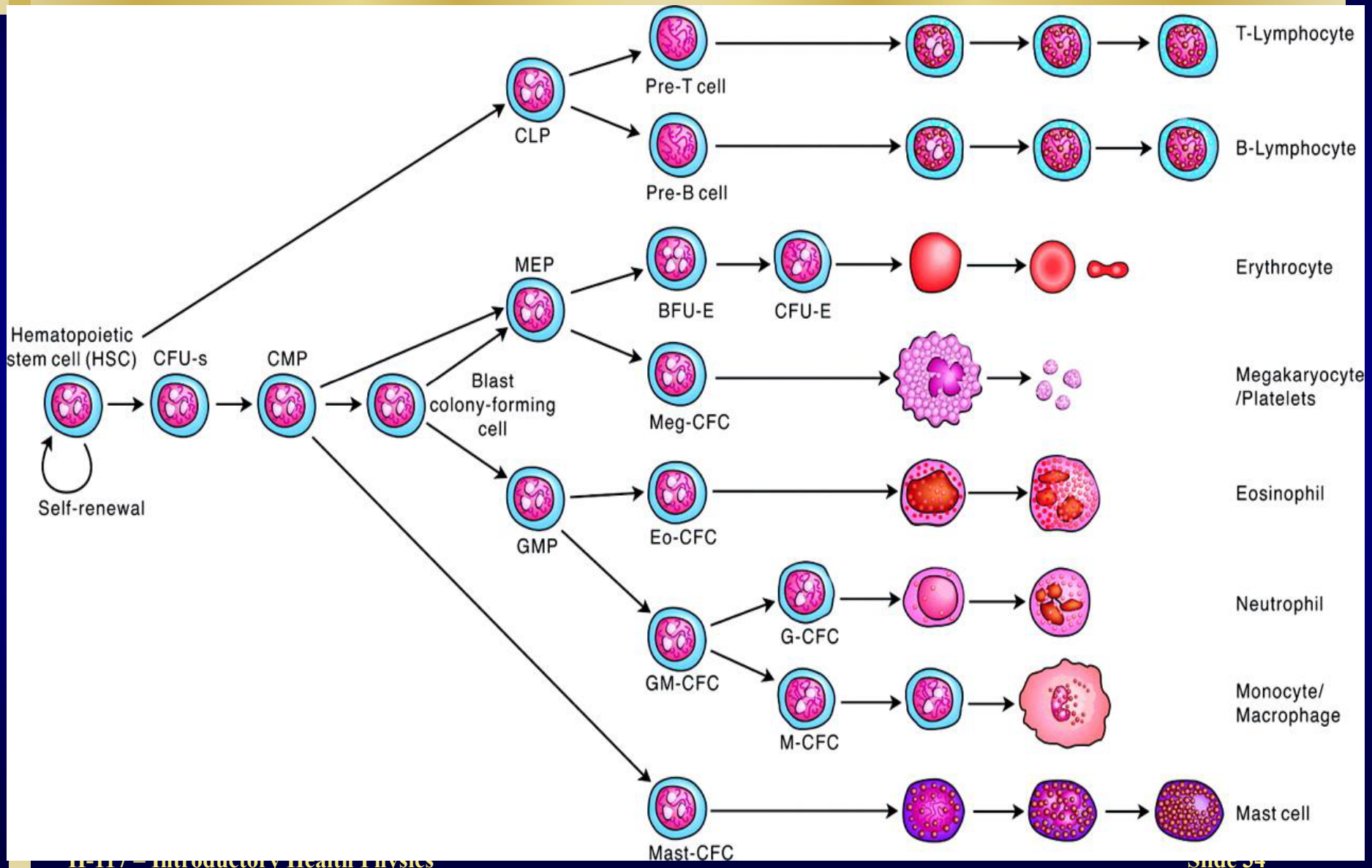
- Blood forming cells
- reproductive and GI cells
- basal skin cells
- nerve, muscle and brain cells



Stem Cells

- **Stem cells are cells that retain the instructions to either continue developing undifferentiated or to form specific tissues**
- **Function is to provide specialized cells while ensuring a means of reproducing additional stem cells if needed**
- **Example: Stem cells in the basal skin layer that produce new skin cells**

Blood Stem Cells



Radiosensitive Tissues

Body tissues most sensitive to massive doses of radiation include:

- **Blood forming organs and**
- **Gastrointestinal (GI) tract**

(Exact nature of the damage will be discussed later)

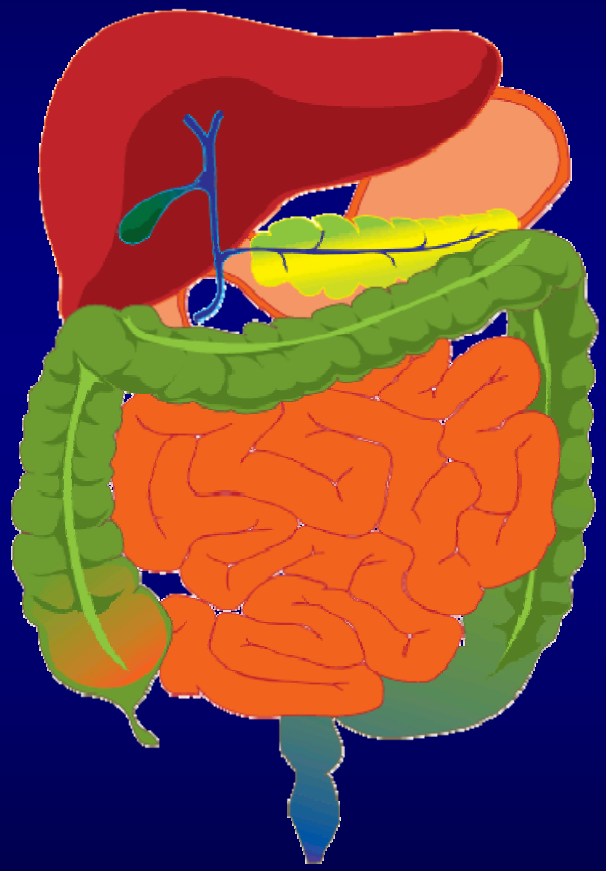
Blood Forming Organs

- Blood cells are produced by cells in the red bone marrow and include:
  - red blood cells (carry oxygen to cells and carbon dioxide away)
  - white blood cells (fight infection)
  - platelets (form clots)
- Damage to stem cells in the red bone marrow inhibits the production of blood cells.

