

# Molecular basis of tumours -2

## Carcinogens



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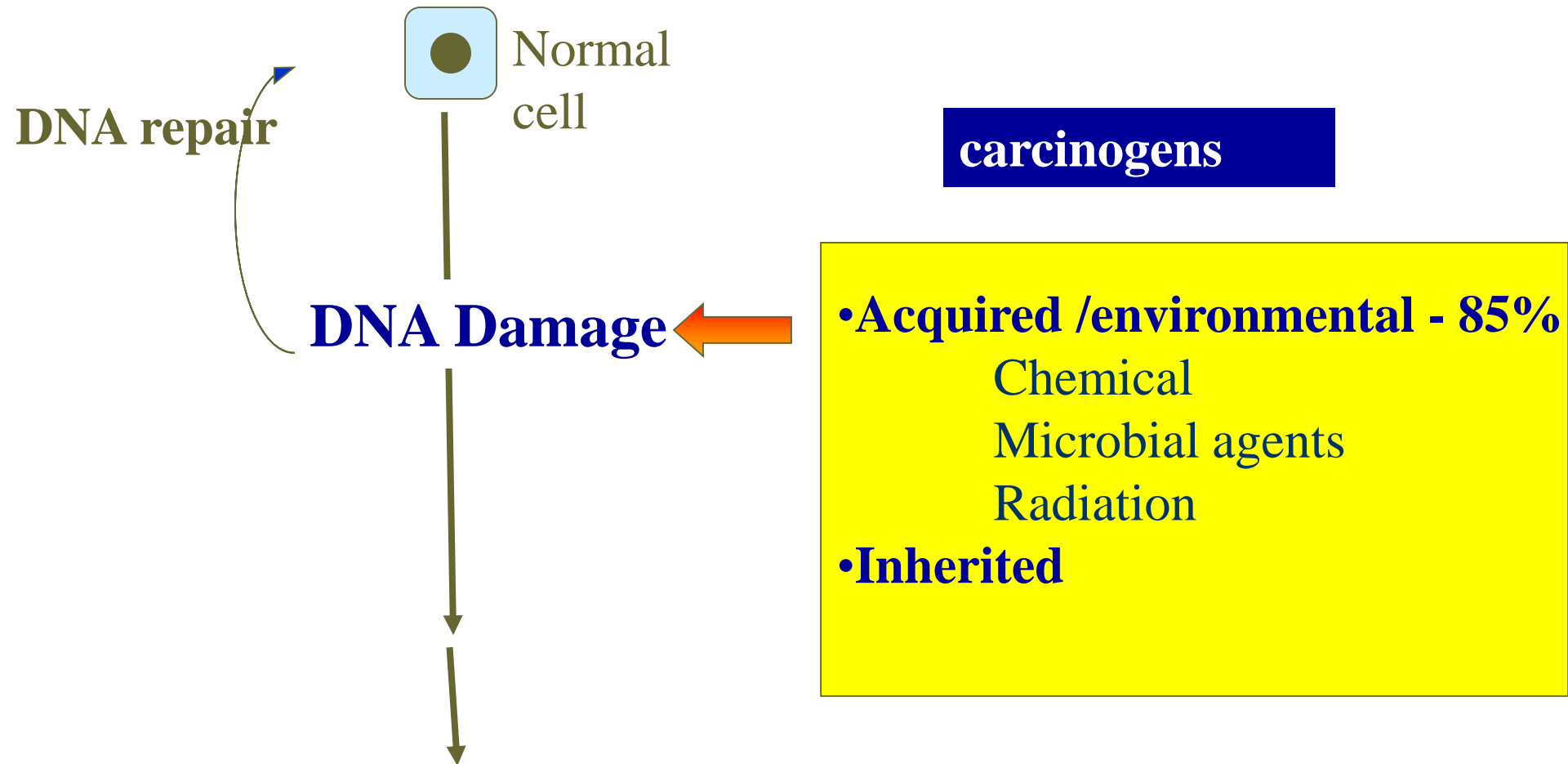
- More than 200 years ago Sir Percival Pott (1714 – 1788) an English Surgeon correctly attributed scrotal skin cancer in chimney sweepers to chronic exposure to soot
- First scientist to demonstrate that a cancer may be caused by an environmental carcinogen.
- Since that time hundreds of chemicals have been identified to be carcinogens

