CHS 2413
Pathology and Physiopathology

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Neoplasia

WHAT IS A TUMOUR?

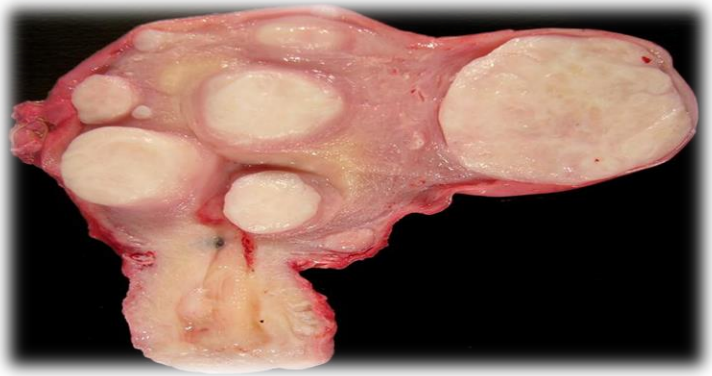
a swelling

inflammatory – abscess

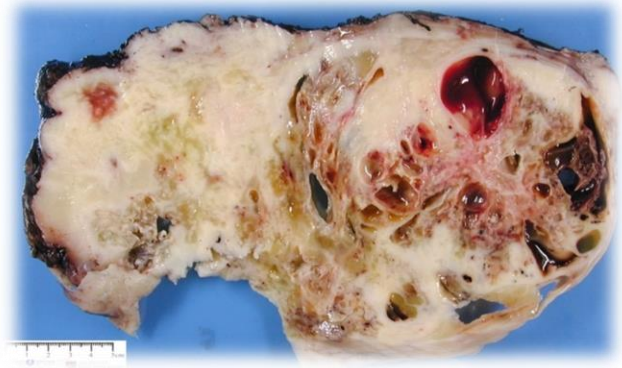
neoplasm - growth

NEOPLASM

- Abnormal growth of cells which persists after initiating stimulus has been removed
- Cell growth has escaped from normal regulatory mechanisms
- Benign
- Malignant



Leiomyoma



Malignant Tumors

INCIDENCE & DISTRIBUTION OF CANCER IN HUMANS

- **Incidence & Mortality Rates**
- Cancer is the second overall leading cause of death (after ischemic heart disease) in the world. The incidence continues to rise, probably reflecting the increasing average age of the population.
- **Major Factors Affecting Incidence**
- The presence or absence of any of the many factors influencing the incidence of cancer must be established during history taking and physical examination of a patient thought to have cancer.

10 อันดับมะเร็งที่พบมากที่สุด

ในประเทศไทยและทั่วโลก ปี 2560-2561

การรายงานอุบัติการณ์ของมะเร็งภายในประเทศไทย พบว่า

- ประชากรเพศชายในประเทศไทยมีอุบัติการณ์มะเร็งตับสูงที่สุดและรองลงมาตามลำดับคือ มะเร็งปอดและมะเร็งลำไส้ใหญ่
- ประชากรเพศหญิงในประเทศไทยมีอุบัติการณ์มะเร็งปากมดลูกสูงที่สุดและรองลงมาตามลำดับคือ มะเร็งเต้านม และมะเร็งตับ

TYPES OF NEOPLASMS

	Benign	Malignant
• Epithelial	adenoma papilloma	Carcinoma
• Connective tissue	fibroma, leiomyoma	sarcoma
• Lymphoid /haemopoietic		
• Germ cell		
• Mixed tumor		

Classification of neoplasms classified by cell differentiation

- ***1. Epithelial neoplasms:***

- A benign epithelial neoplasm is called an **adenoma** if it arises within a gland (eg, thyroid adenoma, colonic adenoma) or a **papilloma** (Latin, *papilla* = nipple) when arising from an epithelial surface.
- Papillomas may arise from squamous, glandular, or transitional epithelium (eg, squamous papilloma, intraductal papilloma of the breast, and transitional cell papilloma, respectively).
- Not uncommonly, descriptive adjectives are incorporated in the nomenclature; eg, colonic adenomas may be villous, tubular or tubulovillous.

EPITHELIAL NEOPLASMS

BENIGN EPITHELIAL NEOPLASMS

1. Papilloma :squamous, transitional
2. Adenoma: Glandular

MALIGNANT EPITHELIAL NEOPLASMS

1.Carcinomas

Squamous:	skin
Transitional:	bladder
Adeno:	stomach, colon
Basal cell:	skin

- ***2. Mesenchymal neoplasms:***

- Benign mesenchymal neoplasms are named after the cell of origin (a Greek or Latin word is used) followed by the suffix -*oma*. The names of these tumors may contain the organ of origin and an adjective, eg, cavernous hemangioma of the liver.

- Malignant mesenchymal neoplasms are named after the cell of origin, to which is added the suffix -*sarcoma*.
- Again, adjectives are commonly used; liposarcomas are classified as sclerosing, myxoid, round cell, or pleomorphic.

Connective(Mesenchyme) tissue neoplasms

Benign connective tissue neoplasms

- Smooth muscle: Leiomyoma
- Fibrous tissue: Fibroma
- Bone: Osteoma
- Cartilage: Chondroma
- Fat: Lipoma
- Nerve: Neurofibroma
- Nerve sheath: Neurilemmoma
- Glial cells: Glioma

Malignant connective tissue neoplasms

- Smooth muscle: Leiomyosarcoma
- Bone: Osteosarcoma
- Fibrous tissue: Fibrosarcoma
- Cartilage: Chondrosarcoma
- Fat: Liposarcoma
- Nerve: Neurofibrosarcoma
- Nerve sheath: Neurilemmosarcoma
- Glial cells: Malignant glioma

- ***3. Leukemias and Lymphomas***
- Neoplasms of blood-forming organs are called leukemias. These disorders are all considered malignant, although some exhibit a slower clinical course than others.
- Leukemias are classified on the basis of their clinical course (acute or chronic) and cell of origin (lymphocytic, granulocytic-myelocytic, monocytic, etc).
- Leukemias are characterized by the presence of neoplastic cells in bone marrow and peripheral blood; they rarely produce localized tumors.

Classification continued

- Tumors of lymphocytes are always malignant – called lymphoma
- Tumors of melanocytes
  - Benign – nevus
  - Malignant - melanoma

LYMPHOID

- Malignant lymphoma (B and T)
- Hodgkins Disease
- *BONE MARROW*
- Acute and chronic leukaemia

GERM CELL

- Testis
- Teratoma
- Seminoma
- Ovary
- Dermoid Cyst

- ***4. Mixed tumors***
- Neoplasms composed of more than one neoplastic cell type are called mixed tumors.
- two epithelial components, as in adenosquamous carcinoma;
- two mesenchymal components, as in malignant fibrous histiocytoma; or
- an epithelial and a mesenchymal component, as in carcinosarcoma of the lung and malignant mixed müllerian tumor (MMMT) of the uterus.