GI Tract

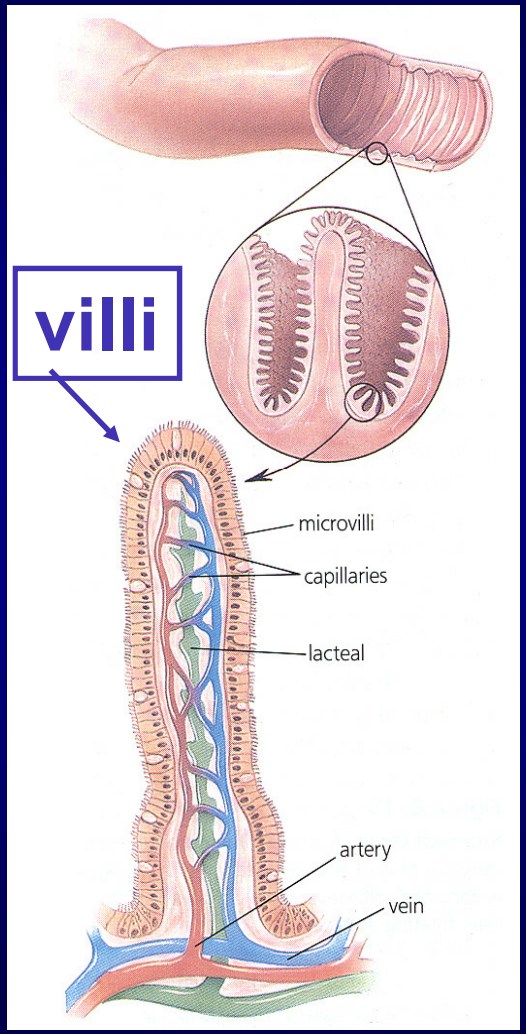
Major components:

- **stomach**
- **small intestine**
- **upper and lower large intestine**



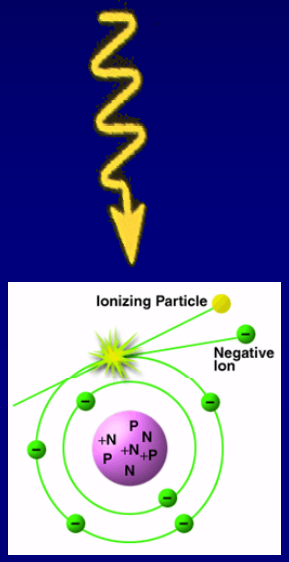
GI Tract (cont)

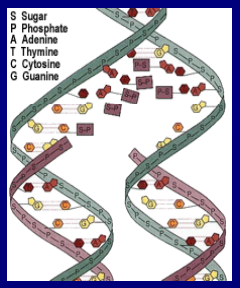
- Regarding radiation damage, small intestine is of greatest interest
- Epithelial lining of small intestine is susceptible to radiation damage
- Epithelial cells are constantly being replaced by rapidly dividing stem cells
- Damage to the stem cells prevents replacement of the epithelial lining and thus inhibits uptake of nutrients.

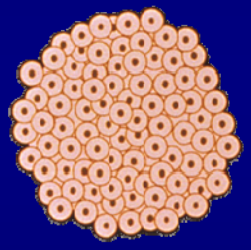


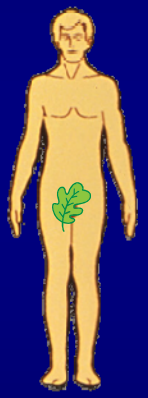
Biological Effects from High Doses of Radiation

Biological Effects Overview









Atom

Molecule

Cell

Tissue

Organ

Whole Body

Radiation ionizes atoms
(knocks out electrons)

High Dose Effects

- Doses above 10 – 20 rad delivered over a short period of time can result in measurable changes to biological tissues

- These effects are called deterministic and include:

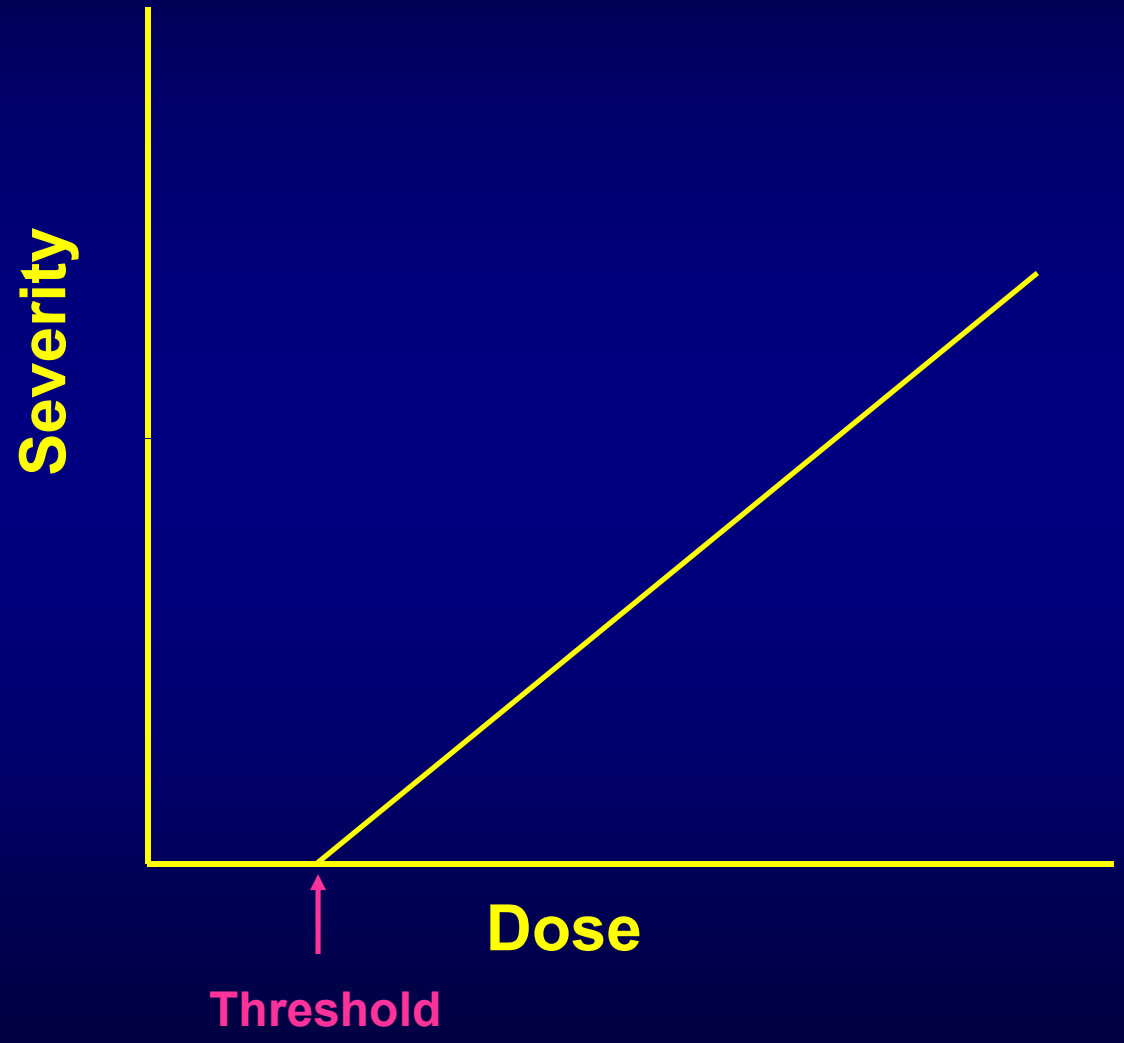
  - Detectable chromosomal aberrations (10-15 rad)
  - Blood count changes (50-100 rad)
  - Sterility (12 rad temporary)
  - Hair loss (300 rad temporary / 700 permanent)
  - Erythema (600 rad)
  - Cataracts (> 50 rad)

