Carcinogenesis

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PA 7.3

- Enumerate carcinogens and describe the process of carcinogenesis

Specific Learning Objectives

At the end of this session, the II MBBS student should be able to-

- Classify and Discuss **Chemical Carcinogens**
- Describe Carcinogenesis in terms of Initiation and Neoplastic Progress
- Describe the mechanism by which exposure to **radiation** can produce cancer
- **Viral Carcinogenesis-** Describe the mechanism by which viruses and other **microbiological agents** can contribute to the development of cancers

Carcinogenesis

Neoplasia –

due to genetic damage caused by

- chemical carcinogens
- radiant energy
- oncogenic viruses

Historical Significance

1761 - Dr John Hill, London Physician Observed the association of nasal cancer among tobacco snuff users in men.

1775 - Percivall Pott, an English surgeon : increased Incidence of scrotal cancer in chimney sweepers in London.

1915 - Yamagiwa and Ichikawa, Japanese Pathologists: Multiple topical applications of coal tar to rabbit ears produced squamous cell carcinomas.

First demonstration that a chemical could produce cancer in animals.

1930's – Kennaway, a british Pathologist : showed for the first time that polycyclic aromatic hydrocarbons , such as dibenzanthracene, are tumorigenic in mouse skin

1940's - James and Elizabeth Miller, Oncologists : first to find the relationship between metabolic activation, and tumorigenesis.

Chemical Carcinogenesis

Chemical carcinogens

↓

weeks, months & years

↓

Cancer

- ✓ Dose
- ✓ Mode of administration
- ✓ Individual susceptibility

Conversion of target cell into neoplastic cell

Cellular proliferation → Neoplasia

Stages of chemical carcinogenesis

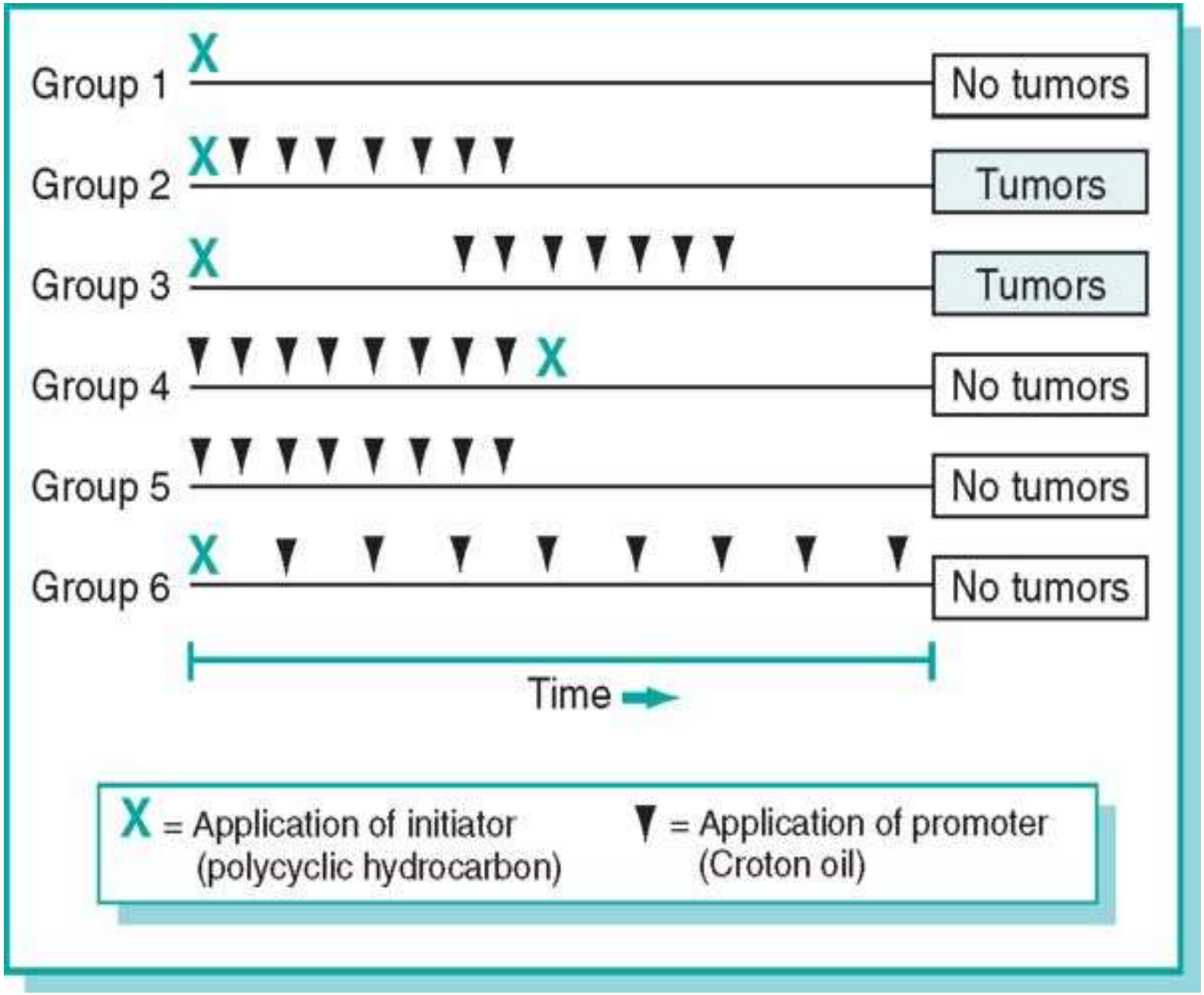
- Initiation of carcinogenesis
- Promotion

