

PATHPHYSIOLOGY CANCER

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Textbook: Chapter 9

Cancer (Neoplastic Disease)

- Second leading cause of death in the US (500,000/year)
- Incidence is increasing, mortality is decreasing; early detection
- Most common type: skin cancer
75% all other malignancies occur in 10 anatomical sites: colon, rectum, breast, lung and bronchus, prostate, uterus, lymph organs, bladder, stomach, blood and pancreas.
- **Cancer deaths:**
Males: lung (31%); prostate (10%); colon & rectum (10%)
Female: lung (25%); breast (15%); colon & rectum (11%); ovaries (5%)
- Major cause of cancer: **cigarette smoking:**
15% of all cancer deaths

Cancer

Cancer: derived from Greek word for crab;
Hippocrates- appendage like projections from crab
Many different diseases

common feature: abnormal cell growth

- shift in control mechanisms for growth and differentiation; infiltration into organs; Interference with normal function

Tumor: “swelling” (classical defn; Greek)

Today- readily defined mass of abnormally growing tissue

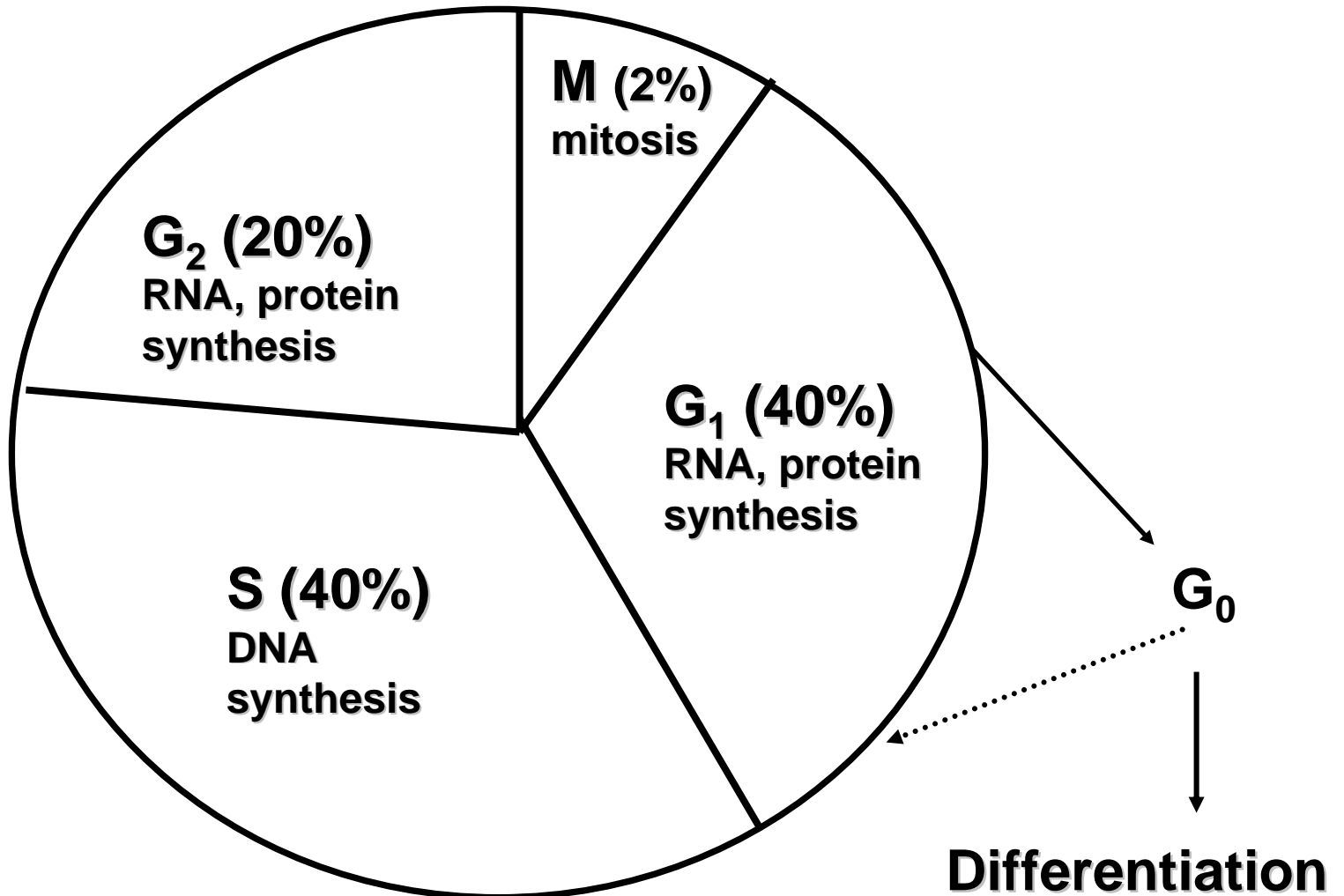
Neoplasm: new growth; autonomous



Abnormalities Associated with Tumors

- **Hypertrophy:** increase in cell size
- **Hyperplasia:** increase in cell number
- **Dysplasia:** abnormal appearance of a cell; (earliest form of preneoplastic lesion); epithelial layer; change in cell size, shape, organization; graded: low → high
- **Metaplasia:** reversible *replacement* of one mature cell by another
ex., epithelial metaplasia: columnar epithelial cells of respiratory tract → squamous epithelium
redirection of differentiation

Cell Cycle



Cell Cycle Phase