- Some of these effects manifest within hours or days after the exposure

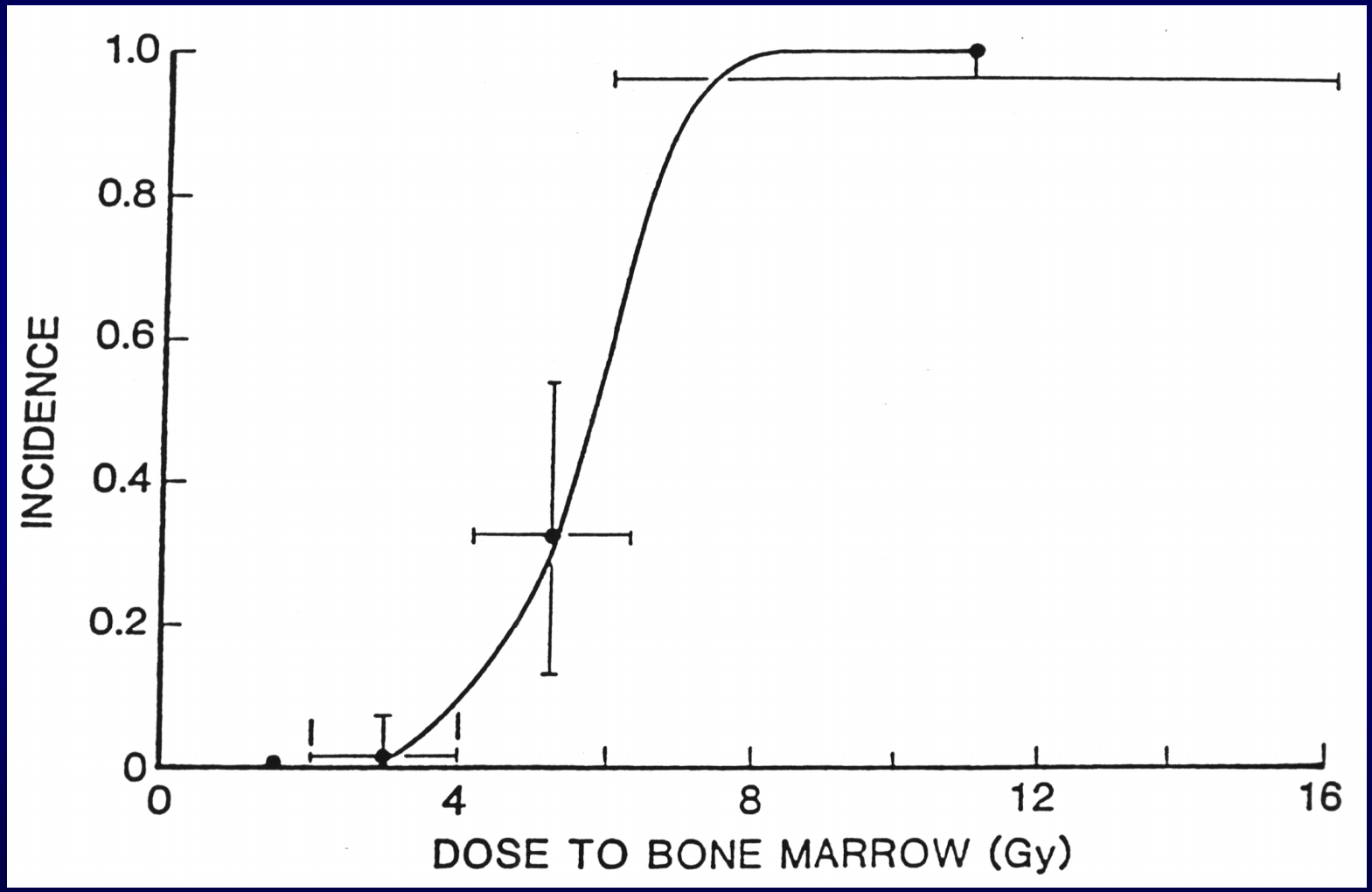
Deterministic Effects

- Deterministic effects have a dose threshold and will not occur at doses below the threshold
- Severity of deterministic effects increases with dose
- These effects can be avoided altogether if dose is kept below the threshold

Deterministic
Dose Response Relationship



Typical Deterministic Dose Response Curve



Acute Radiation Sickness

- Acute Radiation Sickness (ARS) results from a large dose of radiation delivered to the whole body over a very short time period
- ARS can be divided into three syndromes:
  - Hematopoietic or blood Syndrome
  - Gastrointestinal (GI) Syndrome
  - Central Nervous System (CNS) Syndrome

Blood Syndrome

- Dose threshold is about 100 rad
- Chromosome aberrations can be seen at 20 rad but no overt clinical symptoms
- Organ at risk is bone marrow (i.e., blood stem cells)
- Death is possible within 2-8 weeks at doses > 400 rad
- Death is from infection, bleeding, and anemia

