Al Mustaqbal University College
Department of Pharmacy
4th stage
General Toxicology
Lecture: 2

# CHEMICAL CARCINOGENESIS

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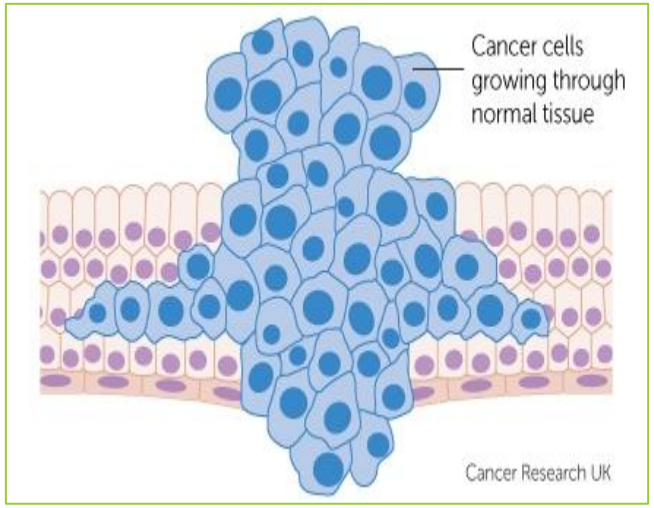
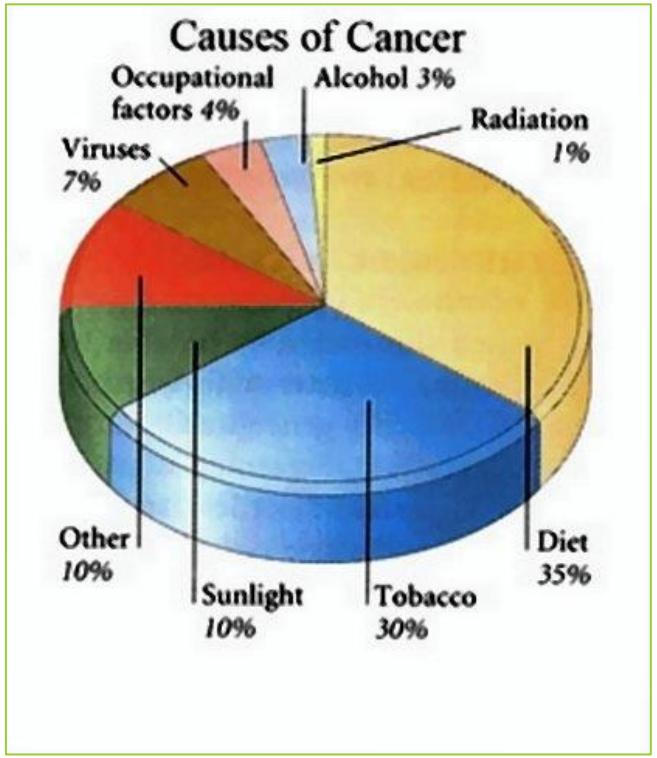
# Definition

- ✓Cancer is a disease in which cells grow uncontrollably and spread to other parts of the body.
- ✓It can start almost anywhere in the human body, which is made up of trillions of cells.
- ✓It is characterized by genomic mutation, modified gene expression, cell proliferation, and aberrant cell growth.
- ✓It ranks as one of the leading causes of death in the world.



# Etiology

- ✓**Multiple causes of cancer have been established including infectious agents, radiation, and chemicals.**
- ✓**Estimates suggest that 70% to 90% of all human cancers have a linkage to environmental, dietary, and behavioural factors.**



