

Carcinogenesis

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References:

- **Robbins & Cotran Pathologic Basis of Disease- 9th edition**
- **IMAGES- Above mentioned book**



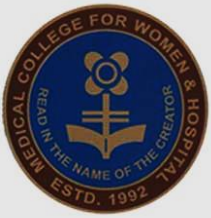
Carcinogenesis

The initiation of cancer formation
It is a multistep process



Carcinogen

Is a **substance** capable of causing cancer in living tissue



Carcinogens/ carcinogenic agents

- **Chemicals**
- **Radiant energy**
- **Oncogenic microbes**



Major Chemical Carcinogens

Direct acting carcinogens

I. Alkylating agents

Beta propiolactone

Dimethyl sulfate

Diepoxybutane

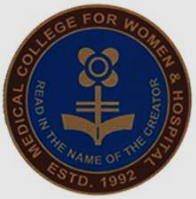
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas and others)

II. Acylating agents

1- acetyl imidazole

Dimethylcarbamyl chloride

- **Require no metabolic conversion to become carcinogenic**
- **Most are weak carcinogens**
- **Some are cancer chemotherapeutic drugs**



Major Chemical Carcinogens

Procarcinogens That Require Metabolic Activation

I. Polycyclic and Heterocyclic Aromatic Hydrocarbons

Benanthracene

Benzopyrene

Dibenzanthracene

II. Aromatic Amines, Amides, Azo Dyes

Beta naphthylamine

Benzidine

III. Natural Plant and Microbial Products

Aflatoxin B

Griseofulvin

Cycasin

Safrole

Betel nut

IV. Others

Nitrosoamines and amides

Vinyl chloride, nickel, chromium, insecticides, fungicides, polychlorinated biphenyls

Require metabolic conversion- ultimate carcinogen

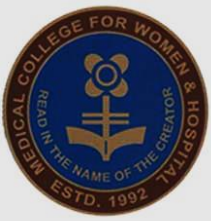


Chemical Carcinogenesis



Steps involved in chemical carcinogenesis

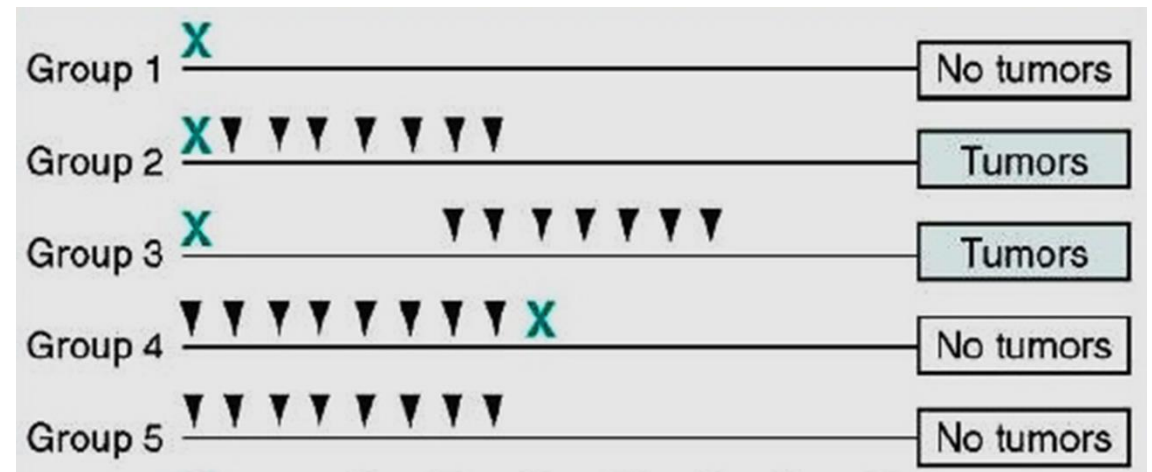
- **Initiation**
- **Promotion**



Steps involved in chemical carcinogenesis

Initiation

- Results from exposure of cells to a sufficient dose of a carcinogenic agent
- An initiated cell is altered
- Potentially capable of giving rise to a tumour
- Initiation **alone is not sufficient** for tumour formation
- **It causes permanent DNA damage**
- It is rapid, irreversible and has **memory**



X = Application of initiator
(polycyclic hydrocarbon)

