NEOPLASIA : 5
CHEMICAL AND RADIATION CARCINOGENESIS

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Key words:

- Carcinogenesis: Pathogenesis of cancer
- Carcinogen - agent causing cancer.
- Oncogen - agent causing neoplasm.
- Mutagen - agent causing mutation.
- Oncogenes – genes causing cancer
- p-onc, v-onc – Proto/viral/ - naming of oncogenes.

How the tumor is initiated ?

1. **Chemical** carcinogenesis
2. **Hormonal** carcinogenesis
3. **Viral** carcinogenesis
4. **Bacterial/parasitic** carcinogenesis
5. **Radiation**
6. **Chronic inflammation** carcinogenesis
7. **Hereditary- Genetic defects**
   as a sum of all things above

Carcinogenesis refers to the process by which a normal cell is transformed into a malignant cell and repeatedly divides to become a cancer. A chemical which can initiate this process is called a chemical carcinogen. Some chemicals which are non-carcinogenic or only weakly carcinogenic can greatly enhance the effectiveness of carcinogenic chemicals. Such "helpers" are called cocarcinogens. They may act by altering uptake or metabolism of carcinogens by cells.

Carcinogenesis may take as long as 15-25 years in humans and in several animal models has been shown to involve two stages, initiation and promotion.

We owe, Sir Percival Pott the knowledge of carcinogenesis. Pott, related the increased incidence of scrotal cancer in chimney sweeps. On his findings, Danish Chimney Sweeps Guild ruled that it's members must bathe daily.

No public health measure since that time, has so successfully controlled a form of cancer……!!!