Tumors consist of heterogeneous populations of cells, some growing, some dormant; in different phases of cell cycle

Phases of Cell Cycle

- M: (mitosis, 2%); prophase, metaphase, anaphase, telephase
- G_1 (Gap 1, 40%): determines length of cell cycle, varies:
 G_0 : dormant cells (not cycling); resting or differentiating
- S: (40%) DNA synthesis
- G_2 (Gap 2, 20%): RNA and protein synthesis

Doubling time: time for total number of cells in a tumor to double; to go through cell cycle once

Genetics of Cancer

Cancer- disease of aging

Mutation Theory: cancer caused by mutations; with time, number of mutations (hits) increases; when sufficient number occurs clonal proliferation of → mutated cell

Types of mutations:

- Mutations in normal genes (proto-oncogenes) controlling proliferation (growth factors, receptors-EGFr, intracellular signaling-ras); become oncogenes
- Suppression of anti-cancer genes or tumor suppressor genes (retinoblastoma gene)
- Resistance to apoptosis (p53 mutations)

Characteristics of Cancer Cells

Altered Growth

uncontrolled proliferation; loss of contact inhibition, loss of cell-cell communication, become autonomous; **immortal**

Altered Morphology

Pleomorphic- many different shapes

Anaplasia

dedifferentiation- loss or lack of differentiation; change in size, shape, DNA content

Characteristics of Cancer Cells

Karyotypic Changes

Polyploidy: cell division produces more than two sets of chromosomes

Aneuploidy: daughter cells receive uneven number of chromosomes

Classification of Tumors

Behavioristic:

Benign

encapsulated

differentiated

rare mitosis

slow growth

little anaplasia

*non-invasive

*no metastasis

Malignant (cancer)