# Etiology

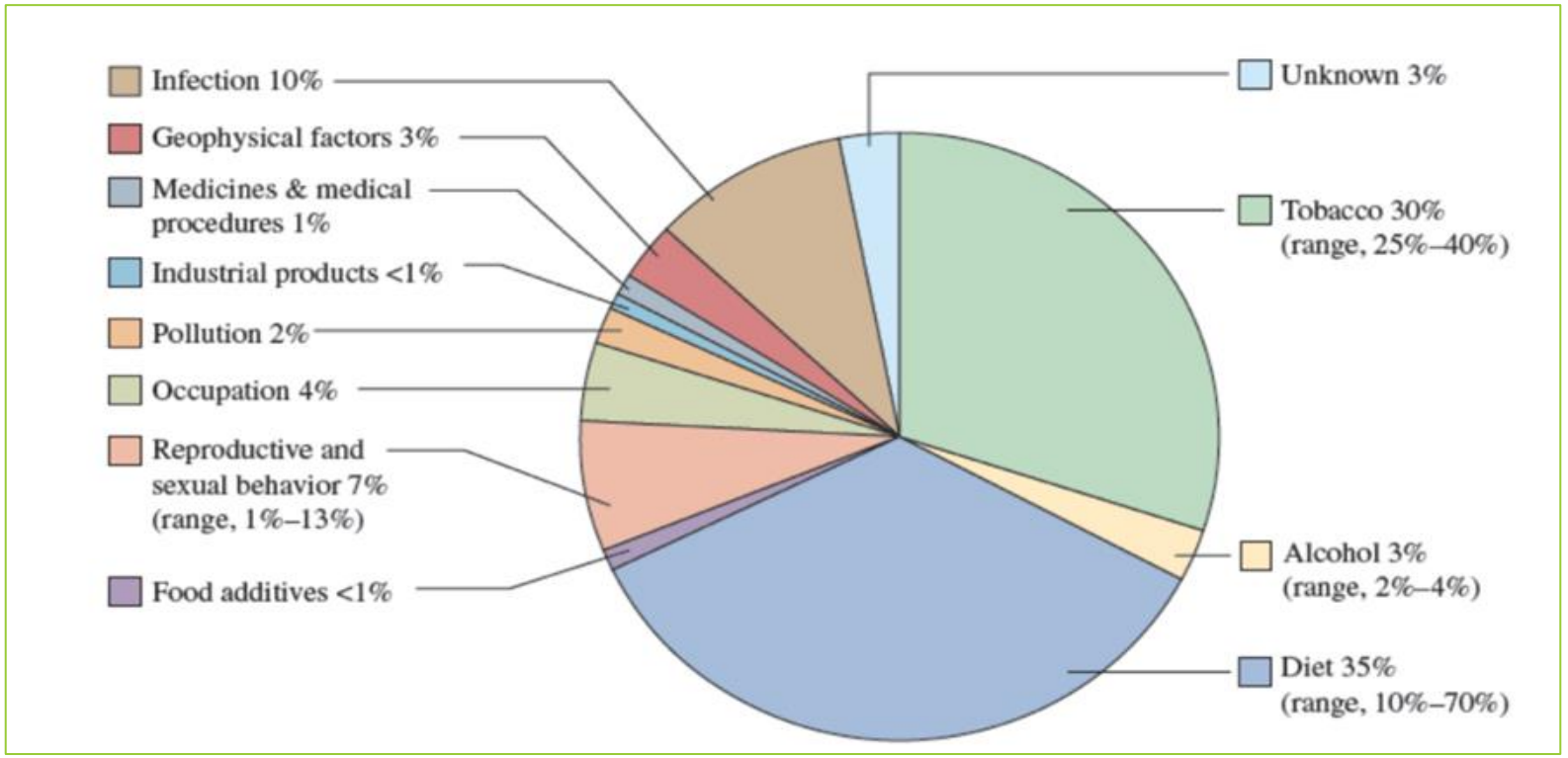
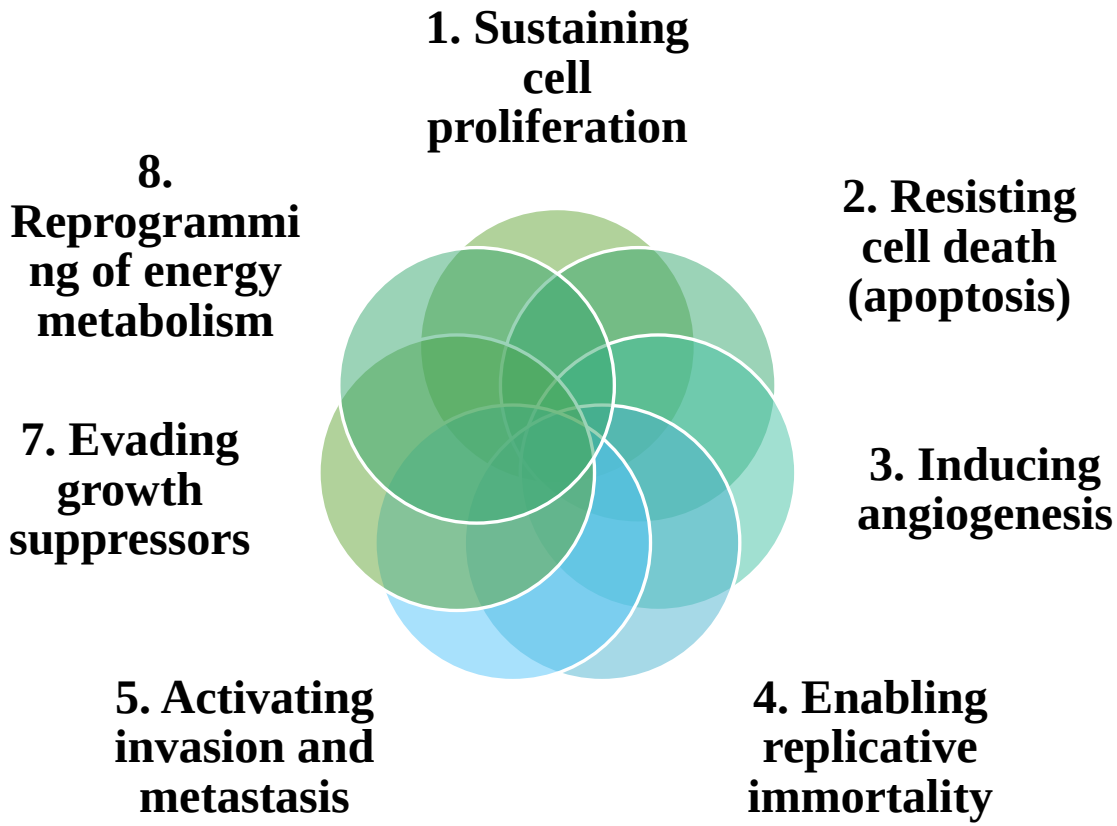