Etiology and Pathogenesis of Neoplasia
Overall Hypothesis

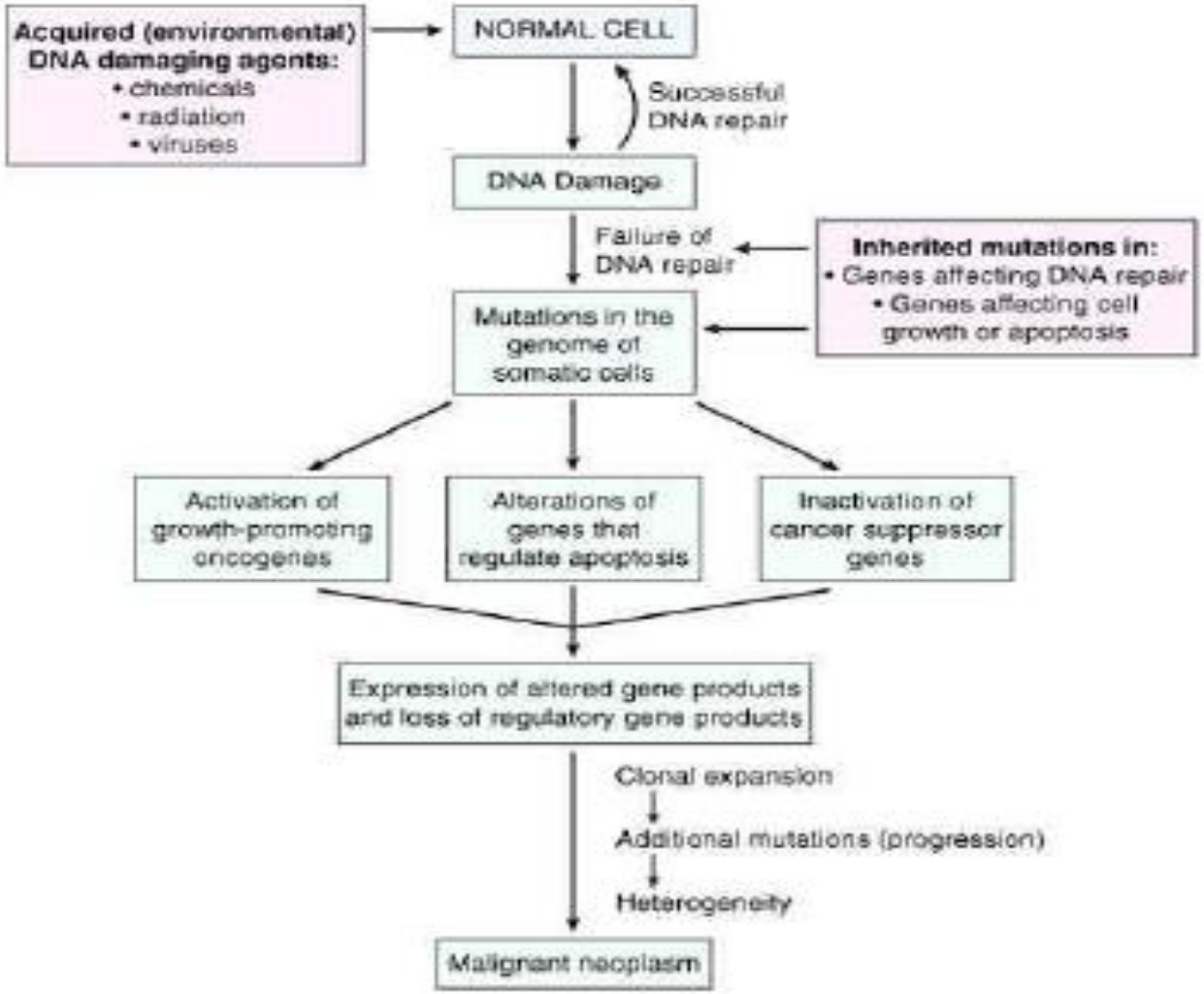

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Chemical Carcinogenesis

- chemical carcinogens are highly reactive electrophiles (electron-deficient atoms) can react with nucleophilic sites (electron-rich) in cells such as DNA, RNA and protein.

-producing lethal damage to cell

Initiation –

Results from exposure of sufficient dose of carcinogenic agent usually genetic, is introduced into a target cell. (genotoxicity)=Interaction with DNA

Initiation:

(1) essentially irreversible & has memory

(2) occurs rapidly after carcinogen exposure

(3) alone does not result in tumor formation

Carcinogen altered cell must undergo atleast one cycle of proliferation so that change in DNA becomes fixed or permanent

Promotion is the process whereby an initiated tissue or organ develop focal proliferations and it requires the presence of continuous stimulation.

A promotor: is a substance which doesn't damage DNA but enhance growth of tumor induced by genotoxic carcinogens e.g.: skin cancer in mice can be induced by application of benzo [α] pyrene (initiator) followed by phorbol ester from cotton oil (promoter).

Promotion

(1) reversible

(2) acts only after exposure to an initiating agent

(3) requires repeated administration of a promoter

(4) is not carcinogenic in itself

Carcinogenesis

- **Initiation**
  - DNA damage eg.Benzpyrene
- **Promotion**
  - Turpentine (co-carcinogens)
- **Malignant transformation:**
  - Visible tumor formation – further DNA damage.