Blood Syndrome

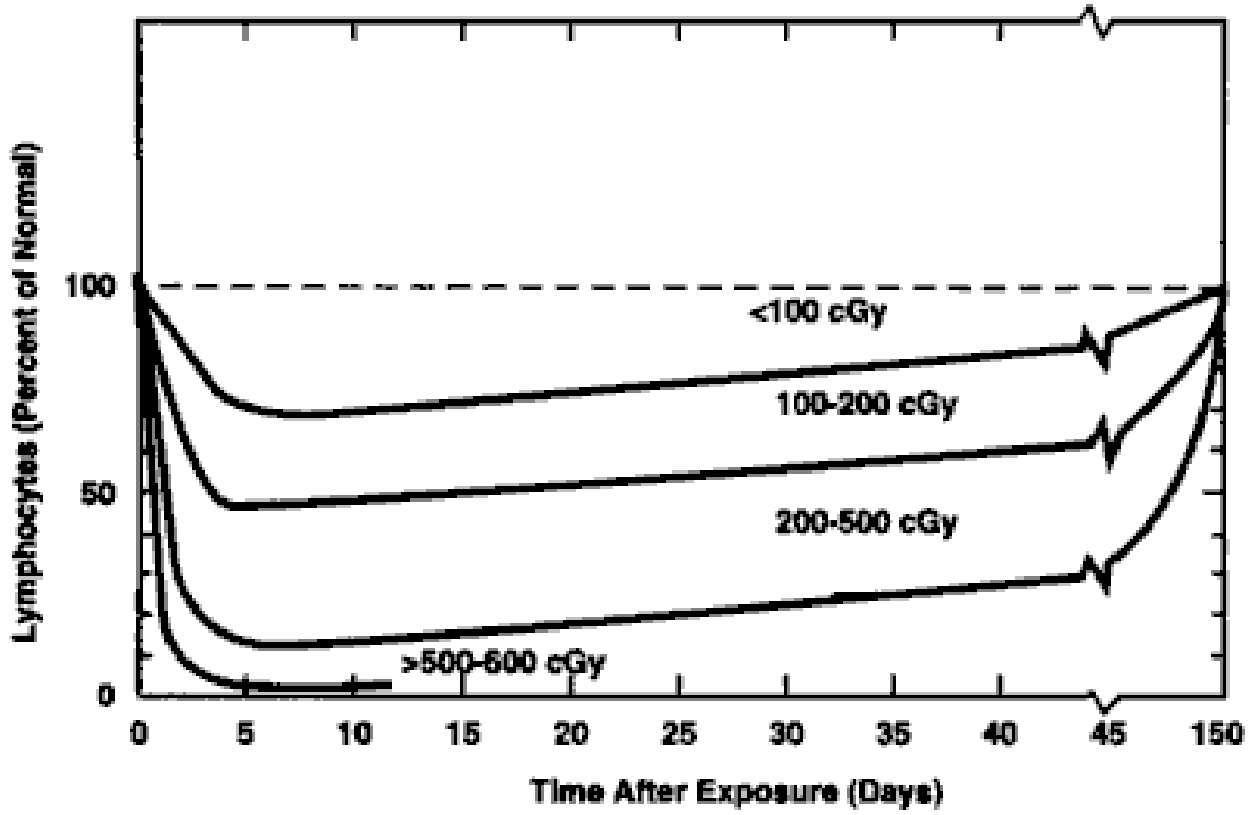
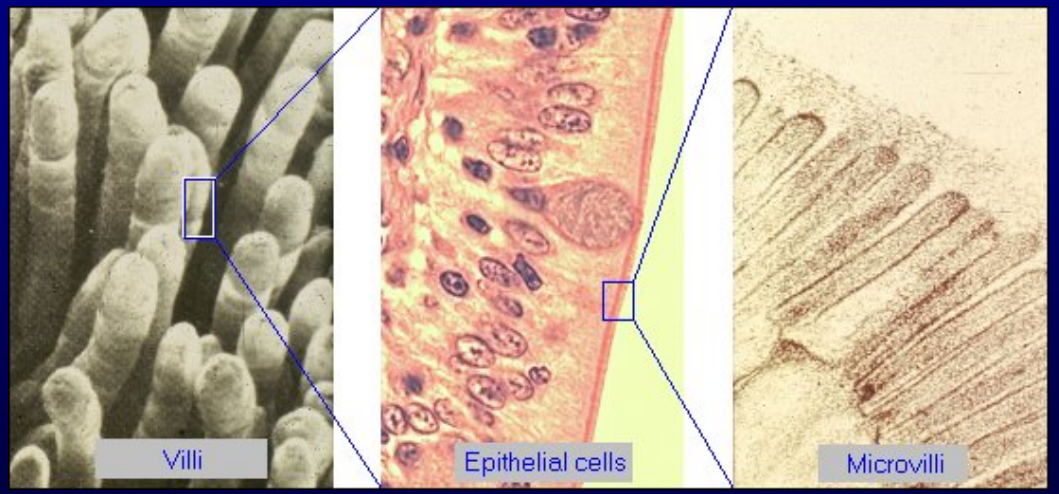


Figure 6-IV. Smoothed Average Time-Course of Lymphocyte Changes in Human Cases from Accidental Radiation Exposure as a Function of Dose

GI Syndrome

- Threshold of about 700 rad
- Tissue at risk is epithelial lining of small intestine
- Effects include nausea, vomiting, and diarrhea
- Death almost certain within 3-14 days at doses over 1000 rad
- Causes of death include infection, bleeding, dehydration, electrolyte imbalance, and circulatory collapse