***Figure A: Proportions of human cancer deaths attributed to various factors***

# Hallmarks of Cancer



# Neoplasia

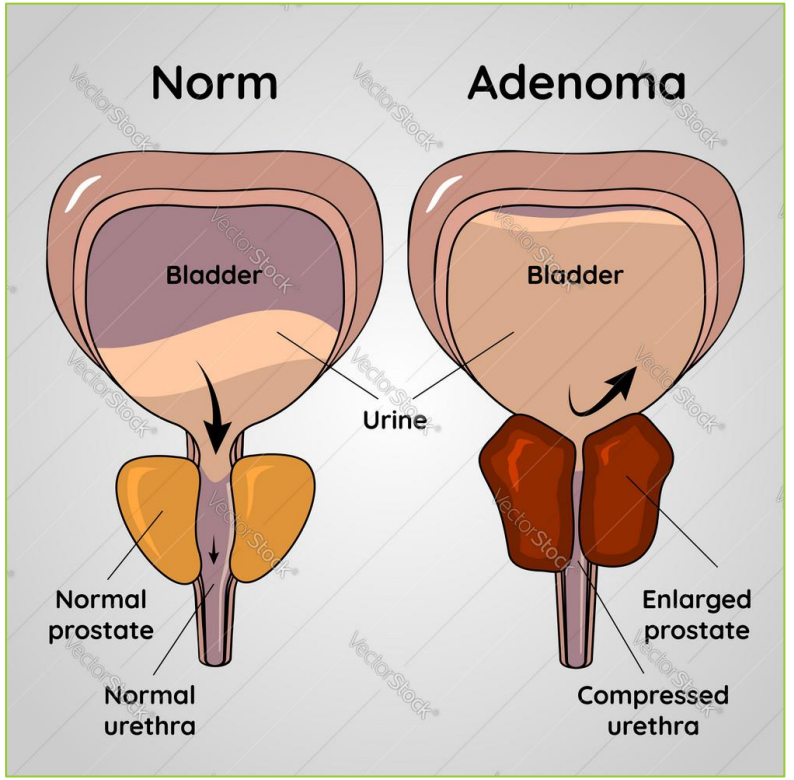
- **Neoplasia** is defined as **new growth** or autonomous growth of tissue.
- A neoplastic **lesion** is referred to as a **neoplasm**.
- A neoplasm can be either **benign** or **malignant**.
- **Both** types of lesions are **induced** by chemical carcinogens.
- **Metastases** are **secondary growths** derived from the cells of the primary malignant **neoplasm**.