Initiation

- ✓ I st stage in carcinogenesis.
- ✓ Causes permanent DNA damage or mutations.
- ✓ Rapid, irreversible & permanent.
- ✓ Alone not sufficient for tumor formation.

Promotion

- ✓ Initiation by itself not sufficient for tumor formation.
- ✓ Carcinogenecity is augmented by subsequent administration of promoters.
- ✓ They are themselves non tumorigenic.
- ✓ Proliferations & clonal expansion of initiated (mutated) cells.
- ✓ Tumors do not result when promoting agent is applied before rather than after the initiating agent.


Group 1
X
No tumors
Group 2
X
Tumors
Group 3
X
Tumors
Group 4
X
No tumors
Group 5
No tumors
Group 6
X
No tumors
Time
X = Application of initiator (polycyclic hydrocarbon)
= Application of promoter (Croton oil)

Initiators

Direct acting compounds –

- induce cellular transformation without undergoing any prior metabolic activation.

- do not require chemical transformation for their oncogenecity.

e.g. alkylating agents, acylating agents

Initiators

Indirect acting compounds (Pro carcinogens) –

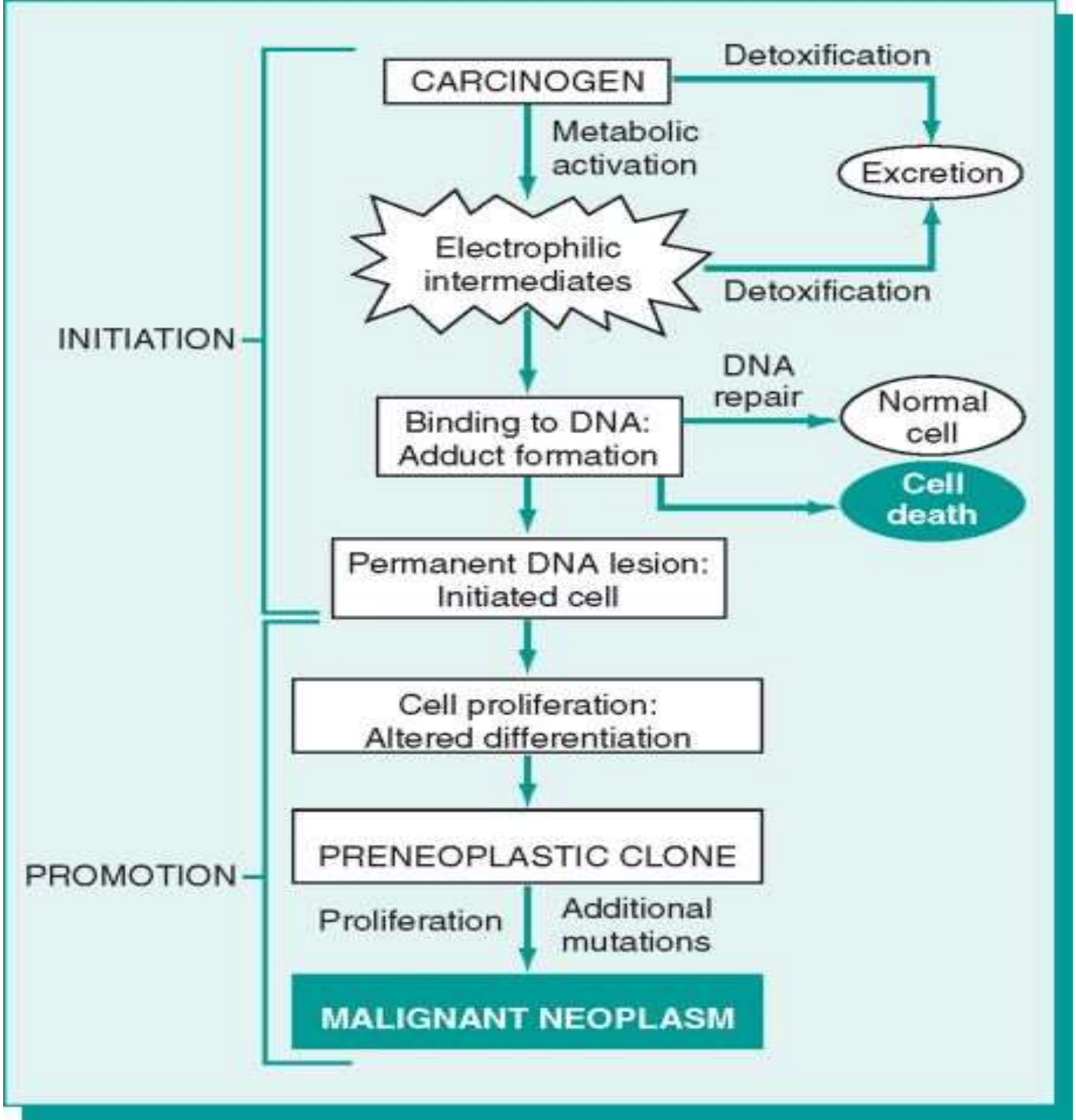
- require metabolic conversion in vivo to produce ultimate carcinogen capable of transforming cell.
  e.g. polycyclic aromatic amines, azo dyes