# Objectives

- Define the major groups of carcinogens
- Mechanism of action of chemical carcinogens
- Know the terms- initiator, promoter, complete and incomplete carcinogens, direct and indirect carcinogens
- Some examples of chemical carcinogens and the tumours they produce
- Viruses that cause tumours
- Mechanism of action of radiation carcinogens

# Carcinogens

- A carcinogen is an agent known or suspected to participate in the causation of cancer.
- These agents are known as carcinogenic/ oncogenic.
- Ultimate site of action of carcinogens is mainly the DNA.
- Carcinogens are therefore mutagenic.



An Abnormal protein, which  
**allow the cell to become a  
tumour cell**

- Carcinogenesis is a multistep process.
- More than one carcinogen may be required to produce a single tumour.
- Once the process of carcinogenesis is started, the presence of carcinogen is not required to continue the process.
- ‘hit-and-run’ theory



# How do we identify carcinogens?

- Epidemiological studies
- Assessment of occupational risks
- Direct accidental exposure
- Laboratory studies on animals
- Transforming effects of cell cultures
- **Mutagenicity** testing in bacteria

Think about examples.....

# Major categories of environmental carcinogens

- Chemicals
- Microbial agents
  - Mainly viruses
  - Bacteria, fungi and parasites
- Radiation energy
  - Ionizing radiation
  - Nonionizing radiation
- Other
  - Hormones

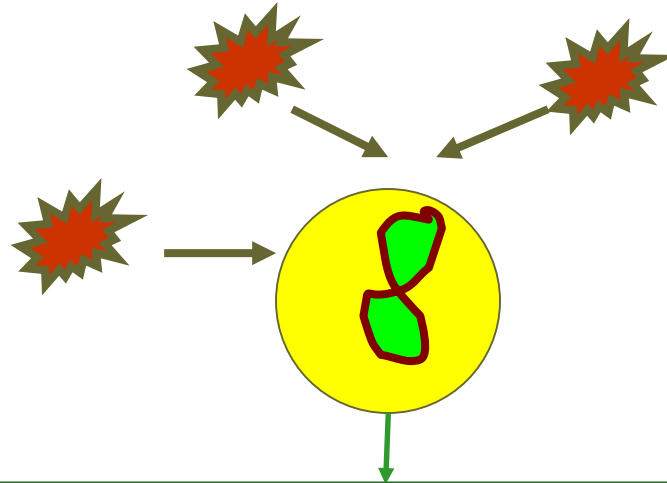


# Chemical carcinogenesis

- Cancer induction by chemicals can be broadly divided into 2 steps
  - Initiation
  - Promotion

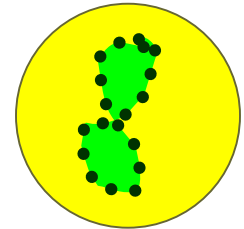
# Chemical carcinogenesis

Exposure of a cell to an **initiator** ( carcinogen)



Rapid  
Irreversible

Permanent damage to the DNA



However initiation alone is not sufficient for tumour formation

# Chemical carcinogenesis

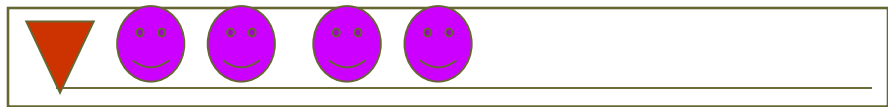
## Promotion

- Promoters can induce tumours in initiated cells
- Promoters are non tumourogenic by themselves
- The cellular changes they make are reversible
- Promoters should be applied after the initiator

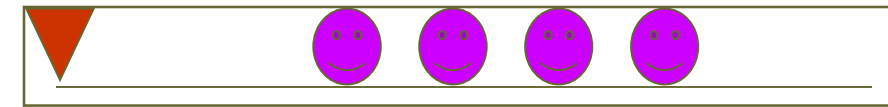
# Initiation and promotion of carcinogenesis



