

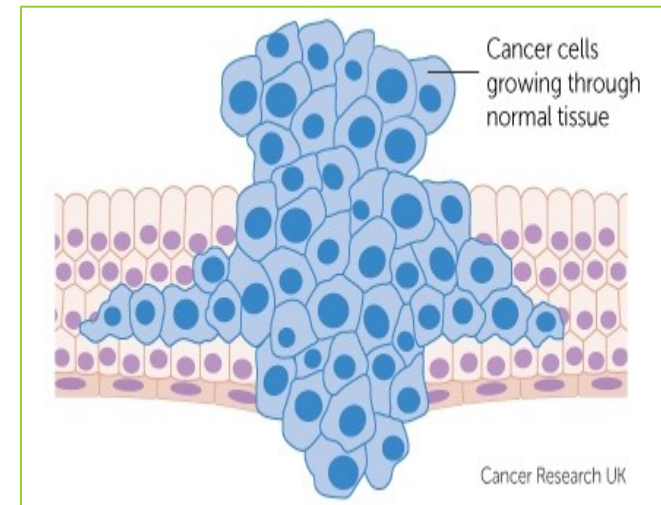
Al Mustaqbal University
College of Pharmacy
4th stage
General Toxicology
Lecture: 2

CHEMICAL CARCINOGENESIS

WEAAM J. ABBAS