# Benign Neoplasms

- **Benign neoplasms** (e.g., adenomas) are lesions characterized by expansive growth, frequently exhibiting slow rates of proliferation that do **not invade** surrounding tissue or other organs.
- Benign neoplasms **can** impair and damage the normal function of an organ through its growth by **impeding** blood flow.

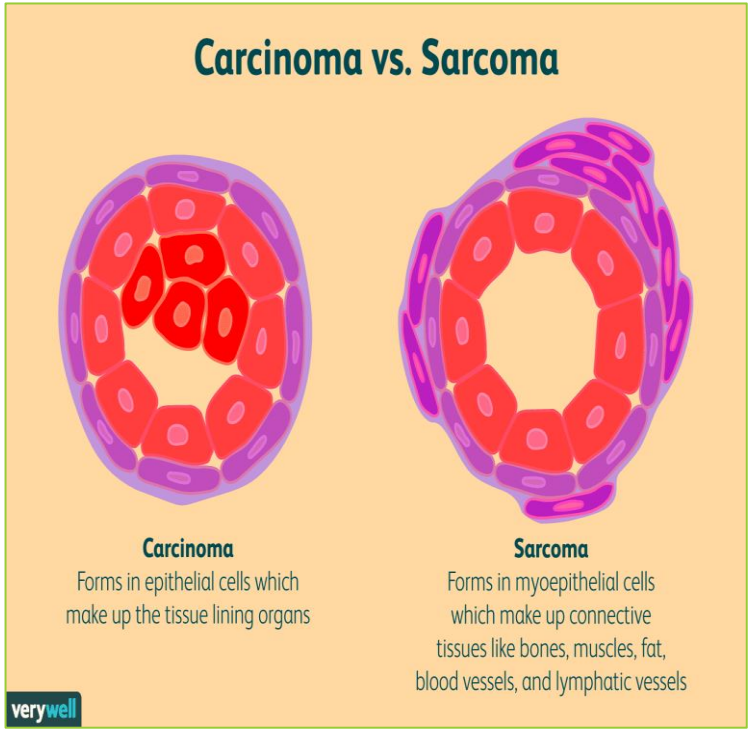
# Benign Neoplasms

- For benign neoplasms nomenclature the tissue of origin is frequently followed by the suffix "**oma**";
- For example, a <u>benign fibrous neoplasm</u> would be termed **fibroma**, and a <u>benign glandular epithelium</u> termed an **adenoma**.



# Malignant Neoplasm

- A **malignant neoplasm** demonstrates **invasive** growth characteristics, capable of spreading not only through the organ of origin but also via **metastasis** to other organs.
- Malignant neoplasms from the **epithelial** origin are called **carcinomas** while those derived from the **mesenchymal** origin are referred to as **sarcoma**.