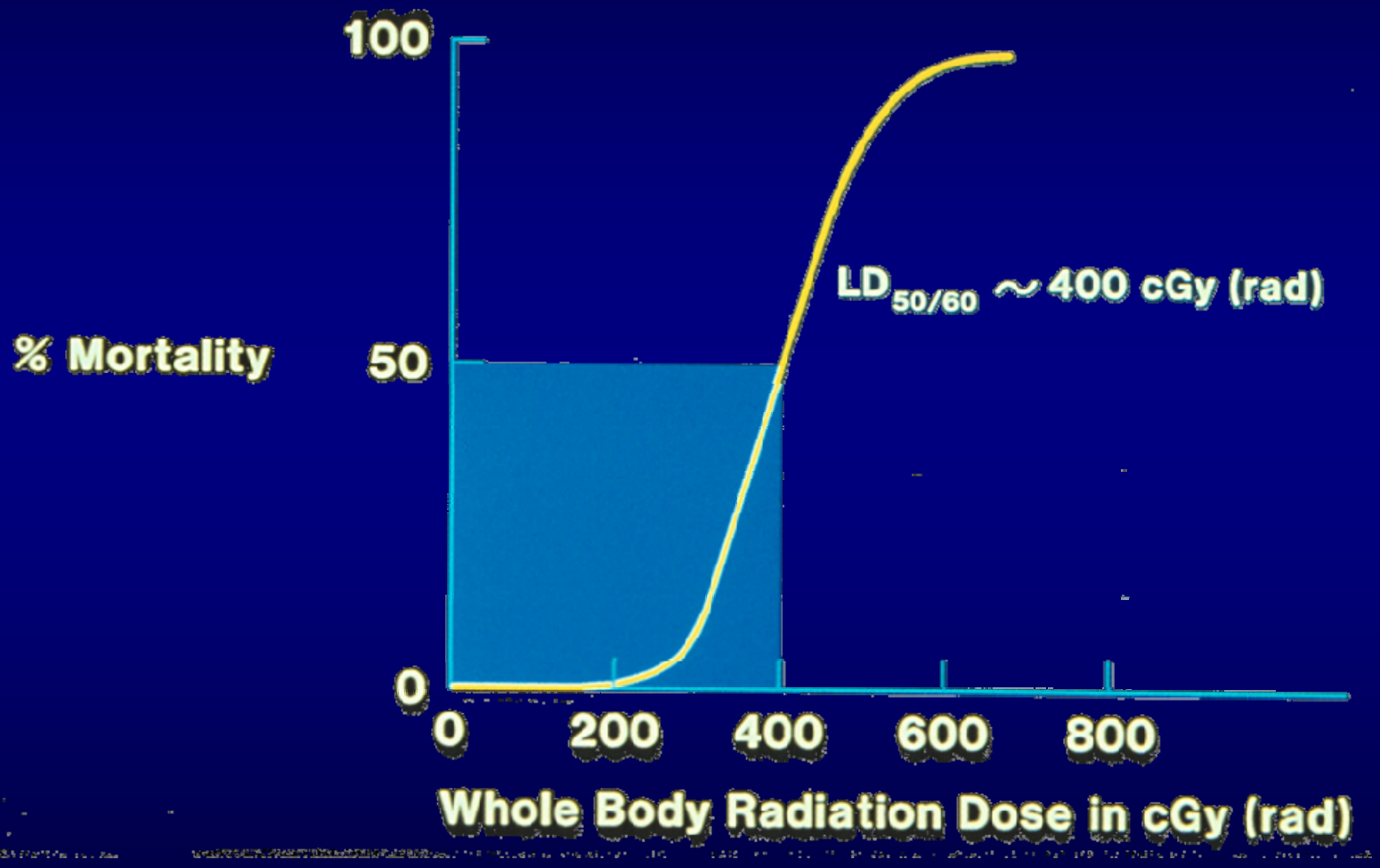
CNS Syndrome

- Threshold of about 2000 rad
- Organ at risk is brain
- Effects include lethargy, convulsions, tremors, loss of muscle control, and coma (in addition to effects from other syndromes)
- Death within hours to a few days for doses > 5000 rad
- Causes of death include respiratory and circulatory collapse

Lethal Dose (LD) 50/60

- Acute dose at which 50% of exposed population will die within 60 days without medical treatment
- LD50/60 for human beings is about 400 rad whole body dose.
- Acute doses above about 1000 rad are usually fatal, even with medical treatment

LD 50/60


100
50
0
% Mortality
$LD_{50/60}$ ~ 400 cGy (rad)
0
200
400
600
800
Whole Body Radiation Dose in cGy (rad)

Range of High Dose Effects

Dose (rad)	Effect
25-50	Detectable changes in blood chemistry but no physical symptoms.
100-300	Some physical symptoms - skin reddening and loss of hair. at the high end of the range, vomiting is caused shortly after exposure.
300-450	Vomiting is first symptom. Major loss in ability to produce blood.
~400 ($LD_{50/60}$)	Death to 50% of the population within 60 days if no medical treatment.
450-1,000	At upper end, bone marrow transplants needed. Fatal within one month without medical care.
1,000-5,000	Vomiting, loss of blood production, failure of GI system. Fatal within several days.
>5,000	Central nervous system failure. Death within hours or days.

Exposure	Significance
1 mSv, major portion of bone marrow	Risk of fatal leukemia is about 1 in 90,000 male, 1 in 125,000 female, as extrapolated from epidemiology at high doses
1 mSv, whole body	Risk of eventual appearance of fatal solid cancer is about 1 in 15,000 male, 1 in 14,000 female
100 mSv, whole body	Elevated number of chromosome aberrations in peripheral blood; no detectable injury or symptoms
1 Sv, reproductive system	Dose for doubling spontaneous mutations
1 Sv, single dose, whole body	Mild irradiation sickness
3.5 Sv, single dose, whole body	Approximately 50% will not survive
4–5 Sv, low-energy x ray, local	Temporary loss of hair
5–6 Sv, single dose, locally to skin, 200 keV	Threshold erythema in 7–10 days, followed by gradual repair; dryness and dull tanning
20 Sv locally to skin from 1 MeV x ray at 300 R/day	Threshold erythema
6–9 Sv, locally to eye	Radiation cataract
10–25 Gy, local, at 2–3 Gy/day	Treatment of markedly radiosensitive cancer
15–20 Gy to skin, single dose, 200 keV	Erythema, blistering, residual smooth soft depressed scar
25–60 Gy, local, at 2–3 Gy/day	Treatment of a moderately radiosensitive cancer
V. Diagnostic x-ray exposures	
200 mR (900 mR reported in 1970)	Mean exposure per dental film per examination in 15–29 yr age group
16 mR	Mean exposure per chest x ray (PA, radiographic, 1984)
500 mR	Mean exposure per chest x ray (photofluorographic, 1964)
5,000 mR/min	Output from properly operating fluoroscope without image intensifier (< 2,000 mR/min with image intensifier)

Industrial Radiography: Acute Extremity Dose

Industrial radiography incidents can result in large acute doses to the extremities. If damage to blood vessels is extensive, amputation may be required.

Industrial Radiography: Acute Partial Body Dose

- In 1979, a California man found a 28 Ci radiography source and placed it in his back pocket for 45 minutes. The dose to his right buttock exceeded 20,000 rad. The dose at a depth of 3 inches exceeded 1,000 rad.
- The reddening and burning caused him to go to the doctor. The doctor thought it was an insect bite at first, until the man indicated he had placed a radiography source in his pocket. Skin grafts were required, and after 2 years, the wound had not fully healed.