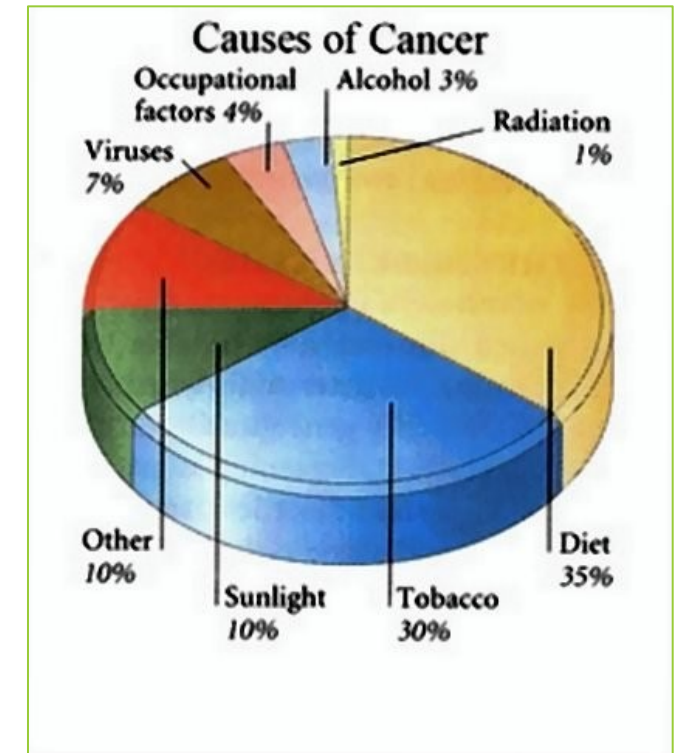
Definition

- ✓ 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

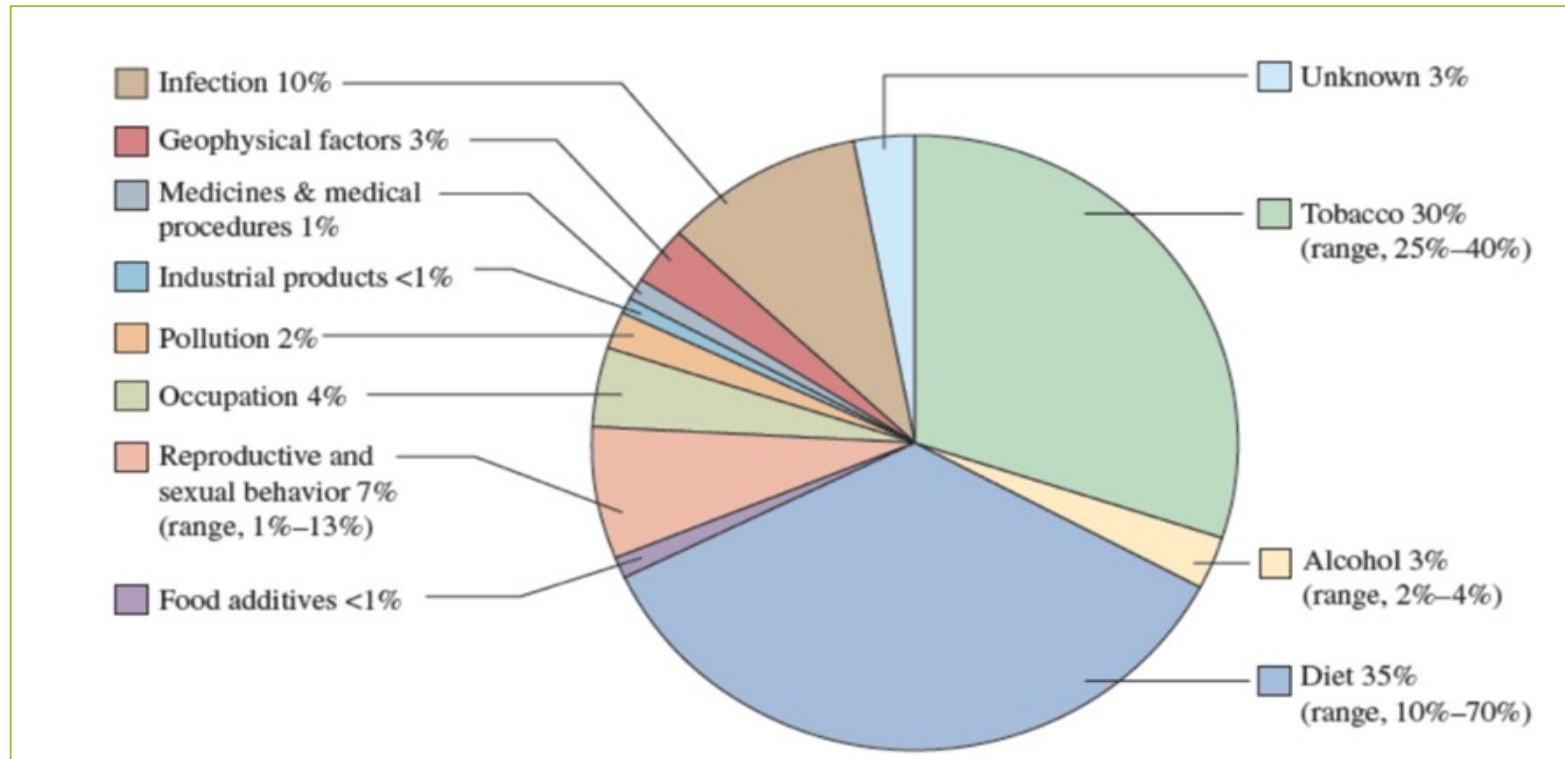
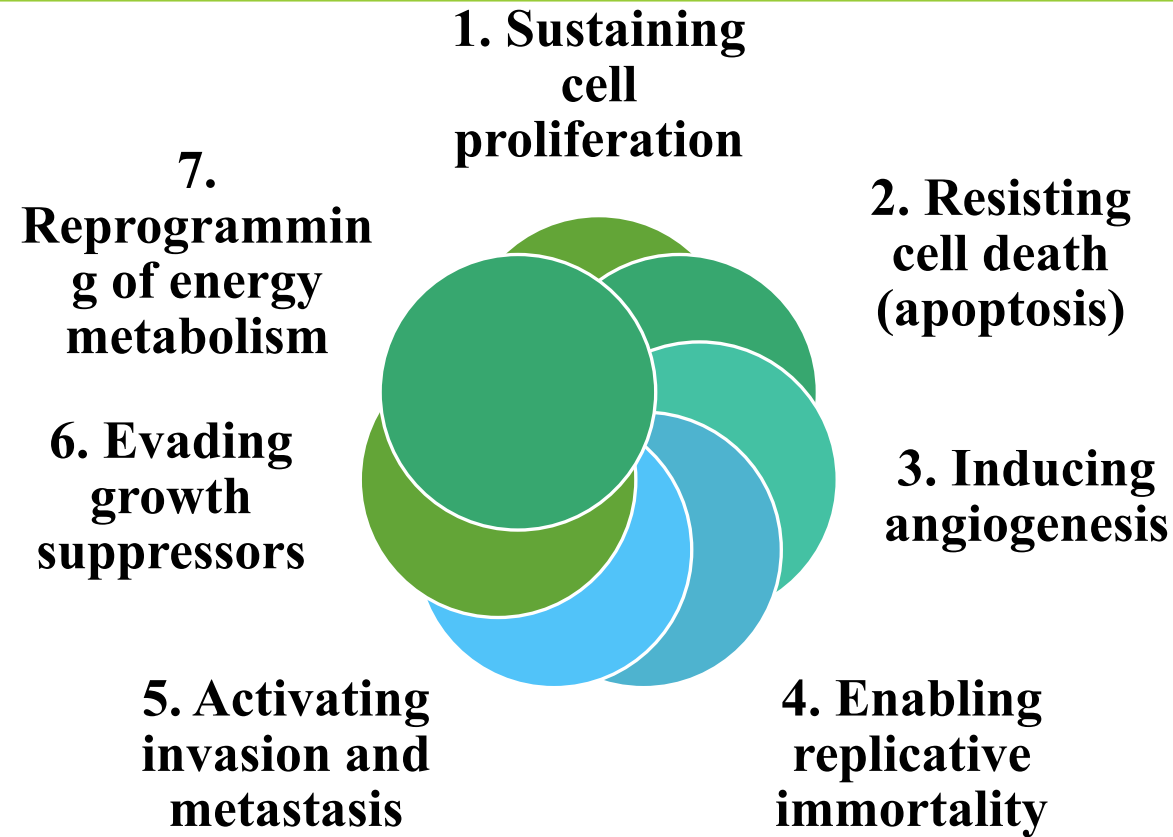