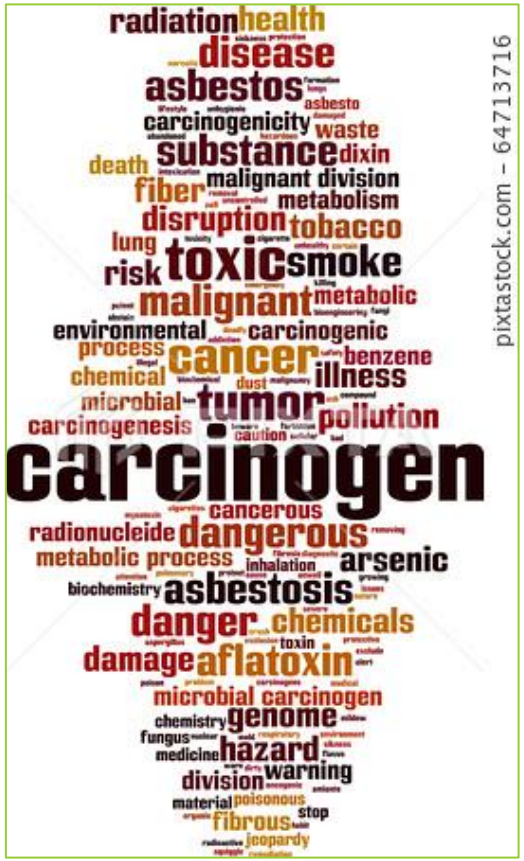


# Malignant Neoplasm

- Thus, a malignant neoplasm of fibrous tissue would be a **fibrosarcoma** while that derived from bone would be an **osteosarcoma**.
- Similarly, a malignant neoplasm from the liver would be a **hepatocellular carcinoma** while that derived from skin squamous epithelium is referred to as a **squamous cell carcinoma**.

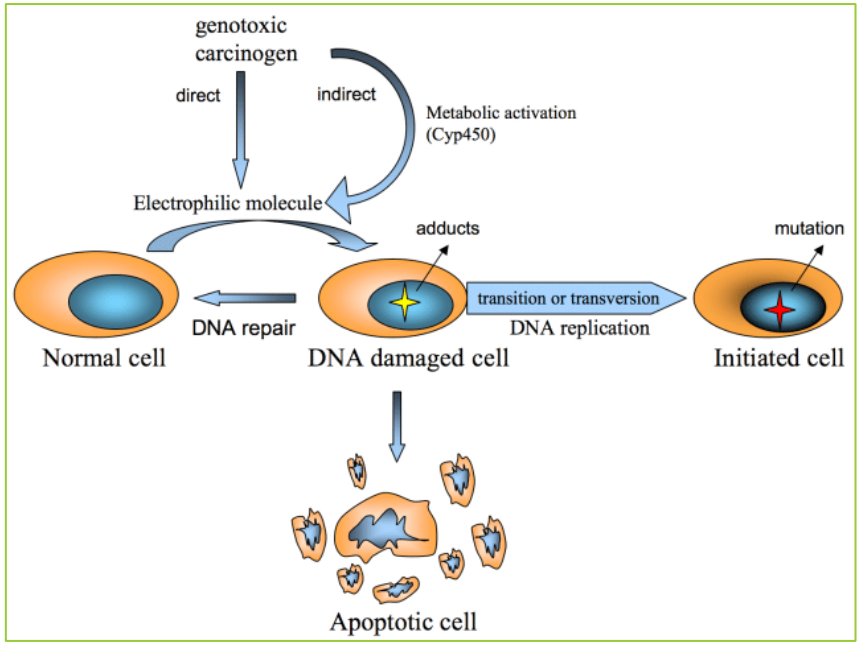
# Carcinogen

- A **carcinogen** is a chemical, physical, or biological (viruses) agent, that causes or **induces** cancer.
- **Carcinogens** have frequently been **divided** simplistically into **two major categories** based on their general mode of action: **genotoxic** and **non-genotoxic**.



# Genotoxic Carcinogens

- **Genotoxic carcinogens** are those agents that **interact with DNA** to damage or change its structure, they are **frequently** mutagenic.



# Genotoxic Compounds

**Genotoxic compounds interact with the nuclear DNA of a target cell producing unrepaired DNA damage that is inherited in subsequent daughter cells.**

**DNA-reactive carcinogens can be further subdivided according to whether they are active in their parent form (i.e., direct-acting: chemicals that can directly bind to DNA without being metabolized) and those that require metabolic activation (i.e., indirect-acting carcinogens: compounds that require metabolism in order to react with DNA).**

# Genotoxic Compounds

✓**Examples of direct-acting carcinogens are:**

❖**Nitrogen or sulfur mustards, Propane sulfone, Methyl methanesulfonate, Ethyleneimine, and Dimethyl sulfate**