Etiology and Pathogenesis of Neoplasia Initiation and Promotion

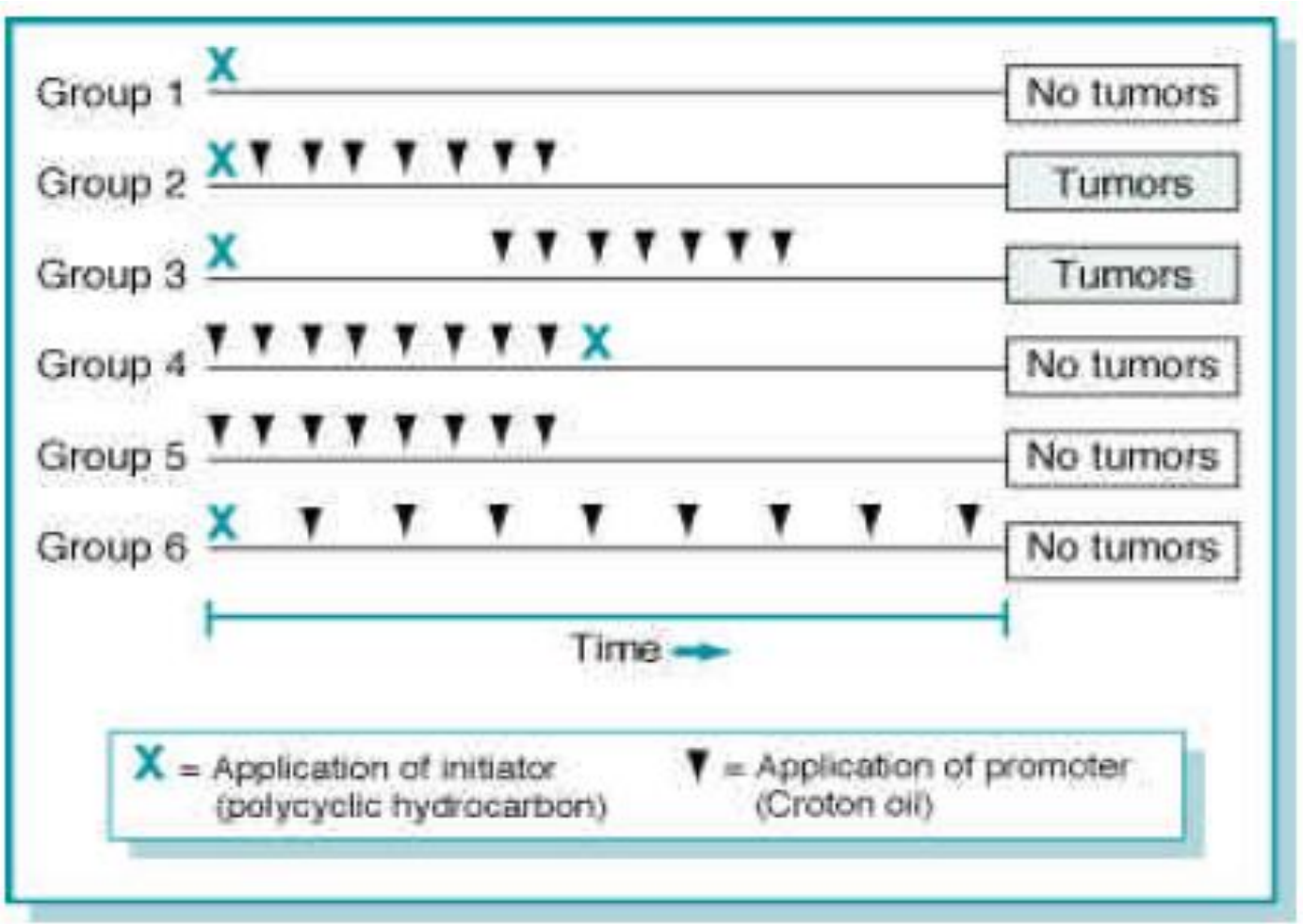

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TABLE 7–11 Major Chemical Carcinogens

Direct-Acting Carcinogens

Alkylating Agents

β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)

Acylating Agents

1-Acetyl-imidazole
Dimethylcarbamyl chloride

Procarcinogens That Require Metabolic Activation

Polycyclic and Heterocyclic Aromatic Hydrocarbons

Benz(a)anthracene
Benzo(a)pyrene
Dibenz(a,h)anthracene
3-Methylcholanthrene
7,12-Dimethylbenz(a)anthracene

Aromatic Amines, Amides, Azo Dyes

2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)

Natural Plant and Microbial Products

Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts

Others

Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Direct-Acting Alkylating Agents

- Weak carcinogens
- Therapeutic agents (cyclophosphamide,Chlorambucil, Busulphan etc.) used as anticancer drugs but induce lymphoid neoplasm, leukaemia & others

Cyclophosphamide also powerful immunosuppressive agents used for Rheumatoid arthritis & others. Risk of induce cancer is low.