- majority are metabolized by cytochrome p-450 dependent mono oxygenases.

Mechanism of action -

- Highly reactive electrophiles (have electron deficient atoms) that react with nucleophilic (electron rich) sites in the cell.

- Reactions – non enzymatic & result in formation of covalents adducts between the chemical carcinogen & a nucleotide in DNA.


CARCINOGEN
Detoxification
Metabolic activation
Excretion
Electrophilic intermediates
Detoxification
INITIATION
DNA repair
Binding to DNA: Adduct formation
Normal cell
Cell death
Permanent DNA lesion: Initiated cell
Cell proliferation: Altered differentiation
PRENEOPLASTIC CLONE
PROMOTION
Proliferation
Additional mutations
MALIGNANT NEOPLASM

Carcinogen

↓

No metabolic activation ↓ Metabolic activation

Reactive electrophile

↓

Target molecules (chiefly DNA)

↓

Permanent DNA damage

(Initiated cell)

Promotion

- Initiation by itself not sufficient for tumor formation.

- Carcinigencity is augmented by subsequent administration of promoters.

- e.g. phorbol esters , hormones , phenols , drugs
- They are themselves non tumorigenic.
- Proliferation & clonal expansion of initiated cells

Table 7-10 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

Carcinogens

- **Direct acting carcinogen**

A. Alkylating agents

1. Beta propiolactone
2. Dimethyl sulphate
3. Diepoxy butane
4. Anticancer drugs (cyclophosphamide , chlorambucil)

B. ***Acylating agents***

1. 1-acetyl-inidazole2
2. .Dimethyl carbamyl chloride

II Pro carcinogens

A. Polycyclic aromatic hydrocarbons – Ca lung, skin,bladder

1. Benzanthracene
2. Benzopyrine

B. **Aromatic amines, Amides, Azo dyes – Ca bladder, HCC**

1. B naphthylamine
2. Benzidine

C. Natural plant & Microbial products

1. Aflatoxin B – HCC
2. Betel nuts

D. Others

1. Nitrosamines & amides –Ca stomach
2. Vinyl chloride, nickel, chromium- Ca lung
3. Insecticides,fungicides

- **Polycyclic aromatic hydrocarbons**: combustion of tobacco, tobacco chewing, smoke, fossil fuel, soot, tar, mineral oil, smoked animal foods, industrial and atmospheric pollutants.
- **B naphthylamine**: bladder cancer in aniline dye and rubber industry workers
- **Azo dyes**: coloring foods: butter yellow, red