✓**Examples of indirect-acting carcinogens are:**

❖**Polycyclic aromatic hydrocarbons and heterocyclic aromatics, Aromatic amines, N-Nitrosoamines, Azo dyes, and Hydrazines**

# Non-genotoxic Carcinogens

- **Non-genotoxic** carcinogens are the agents that **do not directly** interact with nuclear DNA.
- Non-genotoxic carcinogens **may:**
  1. Change gene expression
  2. Modify normal cell function
  3. Bind to or modify cellular receptors
  4. Increase the number of cells in the target tissue

# Non-genotoxic Compounds

✓**Examples of Non-genotoxic Compounds are:**

✓**Chloroform, Melamine, Phenobarbital, Toxaphene, 2,3,7,8-Tetrachlorodibenzop- dioxin (TCDD), Polychlorinated biphenyls (PCBs), Polybrominated biphenyls (PBBs)**

# Mechanisms of Chemical Carcinogenesis

✓**Two major processes are needed with regard to the induction of neoplasia by chemicals:**

1. **Mutational event**
2. **Selective proliferation of the mutated cell to form a neoplasm.**

✓**Additionally, chemicals that induce cancer have been classified into one of two broad categories genotoxic (DNA-reactive) agents and non-genotoxic (epigenetic) agents.**

# Multistage Carcinogenesis

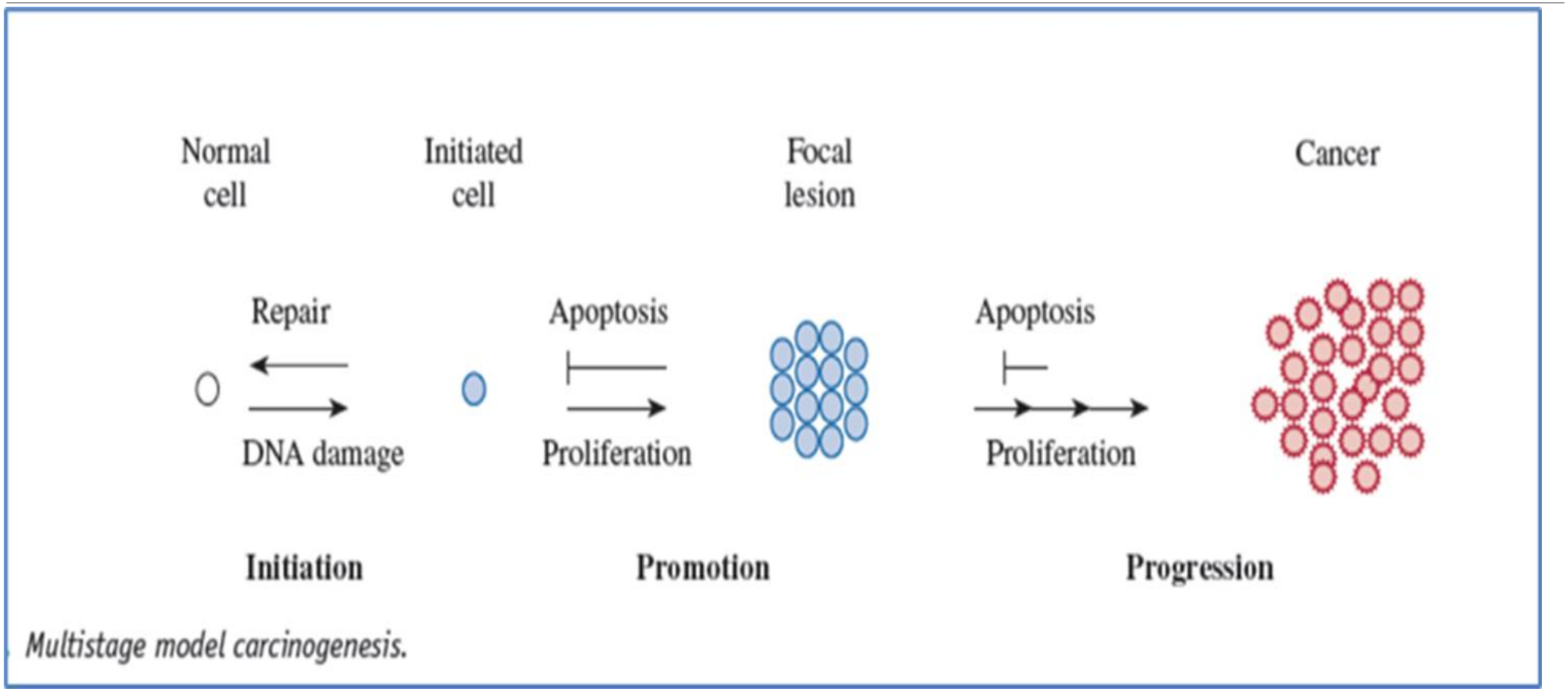
- Once a neoplasm is **formed**, additional intracellular and extracellular changes occur in the process of the development of a malignant cancer
- **Operationally**, three defined stages have been identified including:

1. Initiation
2. Promotion
3. Progression

# Multistage Carcinogenesis

- ✓**These steps follow a temporal sequence of events demonstrable by histopathology and observed in a wide variety of target tissues.**
- ✓**The defining characteristics of each of these stages are used to help characterize the multistage nature of chemically induced tumors.**

# Multistage Carcinogenesis




*Multistage model carcinogenesis.*

# Initiation

- ✓The **first stage** of the cancer process involves initiation, a process that is defined as a **stable, heritable change**.
- ✓This stage is a relatively **rapid**, **irreversible** process that results in a **carcinogen-induced mutational event**.
- ✓**Chemical** and **physical** agents, that function at this stage, are referred to as **initiators** or **initiating agents**.

# Initiation

✓**Among chemicals classified as initiating carcinogens are:**

1. **Compounds such as polycyclic hydrocarbons and nitrosamines**
2. **Biological agents such as certain viruses**
3. **Physical agents such as x-rays and ultraviolet (UV) light**

# Initiation

- ✓**The initiating event becomes "fixed" when the DNA adducts or other damage to DNA is not correctly or incompletely repaired prior to DNA synthesis.**
- ✓**This event can lead to inappropriate base pairing and formation of a mutation.**

# Initiation

✓**Initiation by itself does not appear to be sufficient for neoplastic formation. Once initiated cells are formed, their fate has multiple potential outcomes:**

1. **It can remain in a static nondividing state**
2. **It may possess mutations incompatible with viability or normal function and be deleted through apoptotic mechanisms**
3. **It may undergo cell division resulting in the growth in the proliferation of the initiated cell.**

# Promotion

- ✓The **second stage** of the carcinogenesis process (the promotion stage) involves the **selective clonal expansion** of initiated cells to produce a **preneoplastic lesion**.
- ✓**Exogenous and endogenous agents**, that function at this stage, are frequently referred to as **tumor promoters**, they are **not mutagenic** and generally are **not able to induce tumors** by themselves.

# Promotion

- ✓**The growth of preneoplastic lesions requires repeated applications or continuous exposure to tumour-promoting compounds.**
- ✓**With repeated applications of the chemical only initiated cells continue to clonally expand and divide into a focal lesion.**

# Promotion

- ✓**Carcinogens that function at the tumour promotion stage, in general, are organ-specific.**
- ✓**For example, phenobarbital functions at the tumour promotion stage selectively in the liver but will not promote tumorigenesis in the skin or most other tissues.**

# Progression

- ✓The progression stage, involves the conversion of the preneoplastic lesions to a neoplasm.
- ✓In this stage, additional genotoxic events occur resulting in additional DNA damage including chromosomal damage such as aberrations and translocations.
- ✓The tumour microenvironment is an important component of this process and the presence of “normal” cells and stroma within the lesion is critical for the neoplastic cells to survive and propagate.

# Progression

- During the progression stage, the clonal nature of the neoplastic lesion is typically lost with a polyclonal appearance of cells within the lesion.
- The progression stage is an irreversible stage in that neoplasm formation, whether benign or malignant, occurs.
- With the formation of neoplasia, autonomous growth and/or lack of growth control is achieved.

# Thank Your For Your Attention