Figure A: Proportions of human cancer deaths attributed to various factors

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

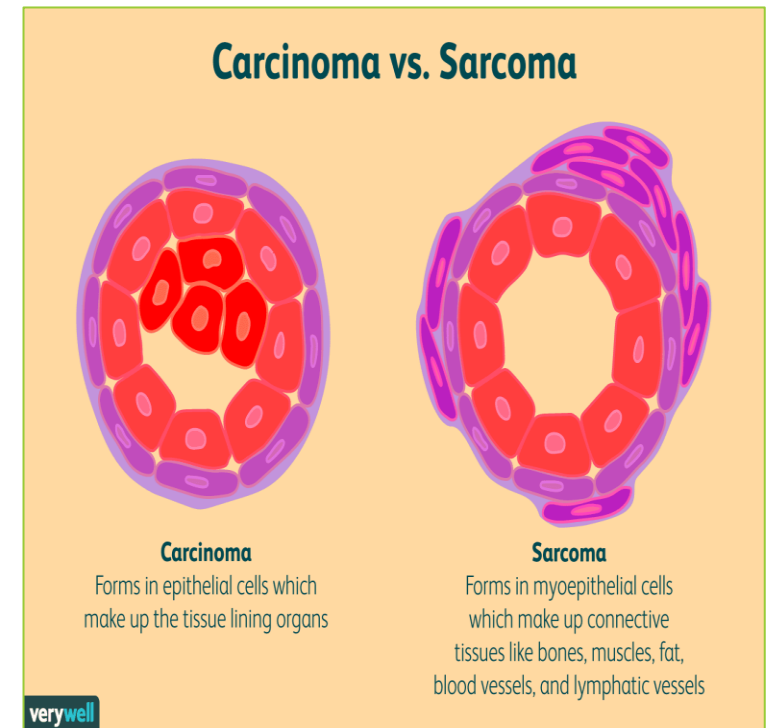
- ❖ For benign neoplasms nomenclature the tissue of origin is frequently followed by the suffix “**oma**”;
- ❖ For example, a benign fibrous neoplasm would be termed **fibroma**, and a benign glandular epithelium termed an **adenoma**.