Polycyclic Aromatic Hydrocarbons

- Require metabolic activation
- Painted on the skin – Skin cancer
- Injected subcutaneously – sarcomas
- Introduced into specific organ – cancer locally
- Combustion of tobacco with cigarette smoking – lung and bladder cancer
- In process of broiling meats and smoked meats produced Polycyclic aromatic hydrocarbons

Aromatic amines and azo dyes

- "ultimate carcinogen" formed by action of cytochrome P-450 oxygenase systems..
- Cancer at the site of metabolism and NOT at the point of entry or absorption. E .g., Azo dyes producing Hepatocellluar CA and not gastric CA
- Beta- naphthalamine after absorption, hydroxylated in active form then detoxified by conjugation with glucoronic acid in liver. when excreted in URINE, nontoxic conjugate is split by urinary glucoronidase- release of electrophilic reactant causing Bladder CA.
- Food coloring Azo dyes i.e. butter yellow, scarlet red dangerous to human

Naturally occurring carcinogens

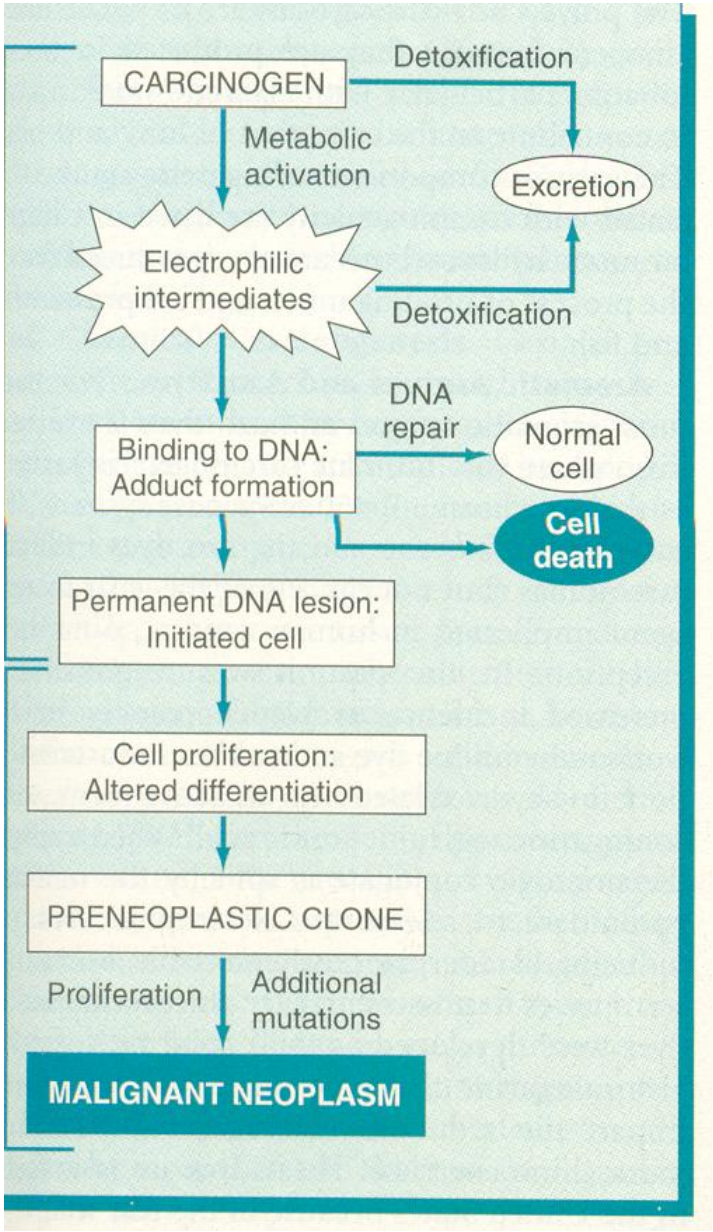
- Produced by plants and microorganisms
- Mycotoxin produced by Aspergillus flavus present on stored corn, rice and peanuts- hepatocarcinogen producing hepatocellular carcinoma in some parts of Africa and china
- Aflatoxin and HBV collaborate in production of HCC

Nitrosamines and Amides

- Nitro stable amines and nitrate used as a food preservative which is converted to nitrites by bacteria in stomach producing gastric carcinoma