Biological Effects from Low Doses of Radiation

Low Dose Effects

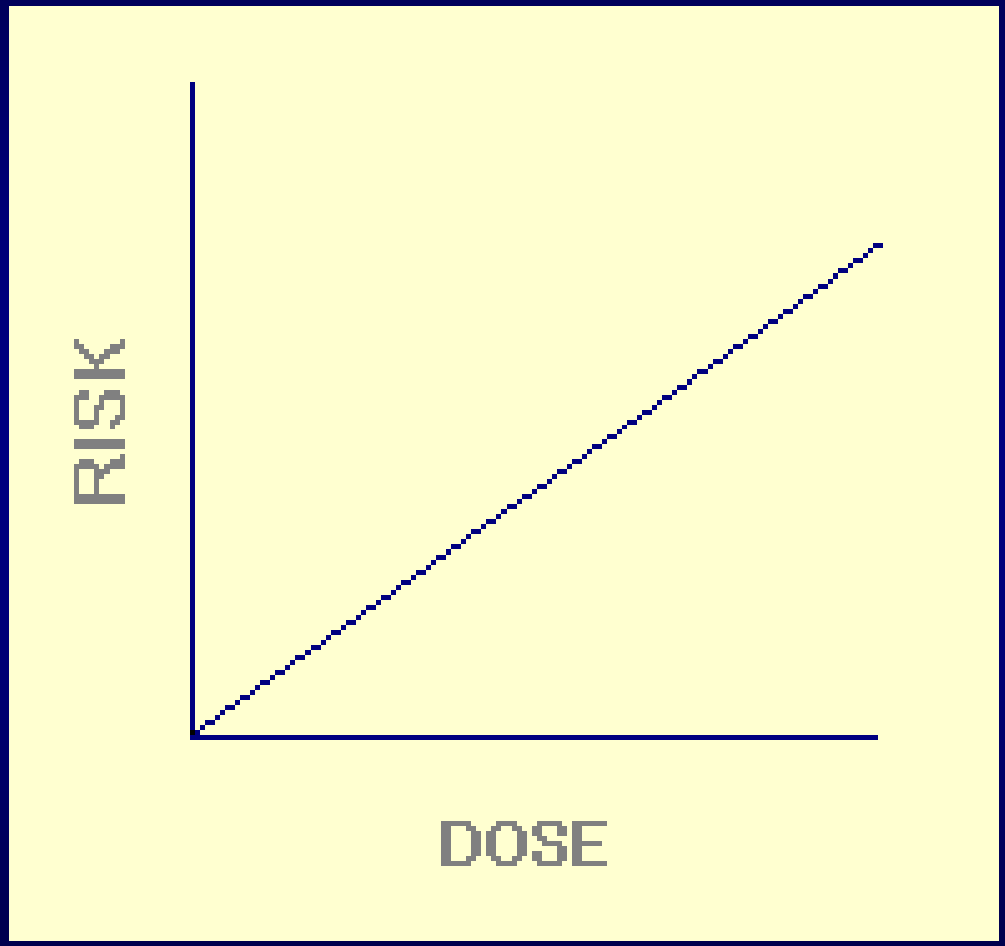
- Principal effects of doses < 10 rad are non-lethal cell mutations
- Most low dose effects are stochastic (i.e., statistical in nature) and include:
  - Cancer
  - Hereditary genetic effects (not proven in humans)
- Stochastic effects take years to manifest

Stochastic Effects

- Cancer is principal stochastic effect
- Radiation induced cancer has been demonstrated in humans through epidemiological studies only at doses exceeding 5-10 rem delivered at high dose rates (HPS Position Statement, “Radiation Risk in Perspective”)
- Leukemia has latency period of 2-3 years, whereas solid tumors have latency periods of 10 to 20 years

Dose-Response Relationship for Stochastic Effects

Linear No Threshold (LNT) Model for Stochastic Effects



Hereditary Effects

- Mutation of sex cells (sperm and egg)
- Mutations are then passed along to offspring
- Radiation-induced genetic effects have been observed in mice and fruit flies
- This has not been clinically observed in humans

In Utero Radiation Effects

- Different from hereditary effects since this is irradiation of a developing embryo/fetus
- During embryonic development, cells divide rapidly and are undifferentiated
- By 8th week, all body systems are present and the embryo is now considered a fetus

In Utero Radiation Effects

- Irradiation of the fetus can cause specific deterministic effects, including malformation of organs during fetal development.
- These effects have a conservative threshold estimated at 0.1 Gy.
- Mental retardation is associated with doses to the brain of the fetus. A reduction of 30 IQ units per Gy is postulated.

In Utero Radiation Effects

Principal effects of *in utero* exposure are:

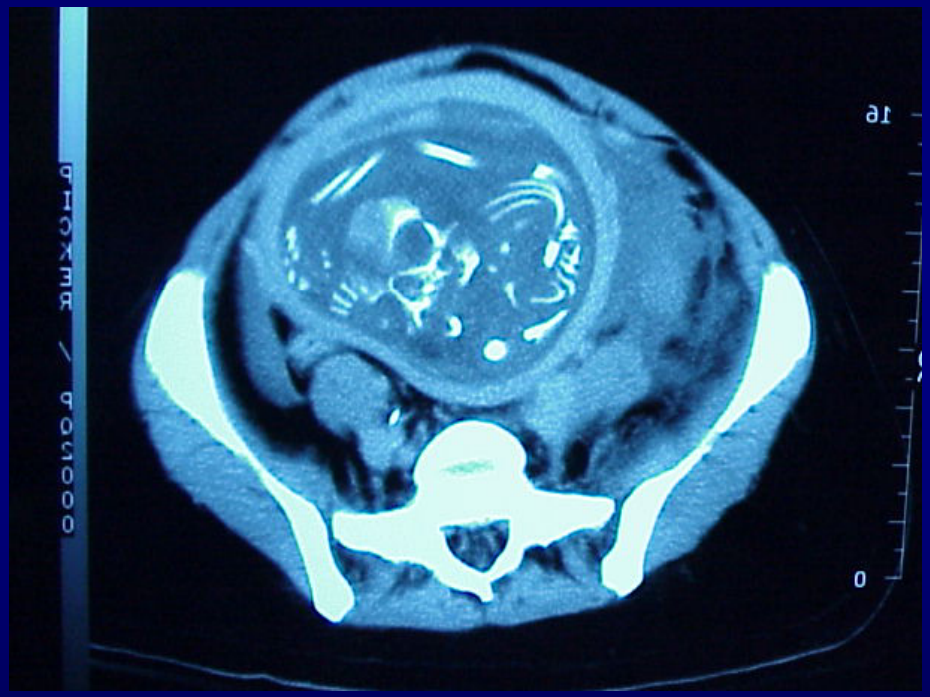
- **growth retardation**
- **mental retardation**
- **childhood cancer**
- **developmental abnormalities**

In Utero Radiation Effects

- Risk of all *in utero* effects per rem is about 1-10 per 1000 births
- Normal risk of fetal abnormalities is about 5-30 per 1000 births

In Utero Radiation Effects

- A CT scan can result in a fetal dose of 20 mGy (ICRP).
- This scan resulted in saving the life of the woman and viability of the fetus.