- **A handful of tumors that are thoroughly malignant have "benign sounding" names. You will just have to learn these!**

  - lymphoma
  - mesothelioma
  - myeloma ("multiple", plasma cell)
  - astrocytoma
  - carcinoid
  - glioma (micro-, oligodendro-)
  - ependymoma
  - seminoma
  - hepatoma (today, "hepatocellular carcinoma")
  - melanoma
  - dysgerminoma
  - leukemia

Factors effect cancer incidence

- Sex
- Age
- Geographic and Environmental Factors
- Hereditary
- Preneoplastic lesions or chronic Inflammation
- Unknown

Sex:

- Prostate cancer in men and uterine cancer and breast cancer in women are obviously sex-specific.
- In other types of cancer, the reasons for the difference in incidence between the sexes are less evident.
- For example, cancer of the oropharynx, esophagus, and stomach is more than twice as common in men, but cancers of the gallbladder and thyroid and malignant melanoma are more frequent in women.

Age:

- The frequency of occurrence of most types of cancer varies greatly at different ages.
- Carcinoma is rare in children, but some leukemias, primitive neoplasms (blastomas) of the brain, kidney, and adrenal, malignant lymphomas, and some types of connective tissue tumors are relatively common. Most of these childhood neoplasms grow rapidly and are composed of small, very primitive cells with large, hyperchromatic nuclei, scant cytoplasm, and a high mitotic rate.

Occupational, Social, and Geographic Factors:

- Occupational factors have been mentioned with reference to an increased risk of bladder cancer in workers in the dye industry and lung cancer in certain miners.
- Because the risk is so high in certain industries, an occupational history is an essential part of a full medical examination.
- Similarly, such social habits as cigarette smoking represent risk factors for development of several types of cancer, and the physician must evaluate the amount of exposure to these factors during history taking.

ปัจจัยด้านพันธุกรรม (Hereditary)

แบ่งออกเป็น 3 แบบ คือ

1.Inherited Cancer Syndromes

-ผลของความผิดปกติของยีนเดียวทาให้เพิ่มอัตราเสี่ยงต่อการเกิดมะเร็งและ โดยมากแล้วยีนเหล่านี้จะถ่ายทอดทางพันธุกรรมแบบ Autosomal dominant pattern

-40% ของผู้ป่วยมะเร็งชนิด Retinoblastoma จะมีญาติพี่น้องเจ็บป่วยด้วยมะเร็งดังกล่าว

-Familial adenomatous polyposis (FAP) ซึ่งเป็นโรคถ่ายทอดทางพันธุกรรมที่เพิ่มความเสี่ยงต่อการเกิดมะเร็งลำไส้ใหญ่

2.Familial Cancers

-มะเร็งที่จัดอยู่ในกลุ่มนี้ไม่สามารถบอกรูปแบบการถ่ายทอดทางพันธุกรรมได้ชัดเจนเหมือนกับกลุ่มแรกและโรคกลุ่มนี้โดยมากจะเกิดขึ้นตั้งแต่อายุน้อยๆ

3. Autosomal Recessive Syndromes of Defective DNA Repair

-โรคที่จัดอยู่ในกลุ่มนี้มีน้อย การถ่ายทอดทางพันธุกรรมจะเป็นแบบ Autosomal recessive ยีนที่ผิดปกตินั้นเกี่ยวข้องกับขบวนการซ่อมแซม DNA (DNA repair)

Other factors

- Childbearing
- Circumcision
- Socioeconomic status
- Geographic area or country
- Eating and drinking habbits,
- Foodstufs...

Cause of Cancers

ความผิดปกติของเซลล์จนเกิดเป็นมะเร็งนั้นประกอบด้วย การเปลี่ยนแปลงหลายขั้นตอนต่อเนื่องกัน ซึ่งโดยมากจุดเริ่มต้น ของการเปลี่ยนแปลงก็คือ การผ่าเหล่าของยีนที่เกี่ยวข้องกับการ เพิ่มจำนวนของเซลล์ ดังที่ได้กล่าวมาแล้วในขั้นต้น และมีหลาย สิ่งหลายอย่างรอบๆตัวมนุษย์ที่สามารถทำให้เกิดการบาดเจ็บ หรือทำให้เกิดการผ่าเหล่าของยีน จนเกิดเป็นมะเร็งได้ ซึ่งจะแบ่ง ออกเป็น 3 กลุ่ม คือ

– กลุ่มสารเคมีก่อมะเร็ง หรือที่เรียกว่า Chemical carcinogens

– กลุ่มรังสีก่อมะเร็ง หรือที่เรียกว่า Radiant energy

– กลุ่มเชื้อโรคที่สามารถก่อมะเร็ง หรือที่เรียกว่า Oncogenic microbes ซึ่งส่วนใหญ่จะเป็นเชื้อไวรัสก่อมะเร็ง หรือ Viral carcinogenesis

Carcinogen

- A cancer-causing agent
- Three classes:
  - Chemical carcinogens (endogenous/exogenous)
  - Physical carcinogens (UV, radiation, asbestos)
  - Oncogenic microbes (mainly viruses)

Chemical Carcinogens as Mutagens

- **Mutagen:** an agent that can permanently alter genetic constitution of a cell
- 90% of known carcinogens are mutagenic
- Most mutagens are carcinogens