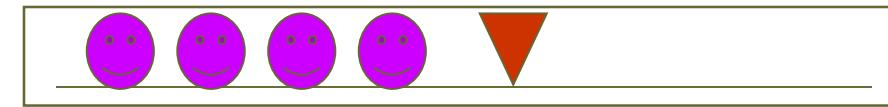
No tumour



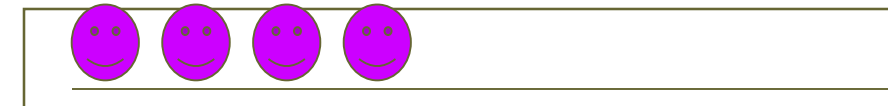
tumour



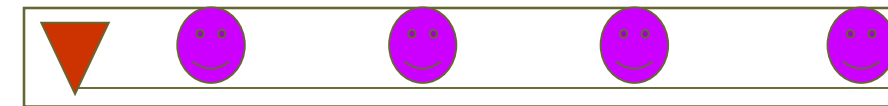
tumour



No tumour



No tumour



No tumour

 initiator

 promotor

# Chemical carcinogens

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graph TD; A[Chemical carcinogens] --> B[Complete carcinogens]; A --> C[Incomplete carcinogens];
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Complete carcinogens

Incomplete carcinogens

Capable of causing  
initiation and  
promotion **both**

Capable of initiation **only**

# Chemicals that initiate carcinogenesis



## Direct acting

Do not require metabolic conversion for their carcinogenicity

Eg; alkylating agents –  
anticancer drug  
Cyclophosphamide

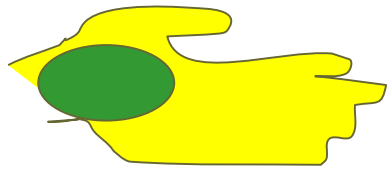
## Indirect acting-procarcinogens

Needs in-vivo metabolic activation to produce ultimate carcinogen, capable of transforming cells

Eg polycyclic hydrocarbons,  
benzo pyrens,  
aromatic amines

# Indirect acting /procarcinogens

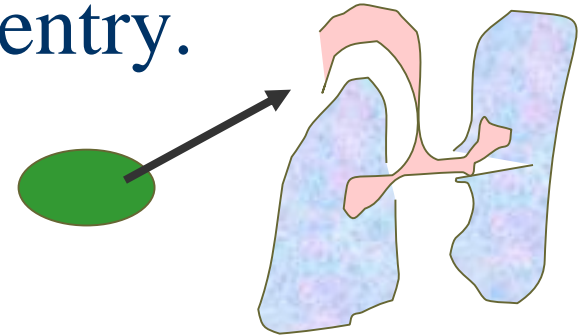
- If the enzyme needed for metabolic conversion is available at the site of entry of procarcinogen, the tumour will occur at the site of entry.



Poly cyclic aromatic  
hydrocarbons



Skin cancer



Lung cancer

- Dietary nitrates  $\xrightarrow[\text{bacteria}]{\text{Gut}}$  Nitrosamine



**Read on different chemical carcinogens and their mechanism of action and the tumours they cause**





# Some chemicals associated with human cancer

Chemical	Occurrence	Tumour
Alkylating agents	chemotherapy	leukaemias
Asbestos	insulation	mesotheliomas
Benzene	solvents	Leukaemias
Nickel	mining	Lung cancer
Nitrosamine	dietary	Gastric cancer
Polycyclic hydrocarbons	Incomplete burning of organic material	Lung, bladder cancer etc..
Vinyl chloride	PVC	Angiosarcoma-liver

# Polycyclic aromatic hydrocarbons

- First chemical carcinogens to be intensively studied
- A procarcinogen & requires hydroxylation to become ultimate carcinogen
- Hydroxylating enzymes are ubiquitous in tissues
  - Skin cancer among painters
  - Lung , bladder cancer in smokers
- Many cancers are associated with PCAH, commonest is the lung cancer
- Many carcinogenic compounds are found in tobacco, commonest is 3,4 benzpyrene