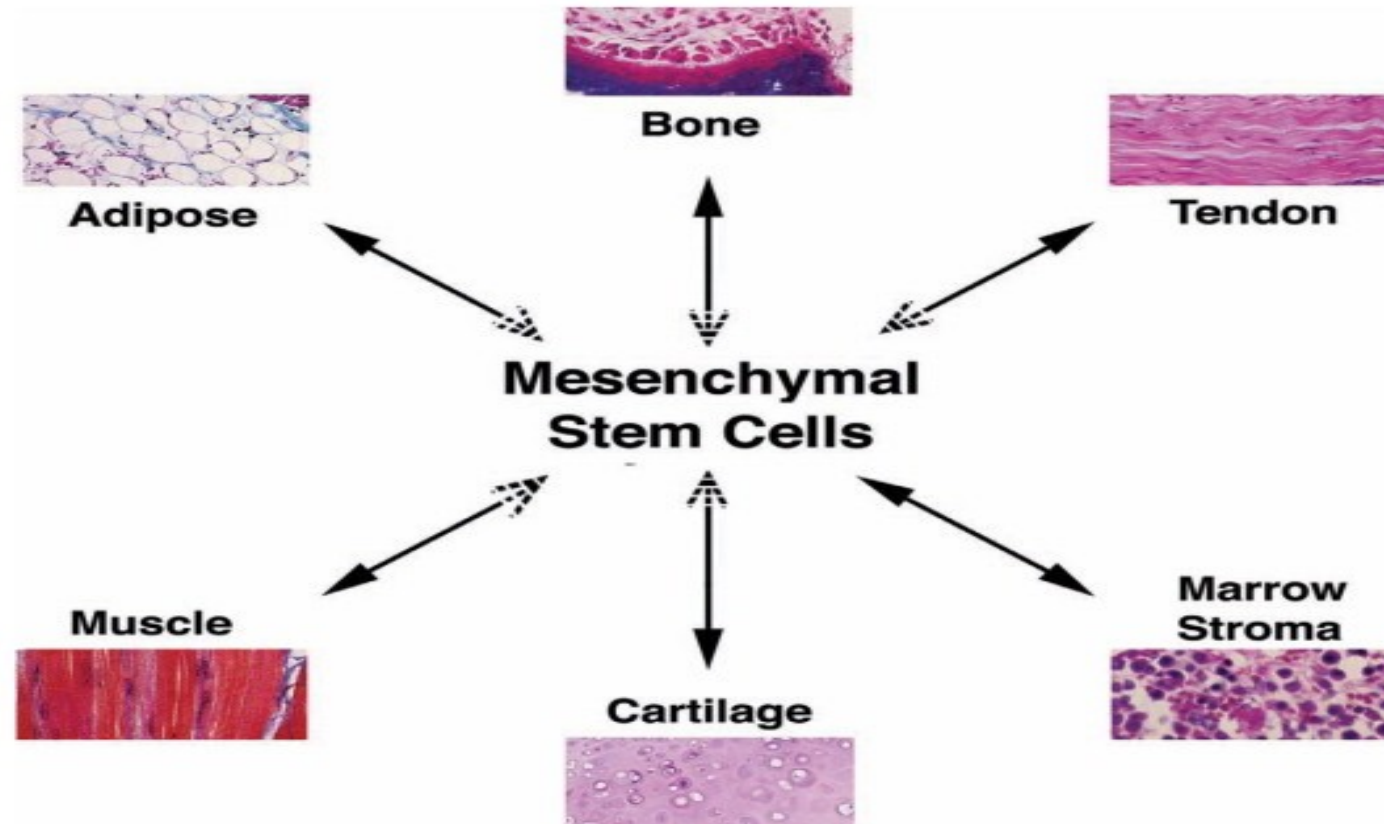
Malignant Neoplasm

❖ 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