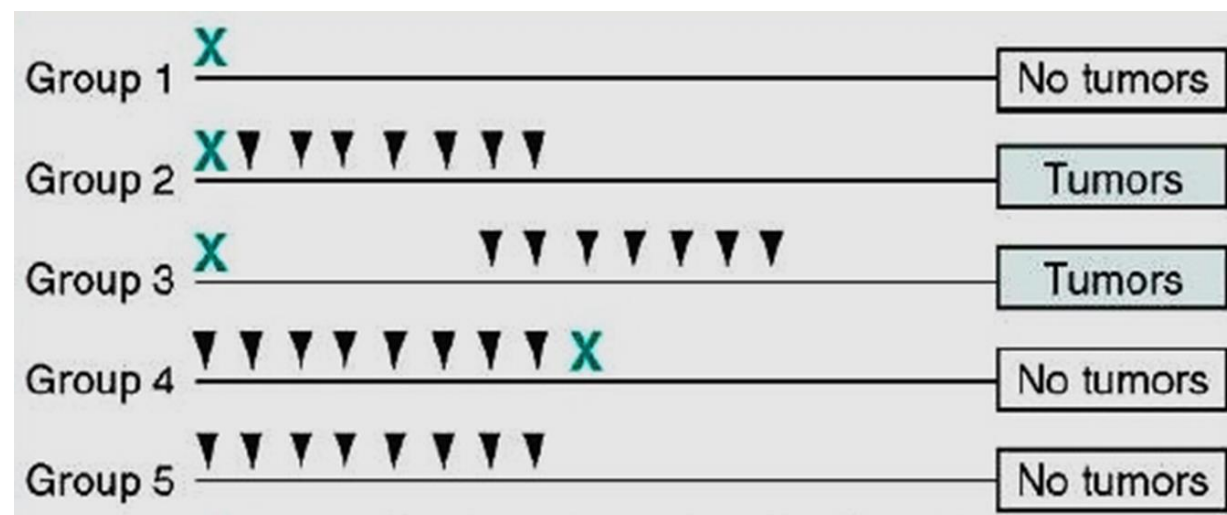
▼ = Application of promoter
(Croton oil)



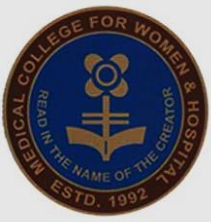
Steps involved in chemical carcinogenesis

Promotion

- Refers to the process of tumour induction in previously initiated cell
- They are **nontumorigenic by themselves**
- Promoters can induce tumours by cellular proliferation of the initiated (mutated) cell
- Do not affect DNA directly
- Cellular changes are reversible



X = Application of initiator (polycyclic hydrocarbon) ▼ = Application of promoter (Croton oil)