nonencapsulated

nondifferentiated

common mitosis

rapid growth

anaplasia

*invasive

*metastatic

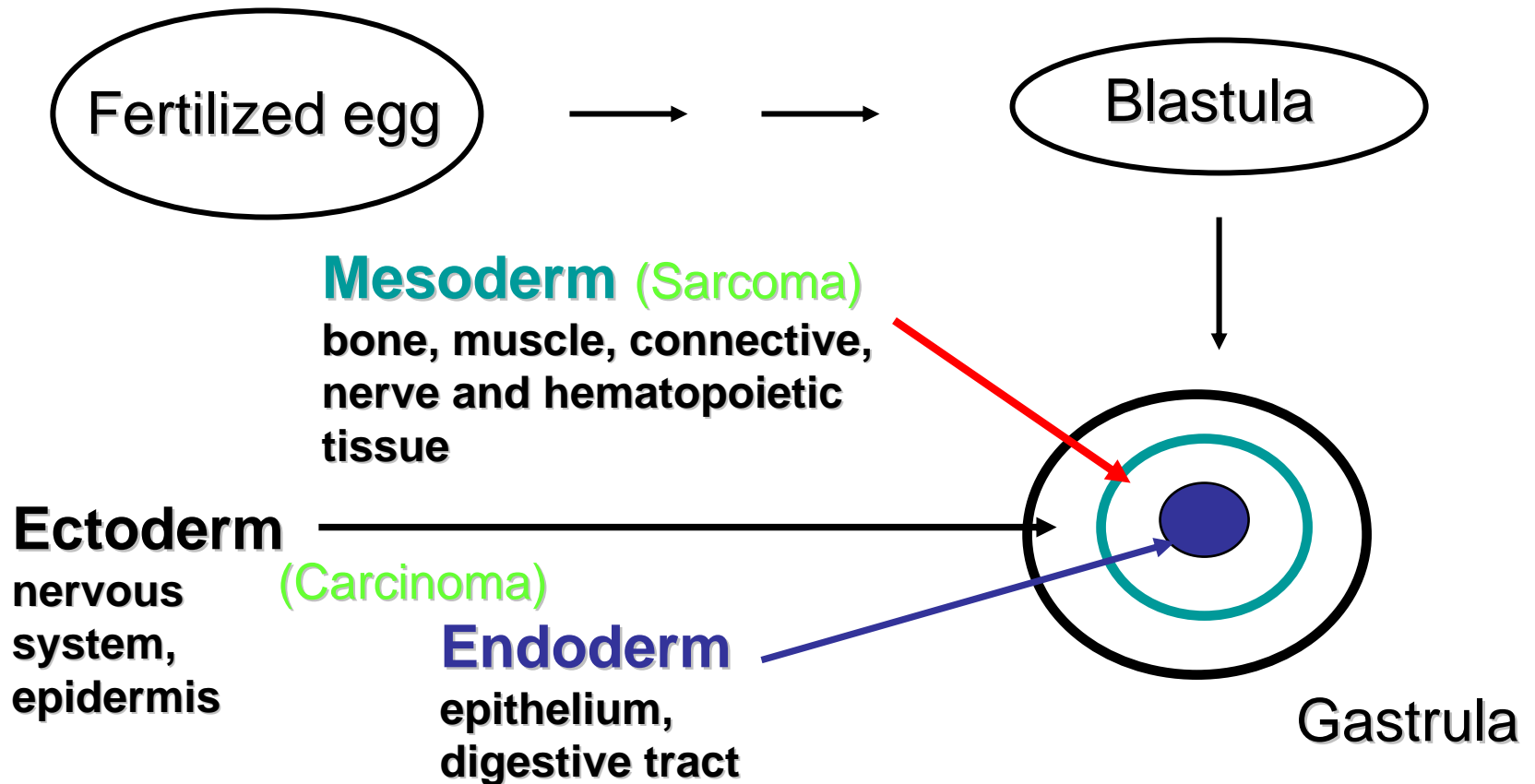
Classification of Tumors

Histiogenetic: based on tissue origin

- **Epithelial:** squamous cells; basal cells; glandular or ductal cells
- **Connective tissue:** bone, cartilage, fibrous tissue
- **Hematopoietic:** leukocytes, lymphatic tissue, plasma cells
- **Nervous system tumors:** nerve tumors

Classification of Tumors

Embryonic Classification



Embryonic Classification

Sarcomas: arise from mesenchymal (mesoderm) or connective tissue;
ex., osteogenic sarcoma (from bone);
rhabdomyosarcomas (from skeletal muscle);
lymphosarcoma (from lymph tissue)

Carcinomas: arise from endothelial and epithelial tissues (ectoderm and endoderm);
ex., hepatocellular carcinoma;
adenocarcinomas- arise from ductal or glandular tissue

Teratomas- neoplasm of multiple tissue origin;
derived from all 3 germ lines

Types of Tumors

Solid Tumors: can occur in any organ or tissue

Carcinomas: originate from endothelial and epithelial cells (ectoderm and endoderm); ex., squamous cell (basal cells skin); glandular epithelium (breast)

Sarcomas: originate in mesenchymal cells (mesoderm); ex., osteogenic sarcoma (osteoblasts, chondroblasts, fibroblasts)

Types of Tumors

Hematologic Malignancies: cancers arising from blood forming organs and cells

- **Leukemias:** WBC – proliferation of immature, committed bone marrow cells; types: ALL, AML, CLL, CML multiple myeloma
- **Lymphomas:** tumor of lymph system
 - Hodgkin's Disease (lymph nodes)
 - Non Hodgkin's lymphoma

Staging Cancer

- **Stage 1:** confined to the organ of origin
- **Stage 2:** locally invasive
- **Stage 3:** spread to regional structures (ex., lymph nodes)
- **Stage 4:** spread to distant sites

Etiology of Cancer

Environmental factors (80-90%)

chemicals, diet, industrial pollution, medical treatment

Immunological defects

Radiation

Oncogenic viruses

Contributing factors:

age, sex, race, genetic predisposition, environmental exposure levels, behavioral habits, occupation