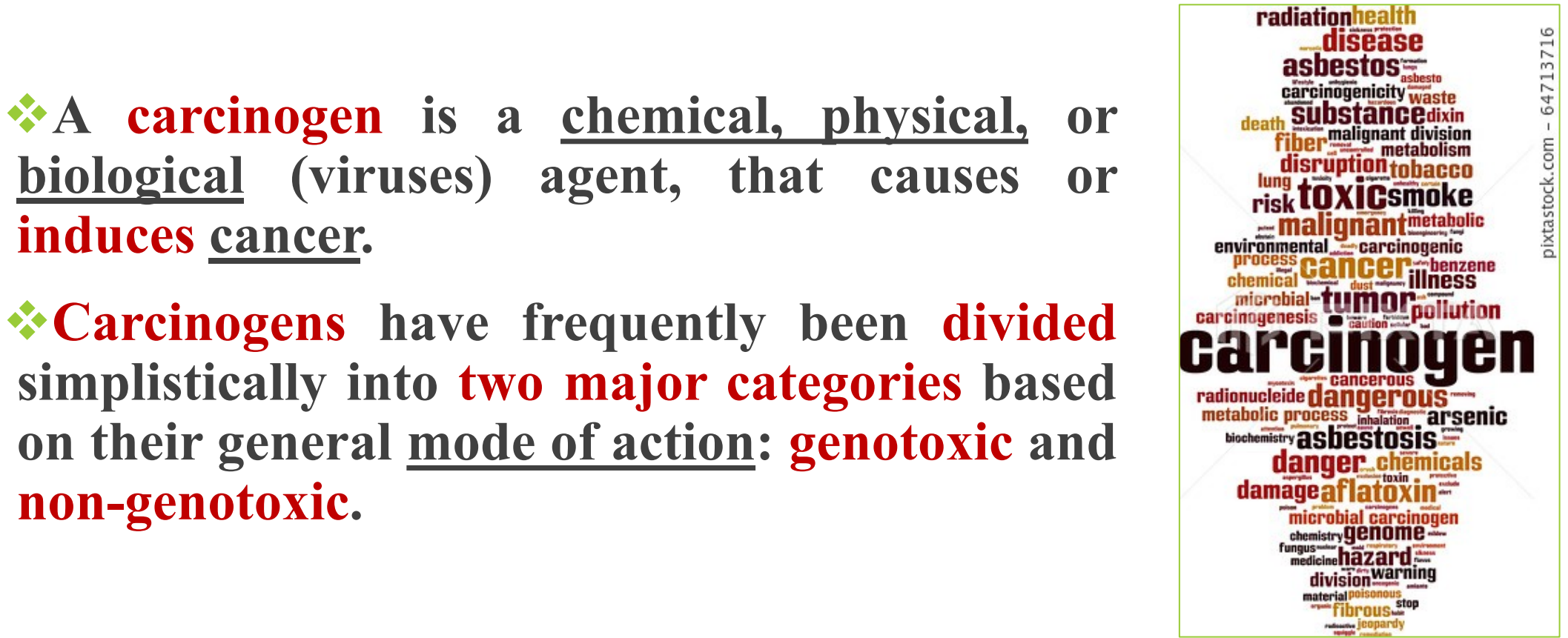


Malignant Neoplasm

- ❖ 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**.