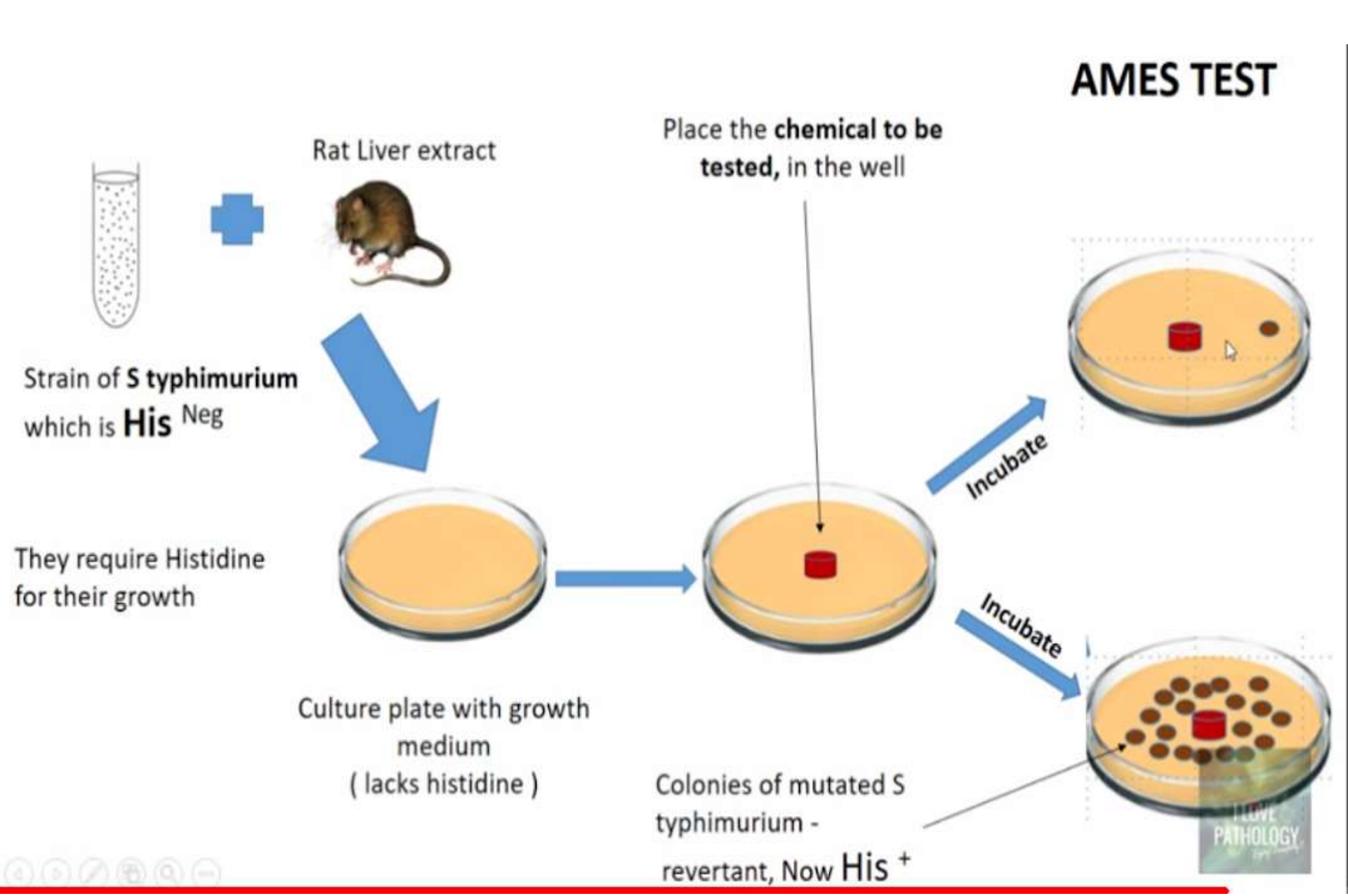
Tests for chemical carcinogenicity

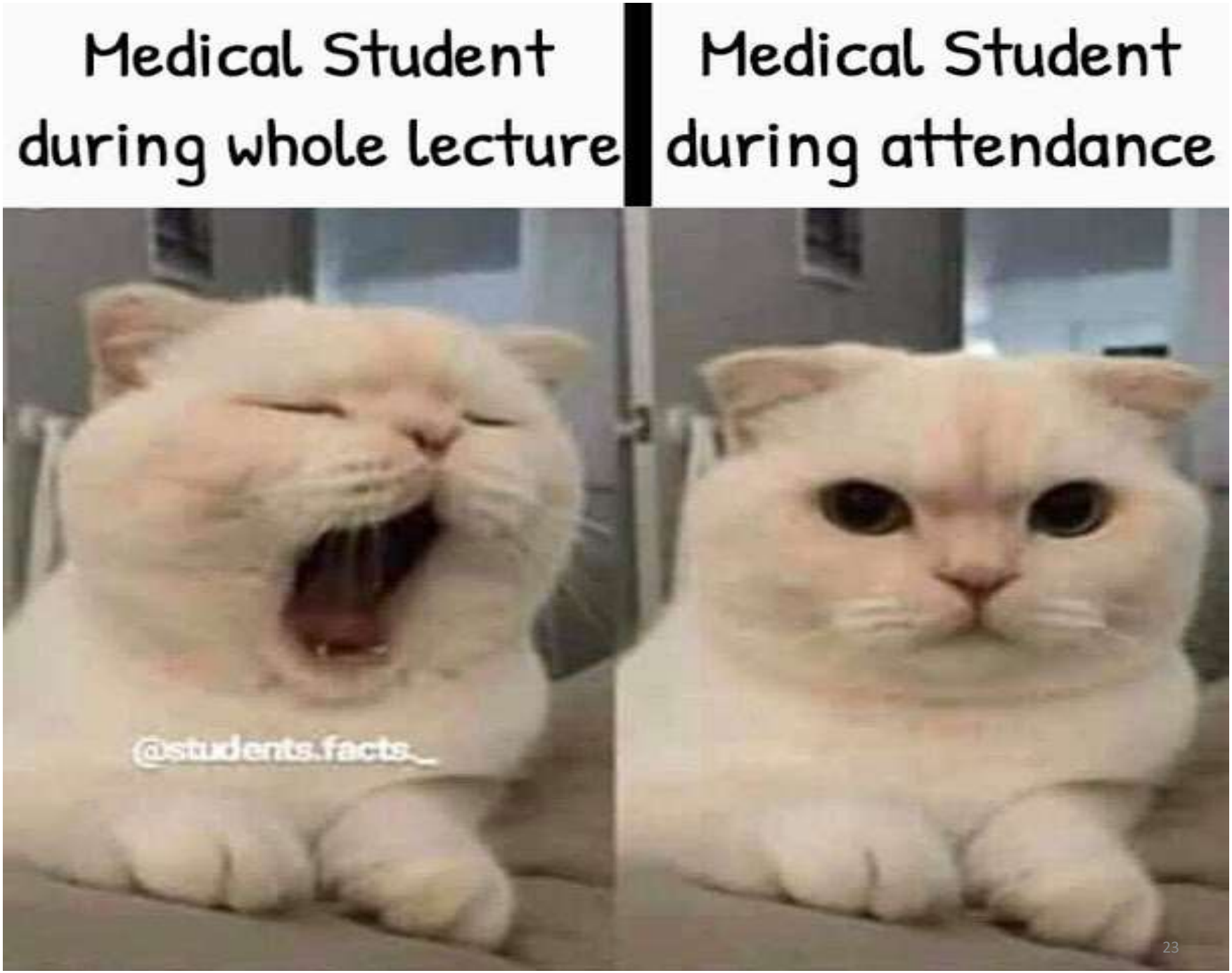
- Experimental induction
- Ames' test

Evaluates the ability of a chemical to induce mutation in a strain of Salmonella typhimurium that cannot synthesize histidine

Diff between Initiator and Promoter

AMES TEST


Rat Liver extract
Place the **chemical to be tested,** in the well
Strain of **S typhimurium** which is **His** Neg
They require Histidine for their growth
Incubate
Incubate
Culture plate with growth medium (lacks histidine)
Colonies of mutated S typhimurium - revertant, Now His +


Medical Student
during whole lecture
Medical Student
during attendance
@students.facts_

Radiation Carcinogenesis

- Radiant energy (UV rays, ionizing radiation) can induce neoplasms.

- UV rays – skin cancers
- Ionizing radiation – Leukaemias, cancers of thyroid, skin, breast, ovary, uterus, lung, myeloma and salivary gland

(medical or occupational exposure,nuclear plant accidents & atomic bomb detonations)

UV RAYS

UV rays –

- ✓ UVA (320-400nm)
- ✓ UVB (280-320nm)
- ✓ UVC (200-280nm)

UVB – cutaneous cancers like SCC, BCC ,
Malignant Melanoma

The degree of risk depends upon

- Type of UV rays
- The intensity of exposure
- The quantity of light absorbing protective mantle of melanin in the skin.