Declared Pregnant Woman (DPW)

- *In utero* exposure presents a greater lifetime risk for developing leukemia and other cancers.
- The DPW provision enables women who are pregnant to limit dose to their developing embryo/fetus on a voluntary basis. It is the woman's prerogative to invoke this provision and she may also rescind the declaration at any time.
- The dose limit to the embryo/fetus of a DPW is 500 mrem during the entire pregnancy. This dose should be uniformly distributed (i.e., about 50 mrem / month).

Dose to Children

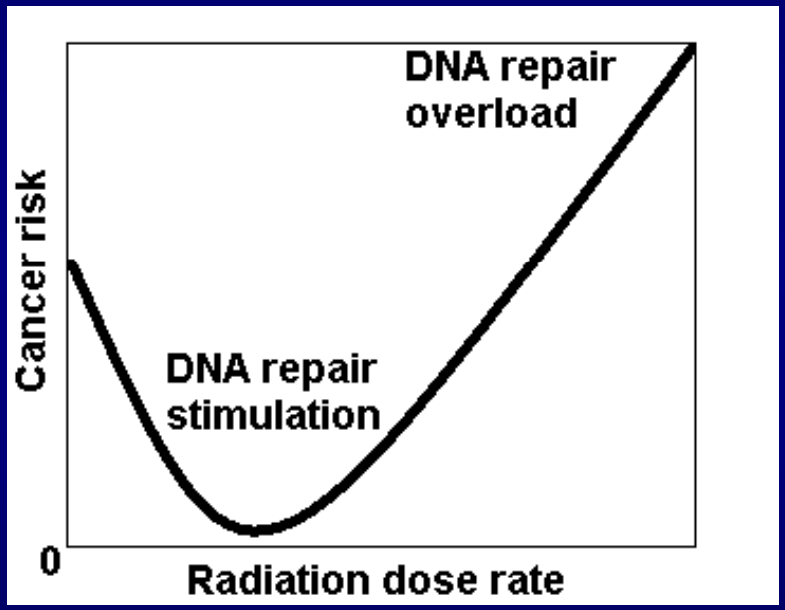
- The number of people receiving medical procedures is increasing. This is important in children, who receive a larger dose for a given procedure and have a longer time to develop cancers.
- For any one person, the risk of death from cancer is about 1 in 5. While estimates vary, a child undergoing a single CT of the abdomen and pelvis increases that risk by 1 in 1,000.

Radiation Hormesis

- Radiation hormesis is the theory that low doses of ionizing radiation are beneficial.
- Some studies of worker populations, animals, and cells have shown favorable health outcomes at low exposures to radiation. However, these studies have not been accepted as proof of a hormetic effect from radiation.
- These studies suggest that exposing cells to to a small amount of radiation (called a conditioning dose) can actually produce an adaptive response that makes cells more resistant to another dose of radiation.

Radiation Hormesis

- Many of the results cannot be reproduced
- Not every type of cell has the capacity for an adaptive response
- The adaptive response does not appear to last long (so the second radiation dose would have to occur soon after the conditioning dose).