Promoters in Human Cancers

- Cigarettes
- UV
- High Fat Diet
- Hormones
- Viral Infections

Human carcinogens

Drugs/therapeutic agents

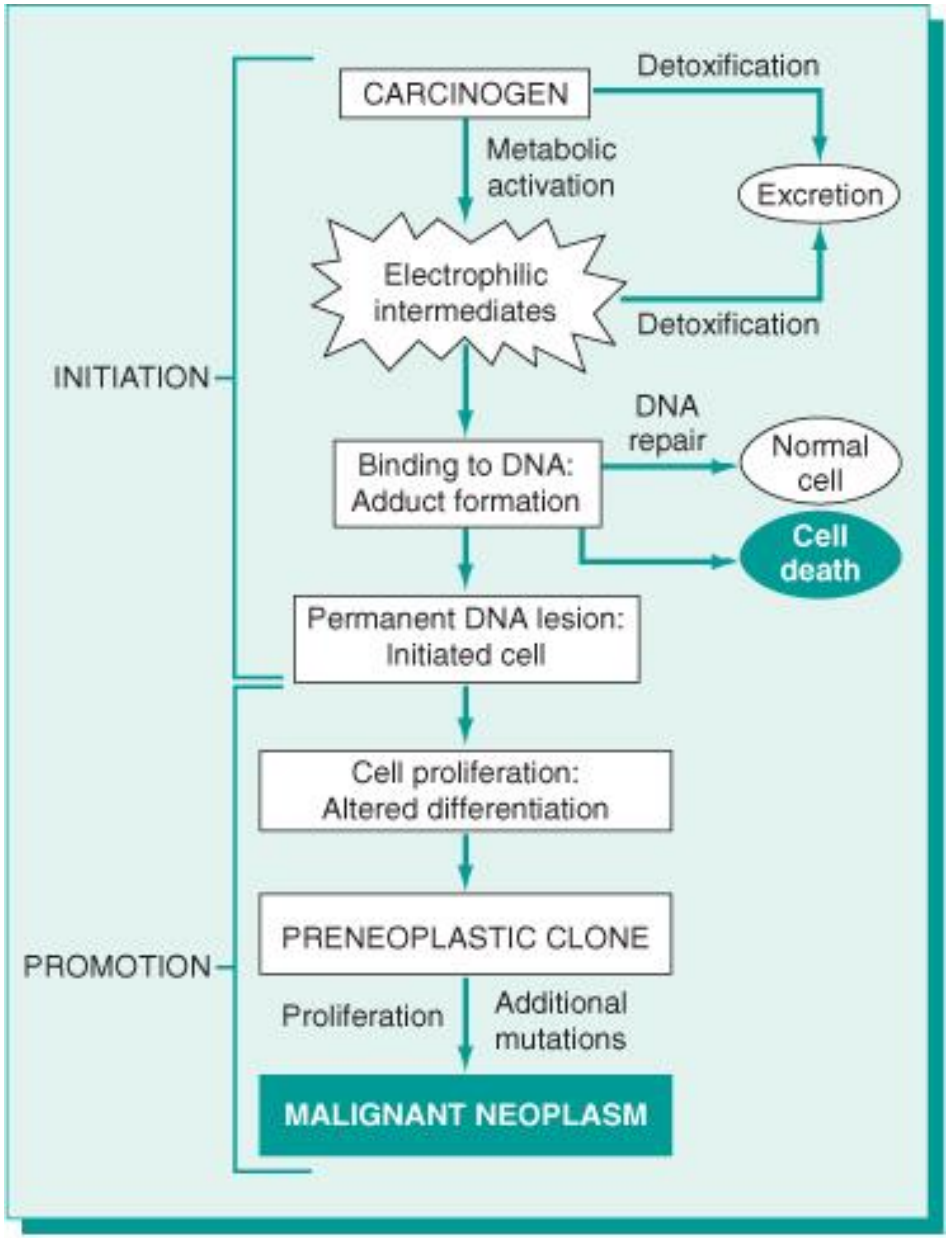
- Adriamycin (doxorubicin)
- Androgenic steroids
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Cyclosporin A
- Diethylstilbestrol
- Ethylene oxide
- Melphalan
- Tamoxifen

Indirect-acting carcinogens

- Polycyclic aromatic hydrocarbons (PAH)
- Produced by incomplete combustion of organic materials
- Present in
  - chimney soot,
  - charcoal grilled meats,
  - auto exhaust,
  - cigarette smoke.

Environmental carcinogens

- Chemicals capable of DNA damage
- Initiators vs Promoters
- Common denominator is “electrophilic intermediates” forming adducts with DNA
- Some are direct acting, others are activated in the body, usually in the liver by cytochrome P-450 enzymes



Human carcinogens - environmental

- Aflatoxins
- Asbestos
- Benzene
- Cadmium
- Coal tar
- Tobacco
- Creosote
- DDT
- Polycyclic aromatic hydrocarbons
- Radon
- Solar Radiation

Aflatoxins

- Another class of indirect-acting carcinogens
- Aflatoxin B1 is one of the most potent liver carcinogens known
  - A common contaminant of grains and peanuts Africa and Asia
  - A probable factor in the high incidence of hepatocellular carcinoma in Africa and Asia (along with Hepatitis B infection)
- Natural product of the mold ***Aspergillus flavus***

Physical Carcinogens

- Ultraviolet light
- Asbestos
- Foreign body carcinogenesis
- Ionizing radiation (X-rays), radioisotopes, nuclear bomb

Cancers caused by UV exposure

- Squamous cell carcinoma
- Basal cell carcinoma
- Malignant Melanoma

Ionizing radiation

- Death of pioneer radiation researchers from neoplasms
- High incidence of leukemia among radiologists recognized in 1940s
- Osteosarcoma incidence in radium dial painters

Radiation

- Ionizing radiation – x-rays, gamma rays, radioactive materials such as Radon gas – all cause a variety of defects to DNA
- UV light (non-ionizing) – primarily sun-exposure and T-T dimerization – skin cancers

Viral Carcinogenesis

- Viral infections account for an estimated one in seven human cancers worldwide
- Majority of these are due to infection with two DNA viruses
- HBV – linked to hepatocellular carcinonoma
- HPV – linked to cervical carcinoma

EBV – involvement in human tumors

- African Burkitt lymphoma
- B-cell lymphomas of immunosuppressed patients
- Some cases of Hodgkin disease
- Nasopharyngeal carcinomas

Helicobacter pylori

- Gastric infection linked to gastric lymphomas and gastric carcinomas
- Detection of *H. pylori* in majority of cases of gastric lymphomas
- Antibiotic treatment results in gastric lymphoma regression in most cases

Human Herpesvirus 8

- **Kaposi sarcoma** - a vascular neoplasm originally described in eastern Europe
- KS is today most common neoplasm associated with AIDS
- Cells contain HHV8 (also called KS-associated herpesvirus) KSHV

Common features of viral carcinogenesis

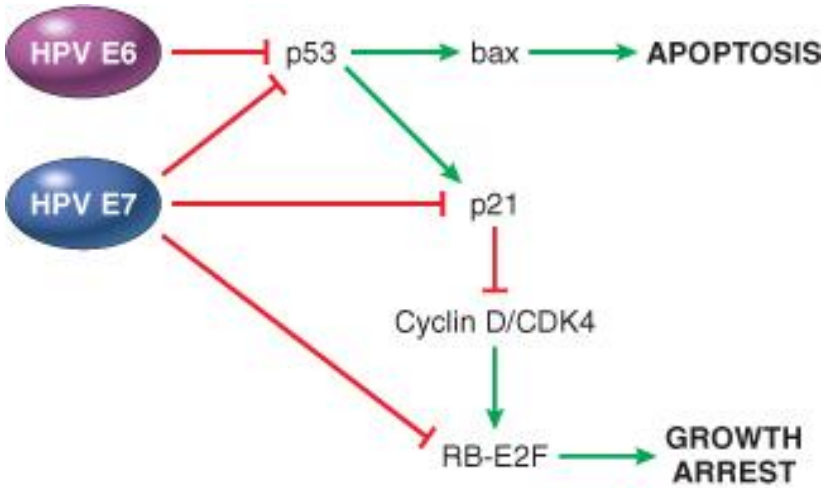
- Oncogenic viruses typically integrate their genomes into host cells and enter a period of “latency”
- May be of DNA or RNA type
- DNA viruses include EBV, HPV and Hepatitis B virus
- RNA viruses include retroviruses like HTLV-1 and indirectly HIV

Viral carcinogenesis

- Human papilloma virus (HPV) prototype
  - Cause warts
  - Some types have stronger cancer causing associations, esp 16 and 18 with uterine cervix cancer - Pap smears of cervix can detect precursor lesions of infection – Rx
  - Viral genes interact with human genes concerned with cell division

How does HPV cause cancer?