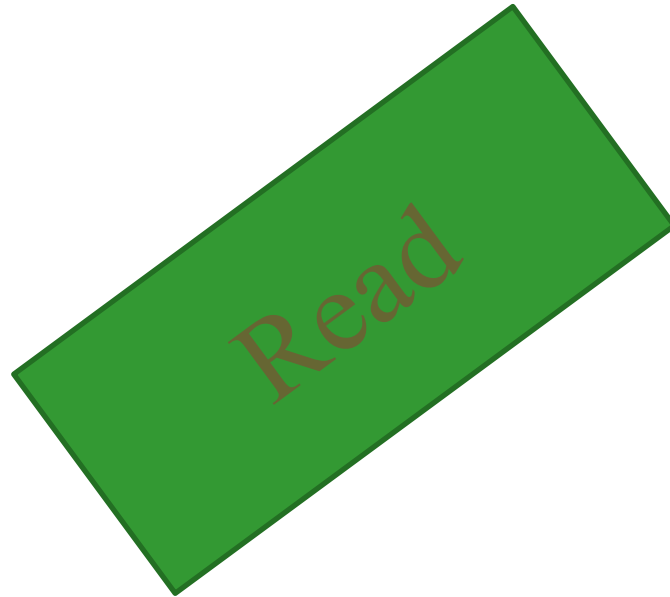
Read

# Aromatic amines

- Used in rubber and dye industry
- Needs hydroxylation in the liver
- $\beta$  naphthylamine  $\longrightarrow$  1-OH-2-naphthalamine
- Immediately conjugated with glucuronic acid in the liver, masking the carcinogenic effect
- However in the urothelium deconjugation occur by the enzyme glucuronidase
- Exposure of the urothelium to carcinogen
- Cancer of urothelium

# Nitrosamines

- Dietary nitrates and nitrites and gastrointestinal cancer
- Used in fertilizers, food additives

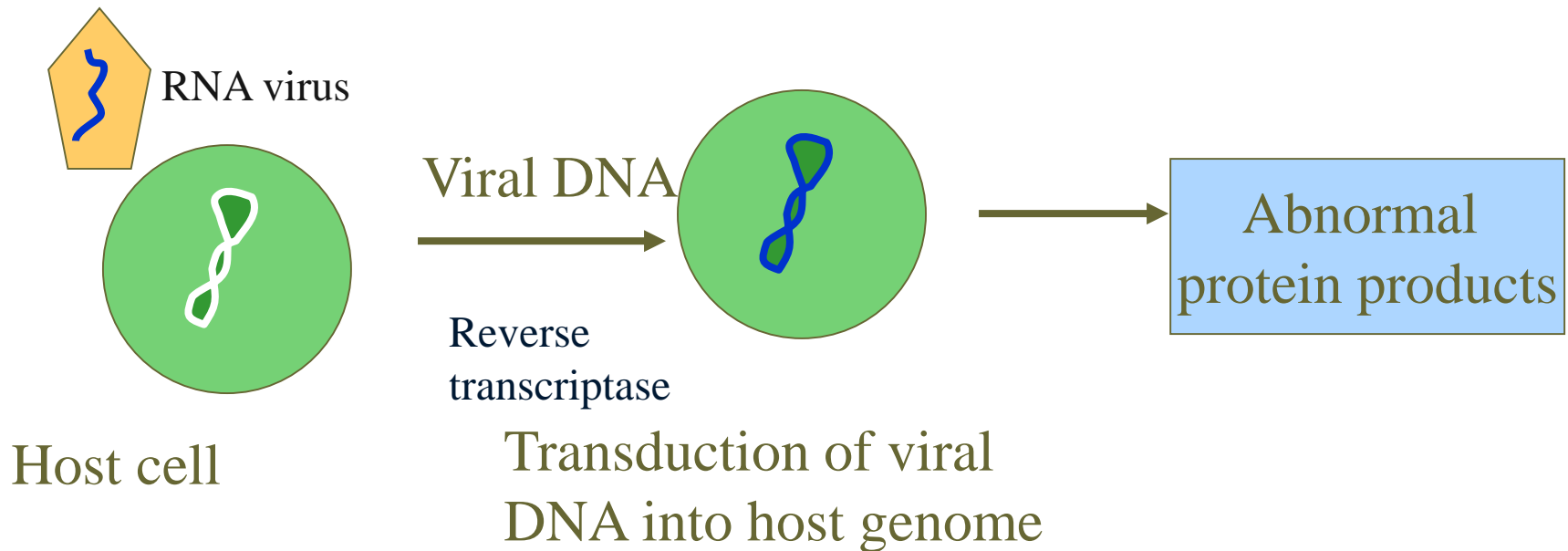


# Microbial carcinogenesis

- Viruses
  - RNA viruses
  - DNA viruses
- Bacteria
- Fungi
- Parasites

# Viral Oncogenesis

- Protooncogenes  $\longrightarrow$  viral oncogenes  
Activation by oncogenic viruses (v oncs)