Carcinogenicity of UVB rays is attributed to

- **Formation of pyrimidine dimers in DNA**
- **Oncogenes & Tumor suppressor genes**

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The DNA damage is normally repaired by Nucleotide Excision Repair (NER) pathway.

- With excessive sun exposure, the capacity of the NER pathway is overwhelmed & hence some DNA damage remains unrepaired.

Xeroderma Pigmentosa – extreme photosensitivity

2000 fold increased risk of skin cancers due to mutations in the gene involved in the NER pathway.

Ionizing Radiations

Electromagnetic (X rays,γ rays) and

Particulate (αparticles, βparticles,protons & neutrons)

Pioneers in development of x rays - skin cancers.

Miners of radioactive elements – Lung cancer

Atomic bomb surviors – Leukemias, solid tumors

Therapeutic x ray irradiation -

Microbial Carcinogenesis

Parasites

Schistosoma Haematobium – Ca bladder

Clonorchis Sinensis – Cholangiocarcinoma.

Fungus

Aspergillus Flavus – Hepatocellular Carcinoma

Bacteria

H. Pylori – Ca stomach, Gastric Lymphoma

Viruses – very important role

Viral Carcinogenesis

DNA Oncogenic Viruses

have direct access to the host cell nucleus &

are incorporated in to the genome of host cell.

Mechanism –

After the host cells are infected with DNA viruses, the viral DNA may integrate into host cell DNA.

Integration results in neoplastic transformation of cell.

DNA Oncogenic Viruses

I. **Human Papilloma Virus** – Ca Cx, SCC, Papilloma

II. **Herpes Virus**

a) EB Virus – Burkitt's Lymphoma(African form)
Some cases of Hodgkin's Lymphoma
Nasopharyngeal Carcinoma
B cell Lymphoma(immuno supressed pts)

b) KSHV – Kaposi's Sarcoma

III. **Pox Virus** – Papilloma

IV. **Hepadenaviruses**

a) HBV – Hepatocellular Carcinoma

Human Papilloma Virus

- HPV types 1,2,4 and 7: skin warts
- Low risk HPV types 6 and 11: genital warts(condyloma acuminata)
- High risk HPV types 16,18,31,33 and 45: Cervical dysplasia- Ca in situ, Ca Cx
- Viral DNA is integrated into the target epithelial cells and there is **overexpression of viral oncoproteins E6 and E7**

- **Oncogenic effects of E6**

- **Degrades p53**

- Degradation of p53 blocks apoptosis

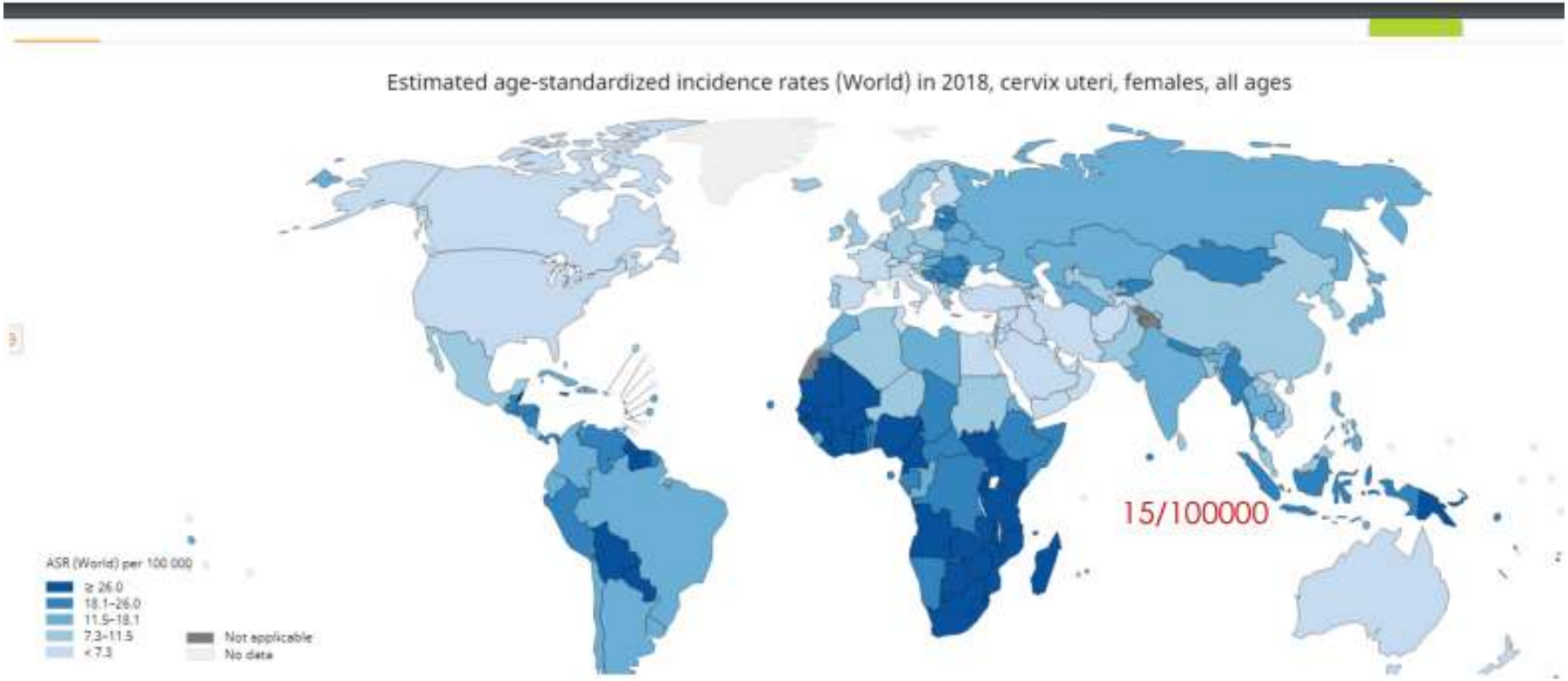
- Stimulates the expression of TERT (telomerase reverse transcriptase)