Professions and industries associated with high risk of cancer

Aluminum industry	polycyclic aromatic hydrocarbons (PAHs)	Lung and bladder cancer
Coal industry	polycyclic aromatic hydrocarbons (PAHs)	Lung, bladder, skin, scrotum cancer
Shoemaking	Benzene	Lymphomas, leukemias
Furniture making	Wood dust	Nasopharyngeal cancer
Fuchsin dye production	Fuchsin, ortho-toluidine	Bladder cancer
Rubber industry	Aromatic amines, solvents	Lung, colon, stomach, bladder, prostatic cancer, leukemia



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Diet & nutrients protecting from cancer :

- *Fruits & vegetables*

  * High level of fibers

  * Antioxidants which decrease damaging effects caused by free radicals and reactive oxygen species on DNA

Examples:

Tocopherol & ß- carotene (carotenoids), vit C

Tomatoes

Green tea

Red grapes

Garlic & onions (allylsulphide + diallylsulphide)

Cruciferous vegetables :

- E.g.: Cabbage - broccoli.

Omega 3 fatty acids:

e.g. : fish oil

Soy products

Red grapes

- Diets play important roles in the development of tumors.
  The following factors should be considered.
  - Natural Foods May Contain Carcinogens:
    Mushrooms»»Hydrazine
    Betal Nut»»Hydrocarbons
  - Food contaminants:
    Aflatoxin B1»»Peanuts
    Nitrosamines»» Canned food
  - Food Processing:
    Smoked and processed Meat»»Polycyclic Hydrocarbons
    Heat Processing of Protein-Rich Foods»»Heterocyclic Aromatic compounds
  - Dietary Fat:
    Hydrogenated oils or trans-fat
  - Alcohol

Radiation Carcinogenesis:

Radiant energy- Ultraviolet rays of sunlight or

- Ionizing electromagnetic and particulate radiation

Ionizing radiation exposure from medical or occupational, nuclear plant accidents, atomic bomb detonation

Produce variety of malignancies after a long latent period

- X Ray workers – Leukemia
- Radio-isotopes – Thyroid carcinoma
- Atomic explosion – Skin cancer, Leukemia

The effects of UV light on DNA differ from ionizing radiation

Radiation

- Ultraviolet rays- Sunlight

  Sq. Cell, basal cell & melanoma

  UVA,UVB ➡ Highest responsible for cancer .

- UVC ➡ Highest mutagen but filter by ozone.
- Depend on :-

  Degree of risk

  Type of UV rays

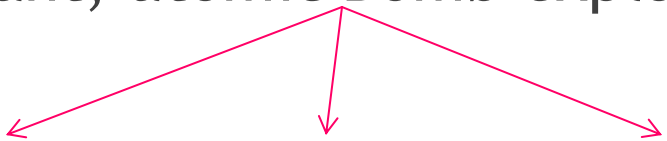
  Intensity of exposure

  Protective mantle of melanin in the skin

- Incidence ➡ High in fair skin – European
  & (Queensland , Australia close to equator)
- DNA pyrimidine dimmers damage repaired by nucleotide excision repair(NER) , pathway which overwhelmed so, DNA damage remains unrepaired leads to transcriptional errors
- Autosomal recessive disorder Xeroderma pigmentosum.
- Extreme photosensitivity, 2000 fold increase risk of skin cancer& neurologic abnormalities.
- Inherited inability to repair UV- induced DNA damage
- UVB also causes mutations in oncogenes & tumor suppressor genes- p53,RAS

Ionizing Radiation

- Electromagnetic (X-rays ,Y-rays),particulates (Alpha & Beta particles, protons, neutrons) Radiation carcinogenic.
- Nuclear plant, atomic Bomb explosion



Leukemia Thyroid Ca Breast, Lung , Colon

All types of leukemia except chronic lymphocytic leukemia

- Increasing level of chromosomal abnormalities.
- Skin , bone & GI tract are relatively resistant to radiation – induced Neoplasia.