# Viral Oncogenesis

- Some viruses act indirectly by causing tissue destruction leading to increased cellular proliferation
  - Eg; hepatitis C virus

# Oncogenic DNA viruses

- Epstein-Barr virus
- Hepatitis B virus
- Human Papilloma Virus (HPV)
- Human Herpes Virus 8 (HHV 8) / Kaposi Sarcoma Herpes Virus KSHV



# Epstein-Barr Virus

- EBV infects B lymphocytes and possibly epithelial cells of nasopharynx
- EBV infected B cells are immortalized.
- EBV gene, latent membrane protein-1(LMP-1) act as an oncogene and causes autonomous proliferation of B lymphocytes
- LMP-1 also inhibits apoptosis by activating Bcl-2
- Causation of B cell lymphomas

# Epstein-Barr Virus

- Implicated in the pathogenesis of
  - Burkitt lymphoma
  - B cell lymphomas in immunocompromized patients
  - Nasopharyngeal carcinomas
  - Rare T cell lymphomas

Read on EBV and cancer

# Hepatitis B Virus

- Strong association between HBV and hepatocellular carcinoma
- Chronic liver cell infection leads to compensatory proliferation of hepatocytes
- Many cytokines, growth factors, chemokines , reactive oxygen species are produced by activated immune cells
- These cause mutagenesis

read

# Human papillomavirus

- There are many subtypes of HPV
- Some types (1,2,4,7) cause benign squamous papillomas (warts)
- High risk HPVs-(16 & 18)
  - Squamous cell carcinoma of cervix and ano-genital region
- High-risk HPV types express oncogenic proteins
  - Inactivation of tumour suppressor genes
  - Activates cyclins
  - Inhibits apoptosis
  - Combat cellular senescence

Read more

# Oncogenic RNA viruses

- Human T cell Leukaemia Virus - type 1 (HTLV 1)
  - T cell leukaemia/ lymphoma
- Hepatitis C virus
  - hepatocellular carcinoma

# Other microorganisms implicated in carcinogenesis

## *Bacteria*

- *Helicobacter pylori* -gastric lymphoma  
-gastric carcinoma

## *Fungi*

- Aflatoxin producing *Aspergillus flavus*  
-*Hepatocellular carcinoma*

## • *Parasites*

- *Schistosoma* -Bladder cancer
- *Clonorchis sinensis* - cholangiocarcinoma

# Radiation carcinogenesis

- UV rays of sunlight
- Ionizing electromagnetic or particulate radiation

# Ultraviolet rays

- damages DNA by forming Pyrimidine dimers
- High risk of skin cancer in people with defective DNA repair genes
- Increased incidence of
  - Squamous cell carcinoma of skin
  - Basal cell carcinoma of skin
  - Melanoma of skin
- Degree of risk depends on
  - type of UV rays
  - Intensity of exposure
  - Protective melanin barrier



# Ionizing radiation

- Causes chromosomal breakage, translocations & point mutations
- Electromagnetic -x rays,  $\gamma$  rays
- Particulate –  $\alpha$  particles,  $\beta$  particles, protons & neutrons
- Vulnerability of various human tissue to radiation are different
  - Most frequent- leukaemias and thyroid cancer
  - Intermediate -Breast, lung & salivary gland cancer
  - Skin and GI tract cancers are rare

# Ionizing radiation and cancer

- Radiology workers
- Mining of radioactive substances
- Military exposure – Hiroshima & Nagasaki in 1945
- Accidental exposures- Chernobyl accident
- Therapeutic exposure

# Hormones as carcinogens

- Oestrogens – endometrial and breast cancer
- Androgens and anabolic steroids- hepatocellular cancer

# Read on

- Genetic predisposition of cancer
- Familial cancer syndromes
- Familial cancers

# Summary.....