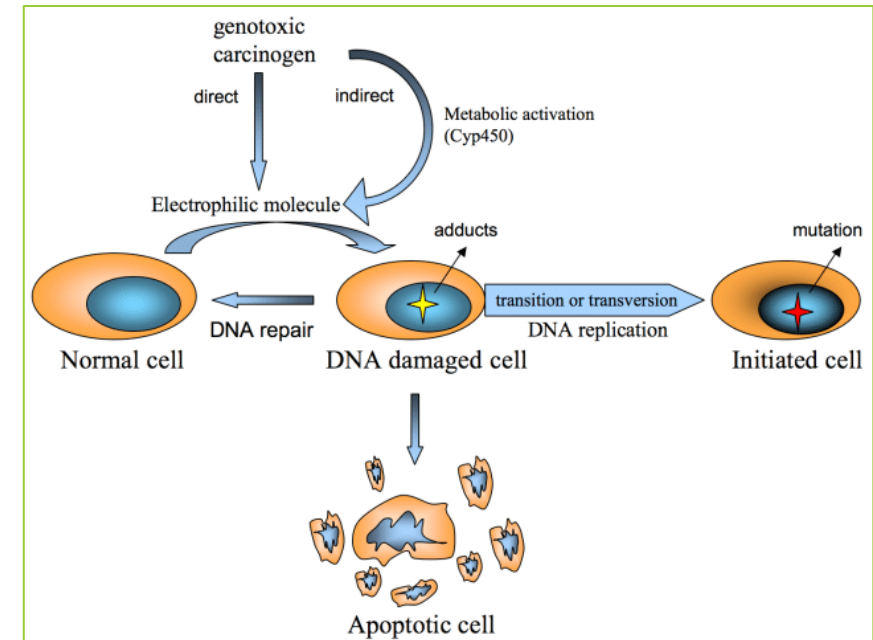
Carcinogen

- ❖ 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

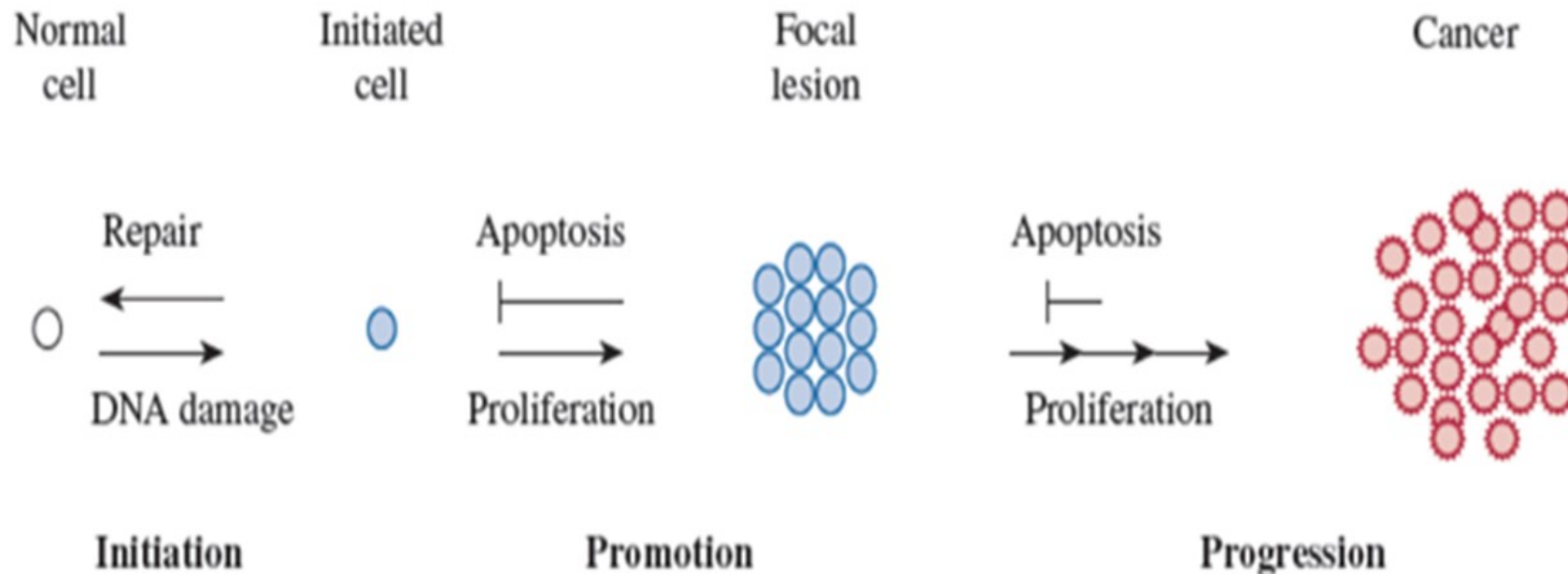
❖ **Operationally**, three defined stages have been identified including:

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 You For Your Attention