- Gene products of certain sub-type (eg 16 and 18) interfere with normal cellular proteins
- Early viral proteins E6 and E7 bind p53 and RB proteins respectively



Other oncogenic viruses

- Epstein-Barr virus (EBV) associated with some lymphomas and nasopharyngeal carcinoma
- Hepatitis B virus associated with malignant liver tumors

Factors Influencing Chemical Carcinogenesis

- Metabolism
- Sex and Hormonal Status
- Diet

Nutritional Oncogenesis

- A diet high in animal fat has been associated statistically with an increased incidence of cancer of the colon and with breast cancer; this observation remains unexplained.

Hormonal Oncogenesis

- ***Estrogens.*** causes endometrial hyperplasia, which is followed first by cytologic dysplasia and then by neoplasia.
- ***Hormones and breast cancer.*** patients taking **oral contraceptives** have shown that the risk of breast cancer is minimally increased in patients taking preparations with high estrogen content. The current low-estrogen contraceptives are not thought to increase the risk of breast cancer.
- ***Diethylstilbestrol (DES).*** Female children who were exposed to diethylstilbestrol in utero have a greatly increased incidence of clear-cell adenocarcinoma, a rare vaginal cancer that develops in young women between 15 and 30 years of age.
- ***Steroid hormones.*** Use of oral contraceptives and anabolic steroids is rarely associated with development of benign **liver cell adenomas.** A few cases of liver cell carcinoma have been reported.

Hormone dependent neoplasms

- Prostate ca
- Breast ca
- Thyroid ca

HOW DO TUMOURS DEVELOP?

- There has to be a change to DNA
- The change must cause an alteration in cell growth and behaviour
- The change must be non-lethal and be passed onto daughter cells

Malignant tumors – use embryonic origin of tissue

Carcinomas come from ectoderm and

Endoderm - epithelial and glandular tissue

Sarcomas arise from mesoderm

connective tissue, muscle, nerve and endothelial tissues

HOW DO TUMOURS DEVELOP?

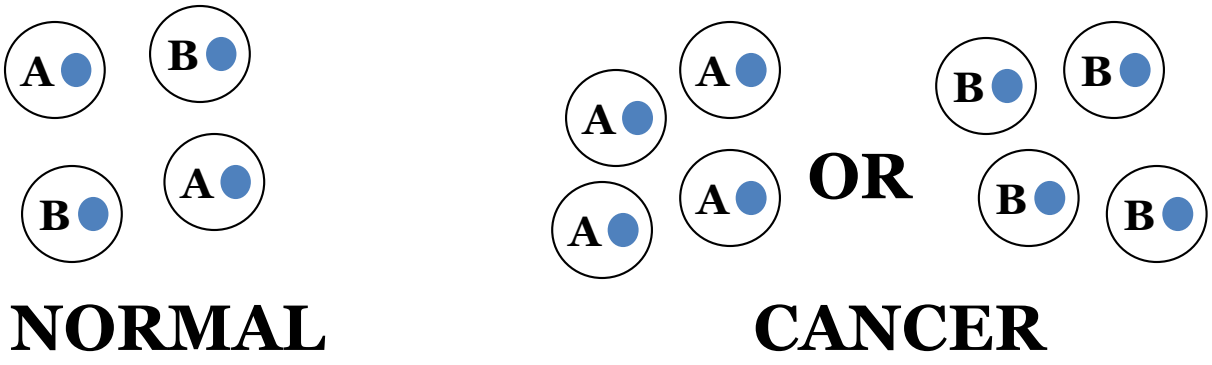
- Alteration is to more than one gene
- Genes concerned are oncogenes/tumour suppressor genes
- Sequence of gene alterations from normal to benign to malignant
- Intrinsic and extrinsic / inheritance and environment key factors

CLONALITY

Alterations in genes regulating growth and behaviour occur in every cell – monoclonal population

Evidence from studying G6PD

In heterozygotes cells contain either G6PD A or G6PD B, but tumours in those people consist of cells that all have the same enzyme



HOW DO NEOPLASTIC CELLS DIFFER FROM NORMAL CELLS?