- **Oncogenic effects of E7**

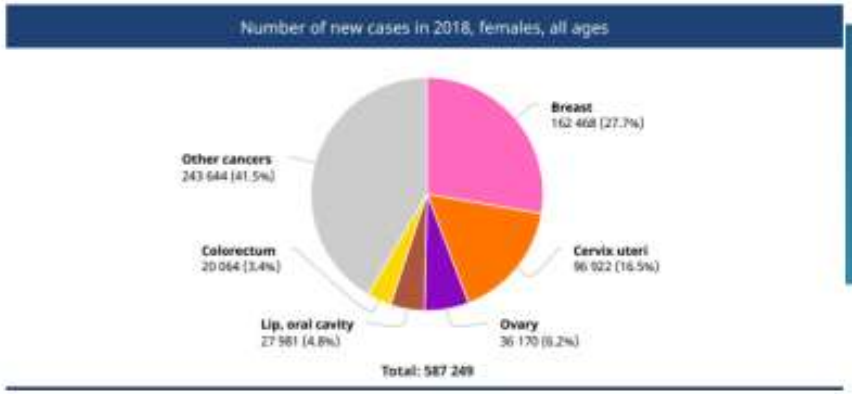
-**binds to RB protein** and removes brakes in the cell cycle

-Inactivates p21 and p27 permitting cell proliferation

-binds and activates cyclin D, E and CDK4 promoting cell proliferation

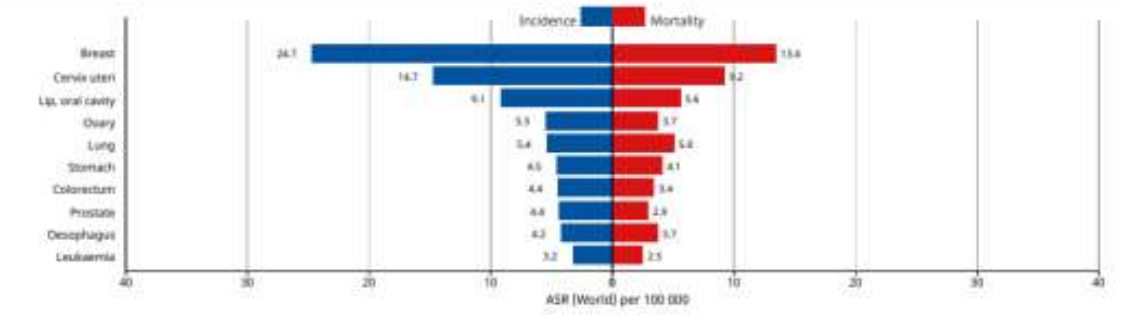


- Cervical cancer is the fourth most common cancer in women. In 2018, an estimated 570 000 women were diagnosed with cervical cancer worldwide and about 311 000 women died from the disease.
- Effective primary (HPV vaccination) and secondary prevention approaches (screening for, and treating precancerous lesions) will prevent most cervical cancer cases.