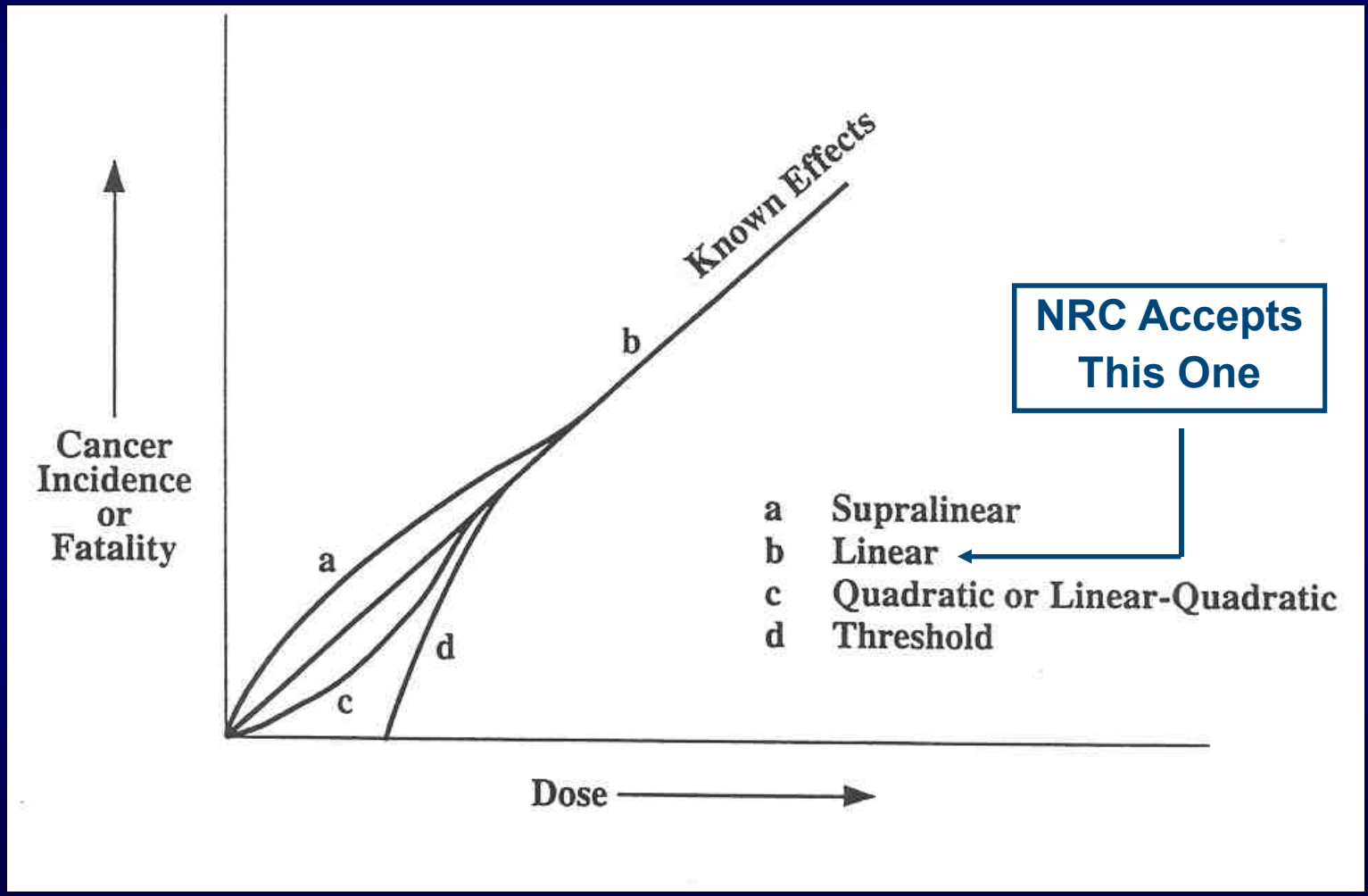


Hormesis Study: Ramsar, Iran

- The highest known background radiation levels (up to 13 mrem/h) have been observed in Ramsar, Iran. This is due to radium-226 that is released from hot springs.
- Blood samples from Ramsar citizens were exposed to 1.5 Gy and compared to samples from a control population that did not live in areas with the background levels of Ramsar.
- Cytogenetic studies showed fewer chromosome aberrations in the samples collected from Ramsar, suggesting that Ramsar citizens had developed a "radiation resistance" from the high background exposure.

Risks from Exposure to Low Doses of Ionizing Radiation

Radiation Dose Response Models



Radiation Risk

- NRC uses linear, no-threshold theory of radiation effects (cancer + genetic)
- 10 CFR Part 20 uses ICRP-30 (1977) risk coefficient of 1.65×10^{-4} per person-rem
- Note that the cancer mortality risk component of the above number is 1.25×10^{-4} per person-rem, while the genetic component of risk is 0.4×10^{-4} (i.e. 4×10^{-5}) per person-rem

Radiation Risk

- More recent NRC Regulatory Guide 8.29, "Instructions Concerning Risks From Occupational Radiation Exposure," uses the more recent ICRP 60 (1990) mortality risk coefficient of 4×10^{-4} per person-rem
- Note that the corresponding mortality risk coefficient for a MOP is 5×10^{-4} per person-rem, due to the portion of the general population under age 18

Radiation Risk (cont)

- Natural cancer incidence is about 2 in 5 (42%)
- Natural cancer mortality is about 1 in 5, or 20%
- Radiation risk coefficient is 4×10^{-4}, or 0.04% per person-rem
- Cancer risk following 1 rem of exposure is 20 % + 0.04% = 20.04%

Radiation Risk (cont)

- 4×10^{-4} means 4 hypothetical cancer deaths per 10,000 (i.e., if we expose 10,000 workers each to 1 rem, we predict an additional 4 cancer deaths, above and beyond the 2000 that will occur naturally, for a total of 2,004)

- If 10,000 person-rem causes 4 additional hypothetical cancer deaths, then it takes 2,500 person-rem to cause one hypothetical cancer fatality

Radiation Risk – Cancer Incidence

- In a lifetime, approximately 42 out of 100 people will be diagnosed with cancer from causes unrelated to radiation. From a previous slide, note that about 20% of the population dies from some form of cancer. So about half of the 42% who develop cancer will survive.

- If 100 people received a dose of 0.1 Sv (10 rem), it is estimated that there will be one additional cancer incidence in this group for a total of 43 cancer incidents.

Cancer Risk from Occupational Exposures

- Epidemiological studies of cancer cases following radiation exposure have been extrapolated down from high dose exposures (atomic bomb survivors, Chernobyl survivors, etc.)
- No data directly proving cancer is caused by exposure to doses less than 5 rem per year

Cancer Risk from Occupational Exposures

Low-Dose Radiation Exposure

"A number of studies over the past 20 years have looked at the impact of environmental radiation exposure in the dose range of 10 cGy or less. Careful analysis of this research revealed no significant increase in the incidence of all cancers combined, or of cancers in specific parts of the body. Research in this area is continuing."

- American Cancer Society Website

QUESTIONS?

END OF BIOLOGICAL EFFECTS OF RADIATION

Relative Biological Effectiveness (RBE)

- Certain types of radiation are more effective at causing biological damage
- The ability of a given type of radiation to damage biological tissue is measured using RBE:

$$\text{RBE} = \frac{\text{Dose of reference radiation to produce an effect}}{\text{Dose of test radiation to produce same effect}}$$

Relative Biological Effectiveness (cont.)

- 250 kVp are typically used as the reference radiation
- Quality factors (Q) are based on RBE values determined for various radiations from both animal and human data

Review Questions

- What is the critical biological target for radiation?
- Can cells repair a portion of radiation damage?
- Is all DNA radiation damage manifested as a disease or defect?
- What percent of the population will develop a cancer at some time in their life?

Review Questions

- Most cancers originate from how many cells?
- What percent of the population will die from a fatal cancer not related to occupational radiation exposure?
- Describe the radiation direct effect
- Describe the radiation indirect effect

Review Questions

- Name one free radical produced in the indirect effect.
- Name one oxidizing agent that is produced during the indirect effect
- State the Law of Bergonie and Tribondeau

Review Questions

- Explain radiation hormesis. Does NRC subscribe to this theory?
- Name some deterministic effects of radiation.
- What are the three acute radiation syndromes?
- What does LD 50/60 stand for? What is its value in rad? in cGy?

Review Questions

- List examples of stochastic effects of radiation.
- Draw a risk vs. dose curve illustrating the LNT
- What is the ICRP 60 cancer mortality risk coefficient for the public?

Review Questions

- A population of 100,000 people in the general public is each exposed to a dose of 100 mrem. Using the appropriate ICRP 60 radiation risk coefficient, estimate the number of hypothetical cancer deaths that might occur from this exposure.

- Approximately how many cancer deaths will occur naturally in the above population?

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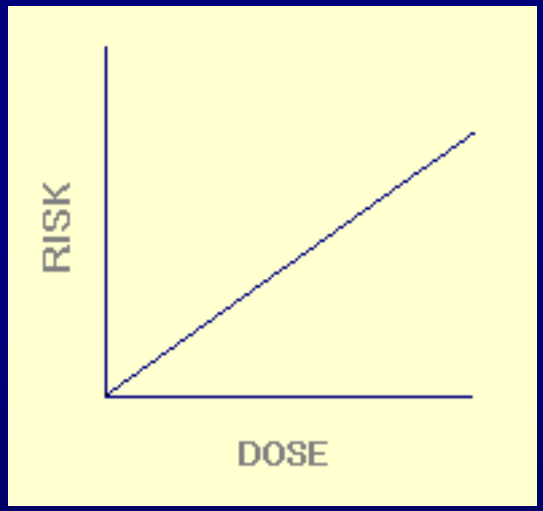

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