Alterations in growth control

- proliferation
- cell death
- factors regulating growth and response

Alterations in cellular interactions

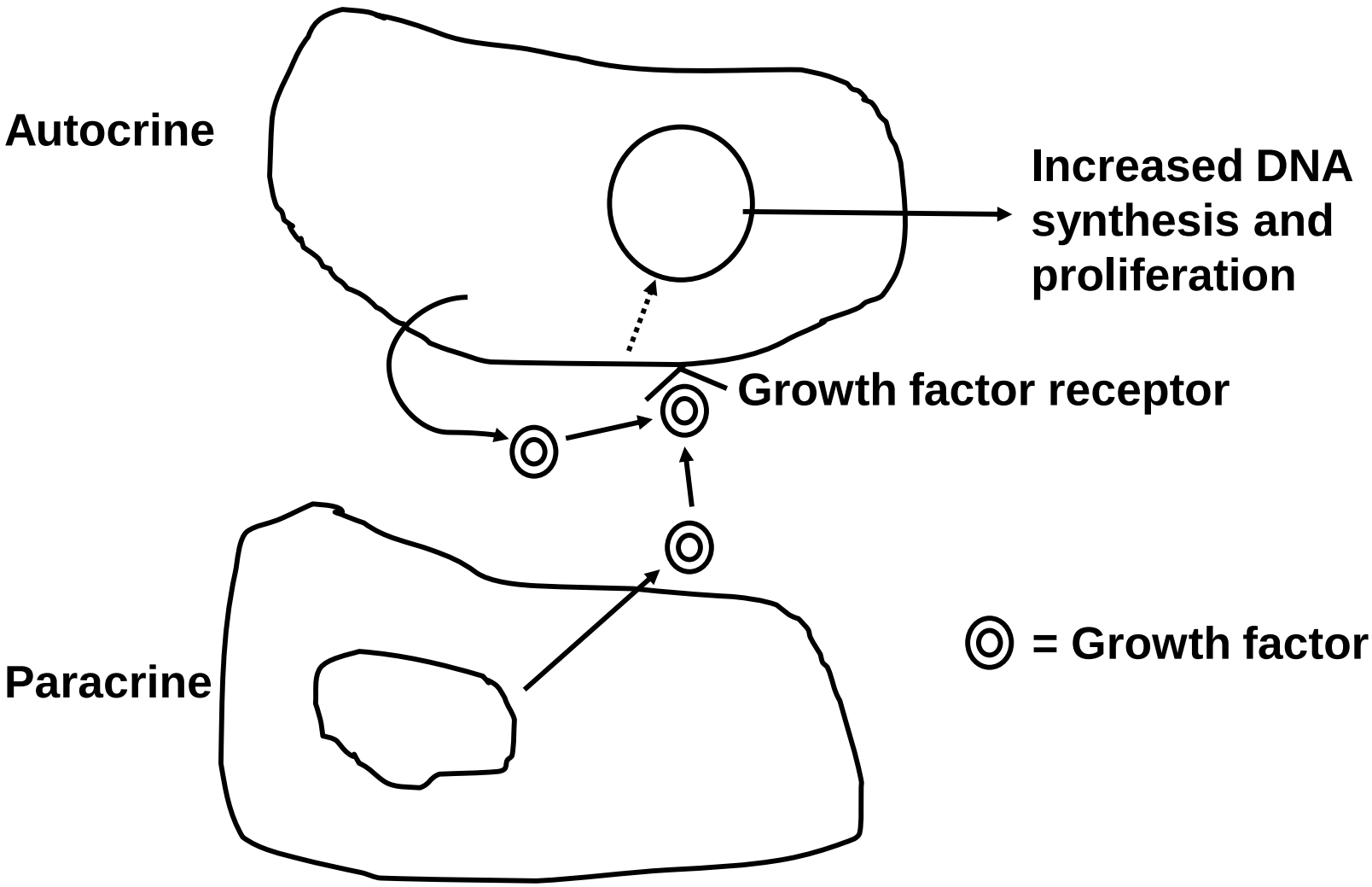
- cell-cell
- cell-stroma

GROWTH CONTROL

- Increased cell proliferation
  - more cells enter cell cycle
  - cell cycle “speeded up”
- Cells have changed life span
- Alterations in cell death-decreased apoptosis
- Modification of cell metabolism
- Angiogenesis

GROWTH CONTROL

- Increased or decreased growth factor receptors or altered receptors
- Synthesis of growth factors – autocrine or paracrine effect
- Excess/modified growth control proteins e.g. oncoproteins

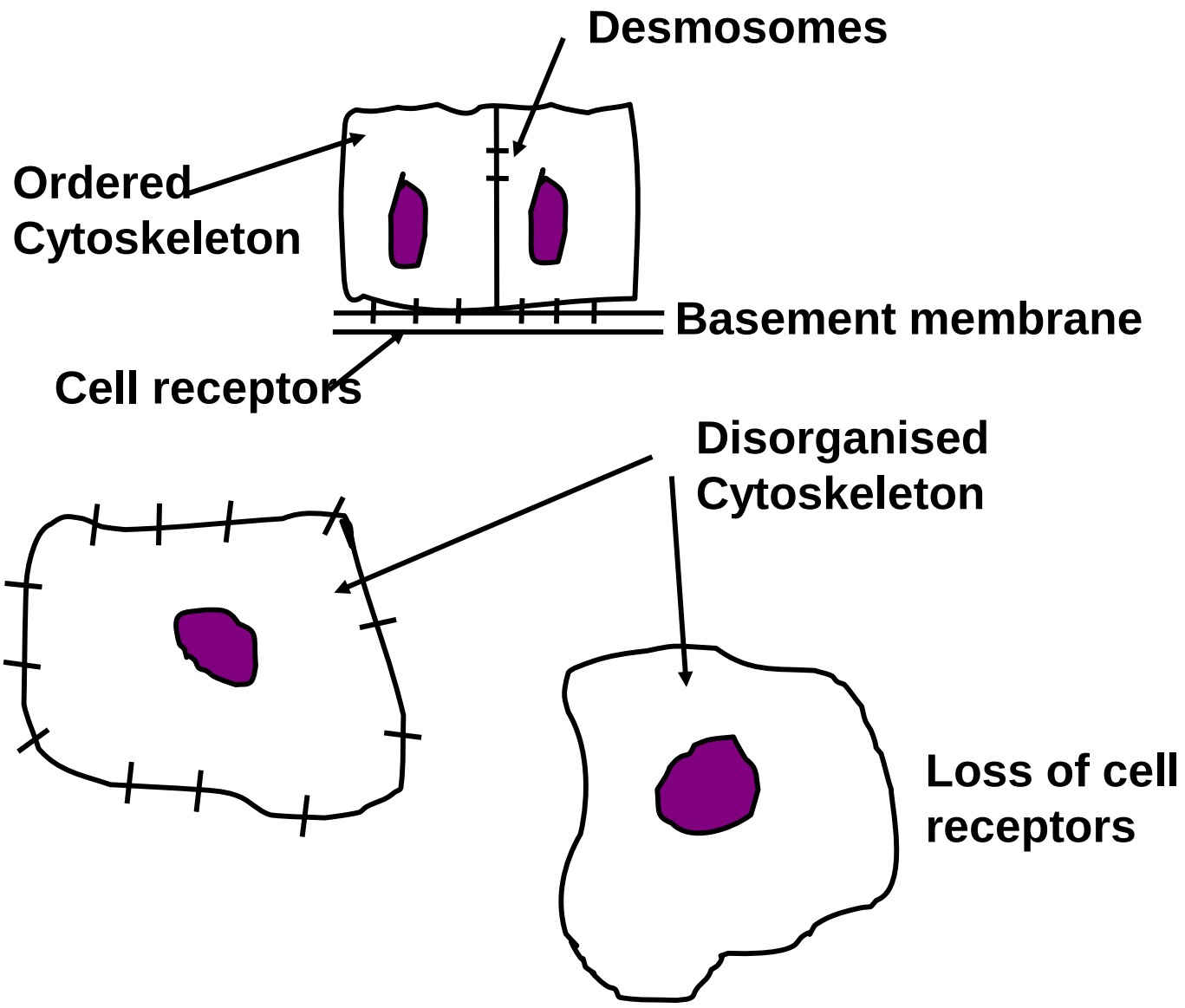

Autocrine
Increased DNA synthesis and proliferation
Growth factor receptor
Paracrine
= Growth factor