Environmental Agents

Chemicals

- **Carcinogens:** chemicals that cause cancer; ex., polycyclic aromatic hydrocarbons, benzo(a)pyrene, 3-methylcholanthrene
- **Co-carcinogens:** work with carcinogens
- **Tumor promoters:** promote the action of carcinogens

initiation → promotion → tumor formation

Environmental Agents

Drugs

- **Immunosuppressive agents**

Immune surveillance: macrophages and T cells

- AIDS: Kaposi's sarcoma
- Renal transplants: reticulo cell sarcoma (150x); others (2x)

- **Common drugs** (<1% of all cancers)

DES, chlorpromazine, reserpine, estrogens, oral contraceptives, anticancer drugs

Environmental Agents

Radiation: most systemically studied

- **Ionizing Radiation:** high energy chronic exposure to x-rays and radioactive chemicals → skin cancer, leukemia;
medical, diagnostic, occupational exposure
nuclear fallout Japan
 ^{131}I for treatment of goiter
- **Mechanism:**
Specific mutations → DNA strand breaks; often requires multiple hits
Ex., Incidence of leukemia in radiologists 1900-1950 (3-4x); Hiroshima survivors (2x)

Environmental Agents

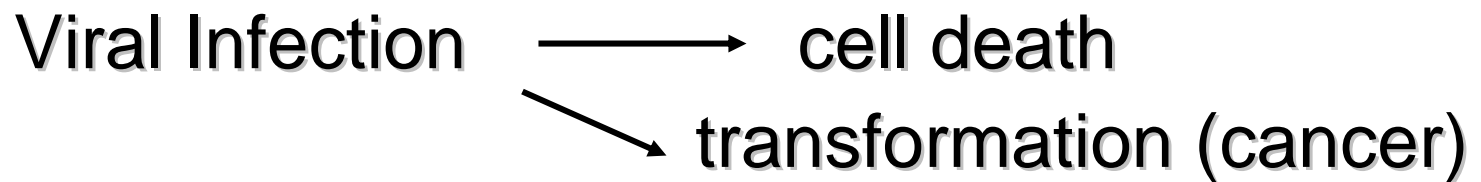
Radiation

- **Ultraviolet Radiation** (2900-3400 Å)
 - Sunlight – greatest source of exposure: results in skin tumors; malignant melanoma
 - Correlate incidence skin cancer to exposure to sun; latitude, clothing, farmers

Environmental Agents

Oncogenic Viruses

- **RNA viruses** (acutely transforming retroviruses)
- **DNA viruses** (HSV, EBV)



Viral oncogenes (RNA or retroviruses)- get inserted into genome; disregulate proliferation

Contributing Factors

Occupation: determines exposure levels

1780: P. Potts

1900's: radium dial painters

1950's: shoe store x-ray machines

1990's: Industrial chemical workers

BCME, CMME

metals

vinyl chloride

benzene

PCB's

asbestos

Contributing Factors

Age:

- Cancer is a disease of aging
- **Latency:** time for for genetic or epigenetic changes to be expresses
- Mutations

Contributing Factors

Hormones:

- Beatson (1800): identified causal relationship between breast cancer and ovaries
- Hormones: maintain internal milieu; abnormal production → derangement of homeostasis → neoplasia
ex. DES (Herbst, 1971)
1st trimester exposure → vaginal adenosis; clear cell and squamous cell carcinoma in female offspring; infertility

Hereditary Factors

Heredity Factors: Most involve environmental interaction with DNA; Polygenic or multifactorial inheritance

- **Autosomal dominant:** no apparent environmental cause; pheochromocytoma, retinoblastoma
- **Autosomal recessive:** usually DNA repair defects; involve environmental agents; xeroderma pigmentosa (UV); ataxia telangiectasia (ionizing radiation)
- **Genetic Predisposition:** cancer genes; breast cancer (3x); lung cancer; colon cancer

Geography

Diet: ingestion of carcinogens (aflatoxin; nitrates, nitrites)
Cancers of digestive tract (ex., stomach cancer)
Incidence: Japan vs. U.S.

Environmental Pollution:

- **Air** large cities increase levels hydrocarbons
urban cigarette smokers increased incidence
lung cancer; greater than heavy rural
smokers; carcinogen interactions
- **Water**

Geography

Occupation

Behavioral Habits

Sun

If change geography, offspring acquire
incidence of new environment