Chemical carcinogenesis

PROMOTERS

- Phorbol esters-plant-derived organic compound
- Hormones
- Phenols
- Drugs



Chemical carcinogenesis

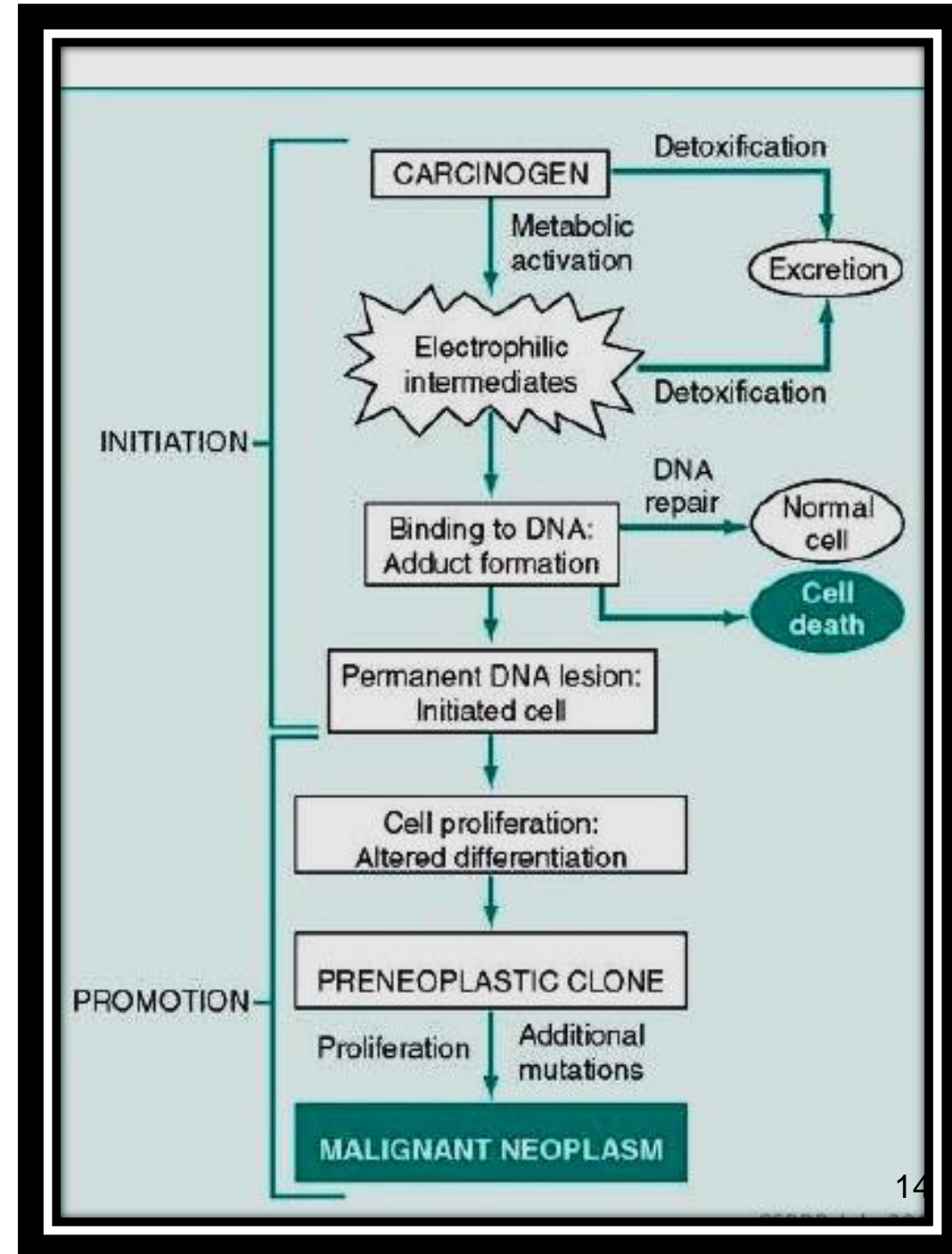
Initiators fall into two categories

- **Direct acting agents-** requires no metabolic conversion to become carcinogenic
- **Indirect acting agents-** requires metabolic conversion to become active carcinogens



General schema of events in chemical carcinogenesis

- Initiating chemical carcinogens are highly reactive **electrophiles** (electron deficient)
- They react with **nucleophilic** (electron rich) sites- DNA, RNA and proteins





Radiation Carcinogenesis



Radiation carcinogenesis

Radiant energy in the form of

- **UV rays**
- **Ionizing radiation**

is carcinogenic



UV rays

- UV rays derived from **the sun** (particularly in fair skinned individuals) associated with increased incidence of
- ***Squamous cell carcinoma***
- ***Basal cell carcinoma***
- ***Melanoma of skin***



Ionizing Radiation

- Electromagnetic (X-rays, gamma rays) and particulate (α particles, β particles, protons, neutrons) radiations all are carcinogenic
- Exposure to radiation during imaging procedures (CT scan) is linked to a very small but measurable increase in cancer risk in children



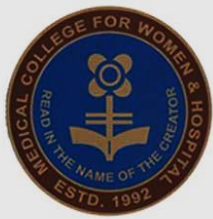
Ionizing Radiation

- **Myeloid leukaemias** followed by thyroid cancer in the young
- Cancers of the **breast, lung and salivary glands** are **less commonly** radiation induced
- **Skin, bone and the GIT** are **relatively resistant** to radiation induced neoplasia



Microbial Carcinogenesis

- Oncogenic viruses-** DNA virus and RNA virus
- Bacteria**



DNA Oncogenic viruses

- **Human Papilloma virus (HPV)**
- **Epstein Barr virus (EBV)**
- **Hepatitis B virus (HBV)**
- **Kaposi sarcoma virus**



Human Papilloma Virus

- At least 70 genetically distinct types of HPV have been identified
- Low risk HPV (type 6 & 11)- **Genital warts**
- High risk HPVs (type 16 & 18)- **squamous cell carcinoma of the cervix, anogenital region, head & neck region (oropharyngeal region)**



Epstein Barr virus (EBV)

- **Burkitt lymphoma (African type)**
- **Nasopharyngeal carcinoma**
- **NHL- B cell type in immunosuppressed individuals**
- **Hodgkin lymphoma (a subset)**



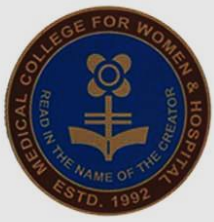
Hepatitis B and C virus

- Cause 70%- 85% of **hepatocellular carcinoma**



RNA Oncogenic viruses

- **Human T- Cell Leukaemia Virus (HTLV) Type 1** causes adult T cell leukaemia/ lymphoma (ATLL)
- **Hepatitis C virus (HBV)** causes hepatocellular carcinoma



H. pylori

- No clinical consequences in great majority of infected individual
- Implicated in **gastric adenocarcinoma** and **MALT lymphoma**