CELLULAR INTERACTIONS

Cell-cell interactions

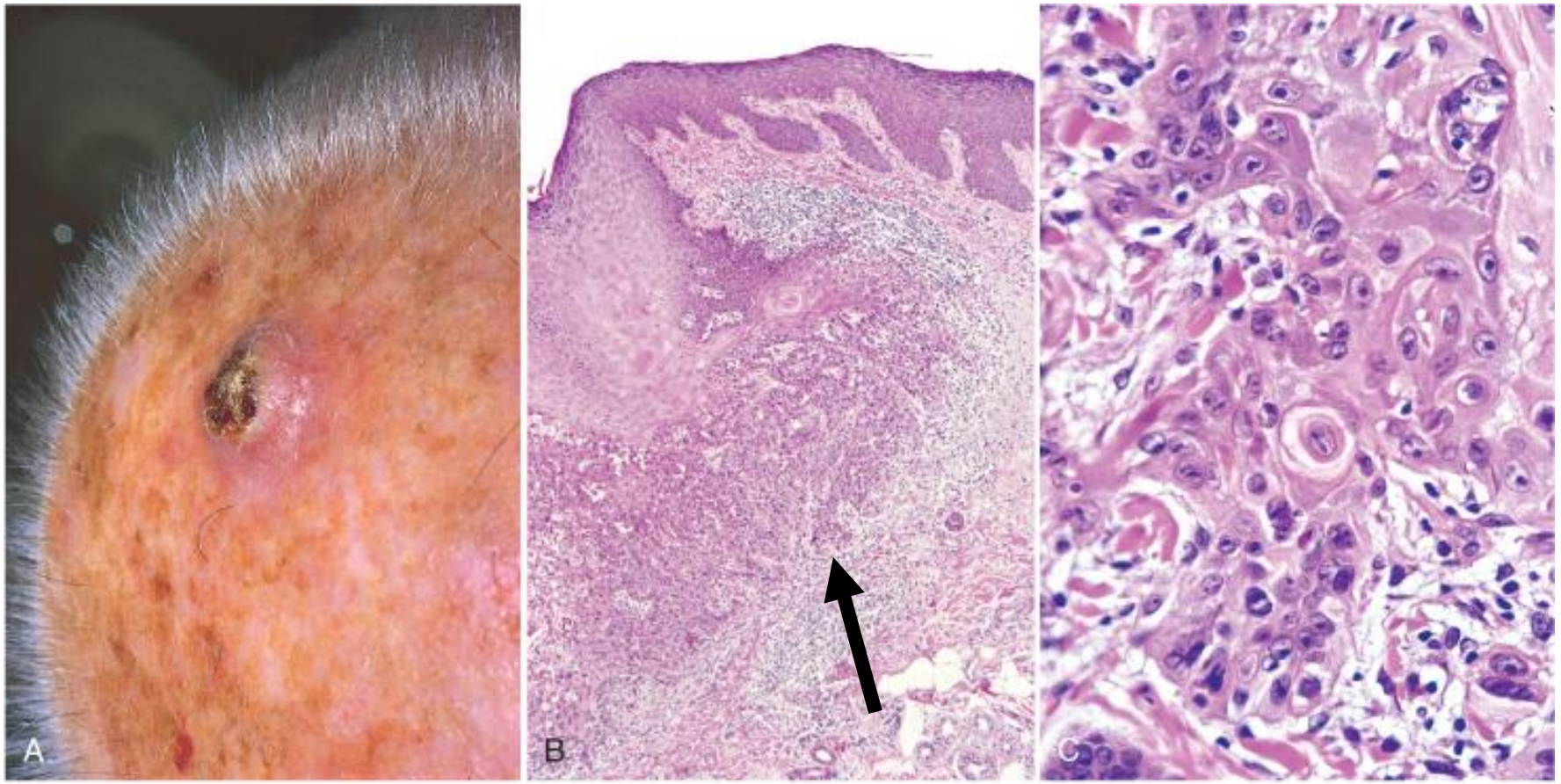
Cell-stromal interactions with basement membrane

Important for cell and tissue differentiation, embryogenesis, growth regulation


Desmosomes
Ordered
Cytoskeleton
Basement membrane
Cell receptors
Disorganised
Cytoskeleton
Loss of cell
receptors

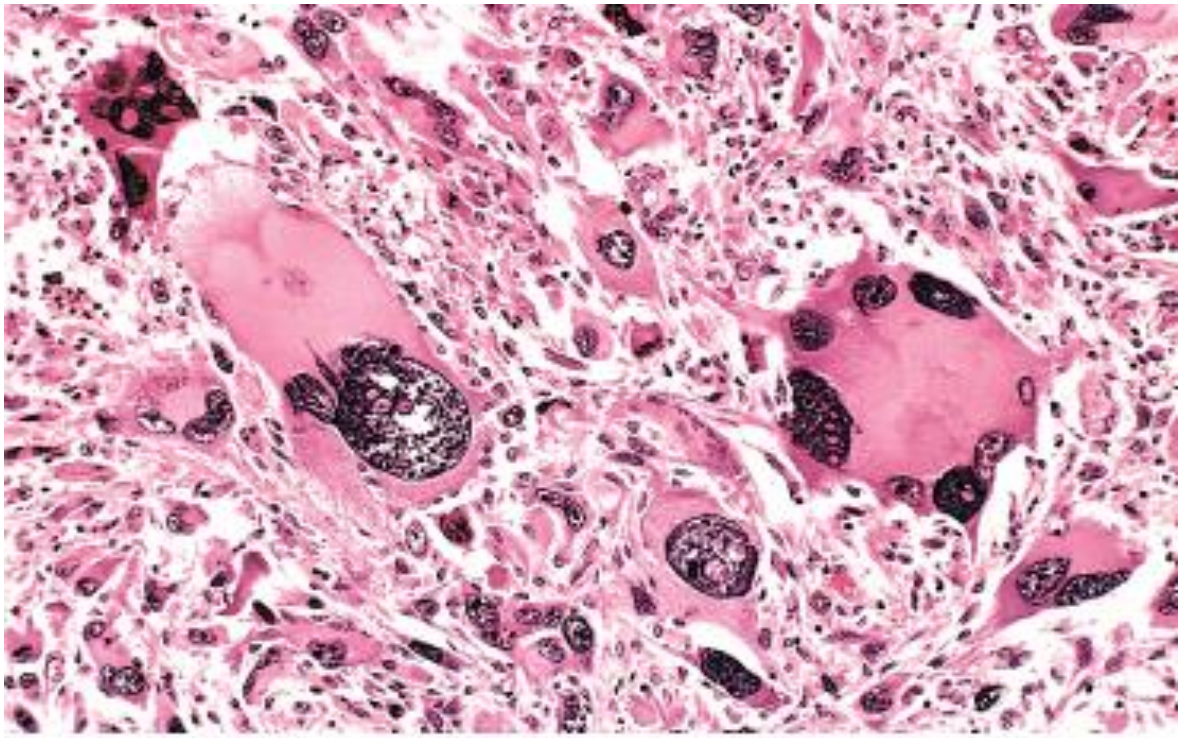
Microscopic features of tumors

- Loss of normal architectural arrangement –



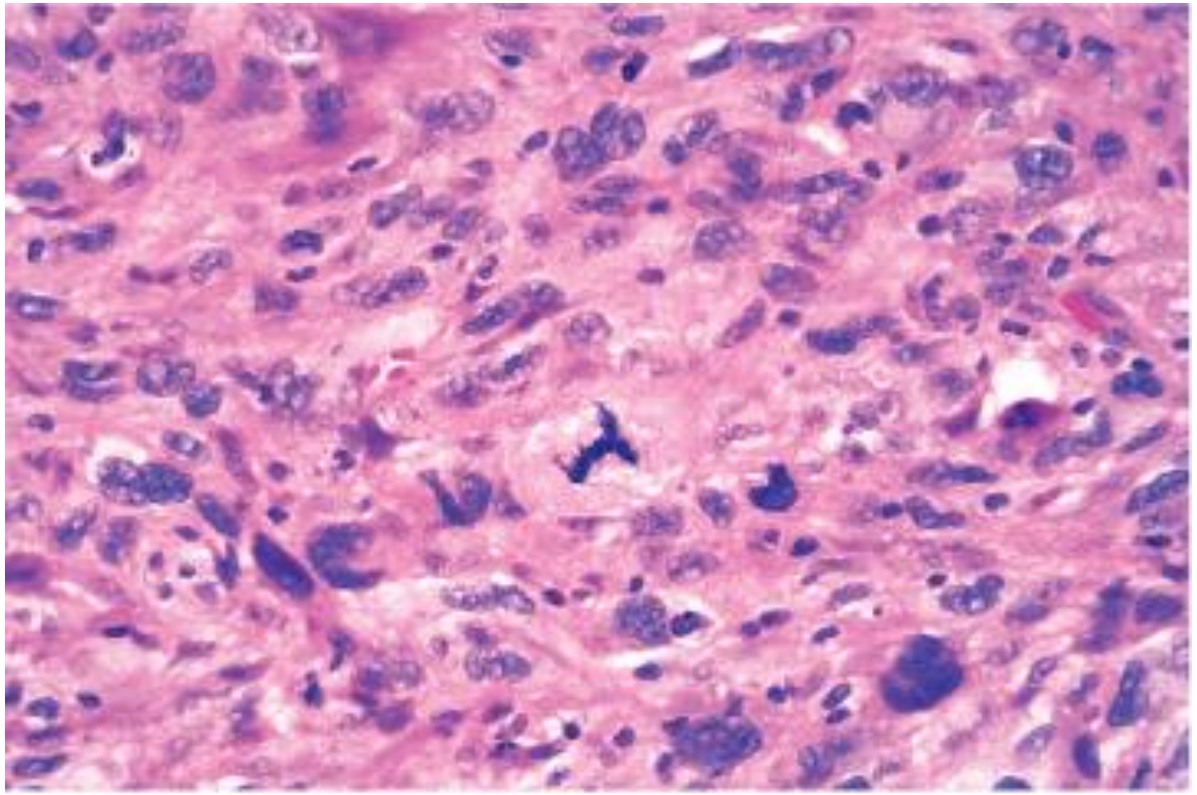
Microscopic features of tumors

- Pleomorphism – variation in size and shape of cells within the neoplasm



Microscopic features of tumors

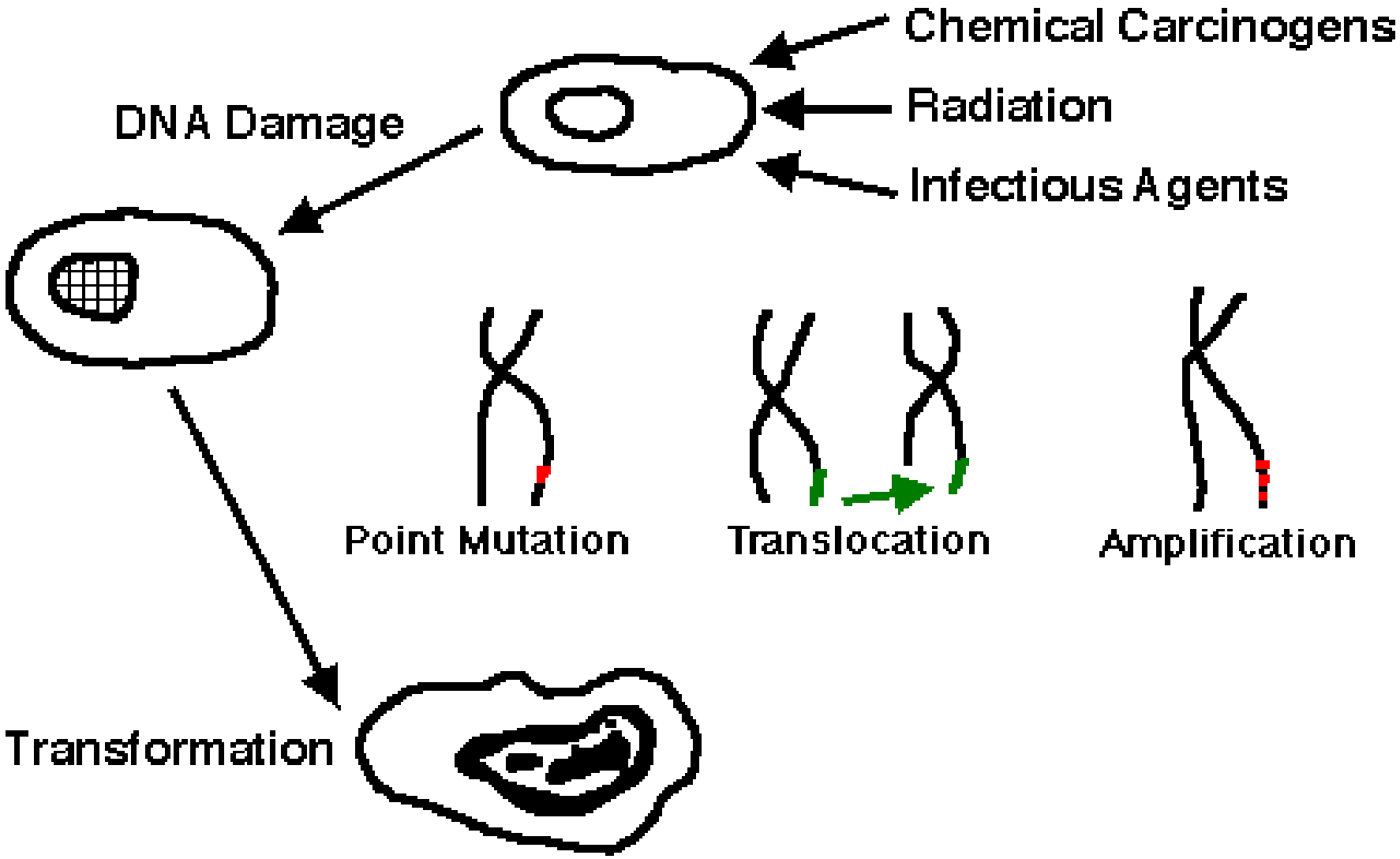
- Mitotic activity - Increased in more malignant tumors and often abnormal in shape



Mechanisms of Gene Activation & Inactivation

- It has been suggested that neoplastic transformation occurs as a result of activation (or derepression) of growth promoter genes (proto-oncogenes) or inactivation or loss of suppressor genes.
- **Activation** is a functional concept whereby the normal action of growth regulation is diverted into oncogenesis. The resultant activated proto-oncogene is referred to as an **activated oncogene** (or a mutant oncogene, if structurally changed), or simply as a **cellular oncogene (c-*onc*).** Activation and inactivation may occur through several mechanisms:

- **(1) mutation,** including single nucleotide loss (frameshift) or substitution (nonsense or missense codon), codon loss, gene deletion or more major chromosomal loss;
- **(2) translocation** to a different part of the genome where regulatory influences may favor inappropriate expression or repression;
- **(3) insertion of an oncogenic virus at an adjacent site;**
- **(4) amplification** (production of multiple copies of the proto-oncogenes), which appear as additional chromosome bands or extra DNA fragments (double minutes);
- **(5) introduction of viral oncogenes** or
- **(6) derepression** (loss of suppressor control)


Chemical Carcinogens
Radiation
Infectious Agents
DNA Damage
Point Mutation
Translocation
Amplification
Transformation

Angiogenesis

- angiogenic factors or vascular endothelial growth factor (VEGF)
- possible source of new therapies

Telomerase

Other factors:

- decreased cell-to-cell adhesion
- secretions of proteases
- ability to grow in new locations

Oncogene	Associated Neoplasms
c-erb-B2	Breast and ovarian carcinomas
ras	Many carcinomas and leukemias
c-sis	Gliomas
c-abl	Chronic myelogenous leukemia, acute lymphocytic leukemia
c-myc	Lymphomas
BRCA-1	Breast and ovarian carcinomas
APC	Colonic adenocarcinomas
NF-1	Neurofibromas and neurofibrosarcomas
Rb	Retinoblastomas, osteosarcomas, small cell lung carcinomas
p53	Many carcinomas
bcl-2	Chronic lymphocytic leukemia, lymphomas

Epigenetic hypothesis

- The main evidence for the role of epigenetic mechanisms in neoplasia comes from cancers produced by chemicals that have no known effect on the genetic apparatus of the cell.
- It is postulated that these chemicals may serve as promoters by binding various growth regulatory proteins, thus rendering them inactive.

Hypothesis of Failure of Immune Surveillance

(1) Neoplastic changes frequently occur in the cells of the body.

(2) As a result of alteration in their DNA, neoplastic cells produce new molecules (neoantigens, tumor-associated antigens).

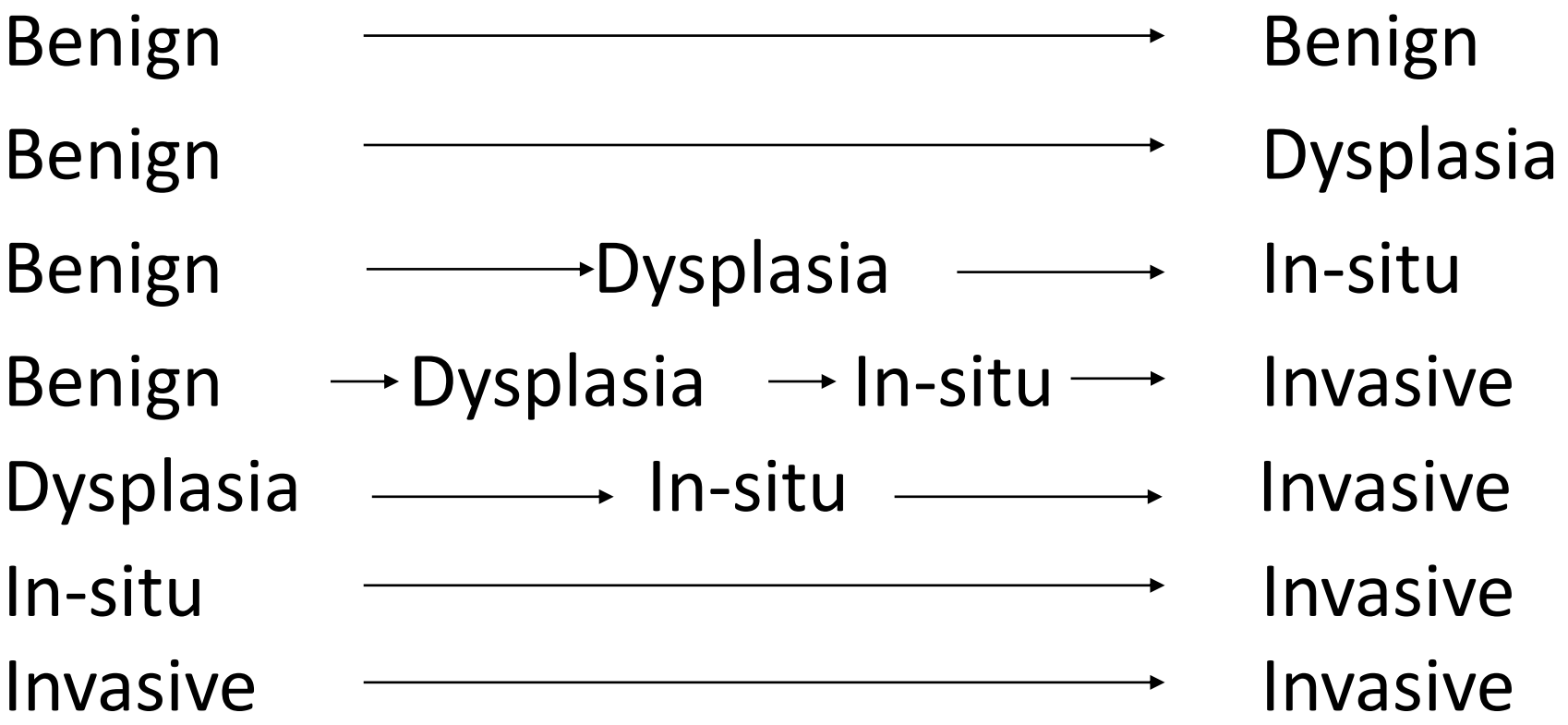
(3) The immune system of the body recognizes these neoantigens as foreign and mounts a cytotoxic immune response that destroys the neoplastic cells.

(4) Neoplastic cells produce clinically detectable neoplasms only if they escape recognition and destruction by the immune system

Precursors of neoplasia

1. Chronic inflammation
2. Hyperplasia
3. Metaplasia
4. Dysplasia
5. Neoplasia

POSSIBLE EVENTS



Biology of tumor growth