India-Statistics

- 96,922 new cases
- 60,078 deaths
- **62% mortality rate**



Rank 3 overall and Rank 2 in women

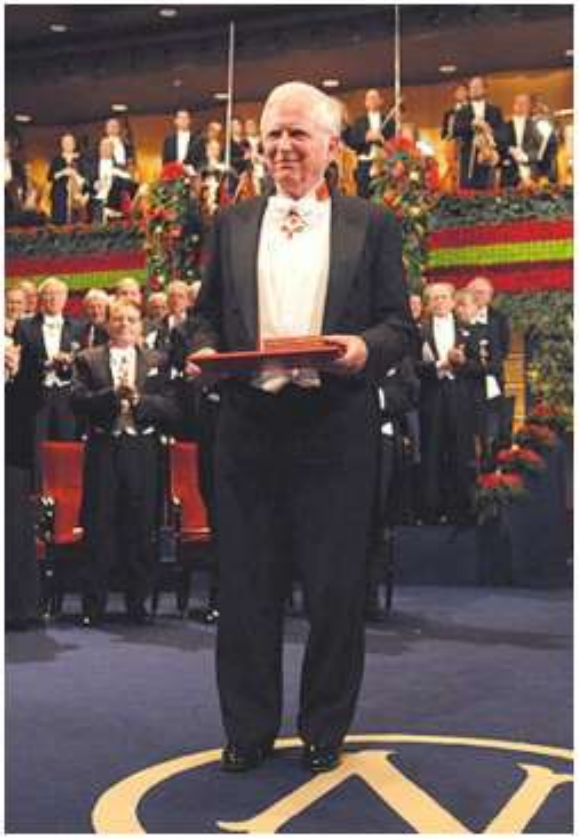
India contributes to nearly 20% of world's burden of cervical cancer

https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.p

Traditional RISK FACTORS

- Increased risk for Cervical Cancer associated with
  - Sexual activity : no. of sexual partners, early sexual activity
  - Early age at first pregnancy
  - Parity
  - Low socioeconomic class
  - Cigarette smoking
  - Immunosuppression from any cause including HIV
  - Vitamin deficiencies
  - Oral contraceptive use
  - STD: HSV
- Interval since last Pap smear

Professor zur Hausen receiving the **Nobel prize for Medicine** for his discovery of the association of **HPV with cervical cancer**

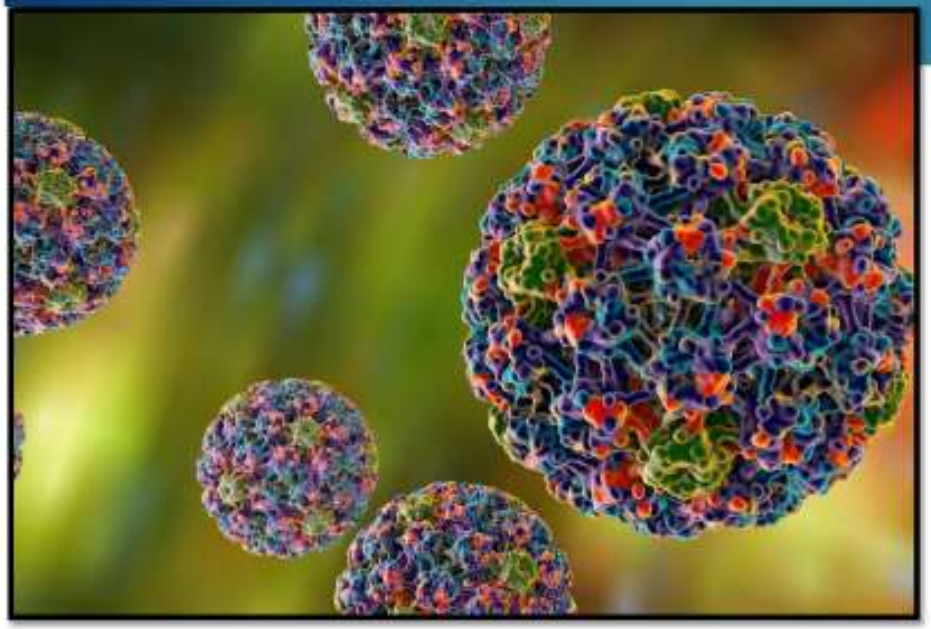


The Beginning of the Revolution….

Prof. Harald zur Hausen

- By his discovery, He changed the way we looked at Cervical Cancer!
- Cervical Cancer may be viewed as a Sexually Transmitted Infectious Disease!- a cancer caused by a viral infection!

HUMAN PAPILLOMA VIRUS



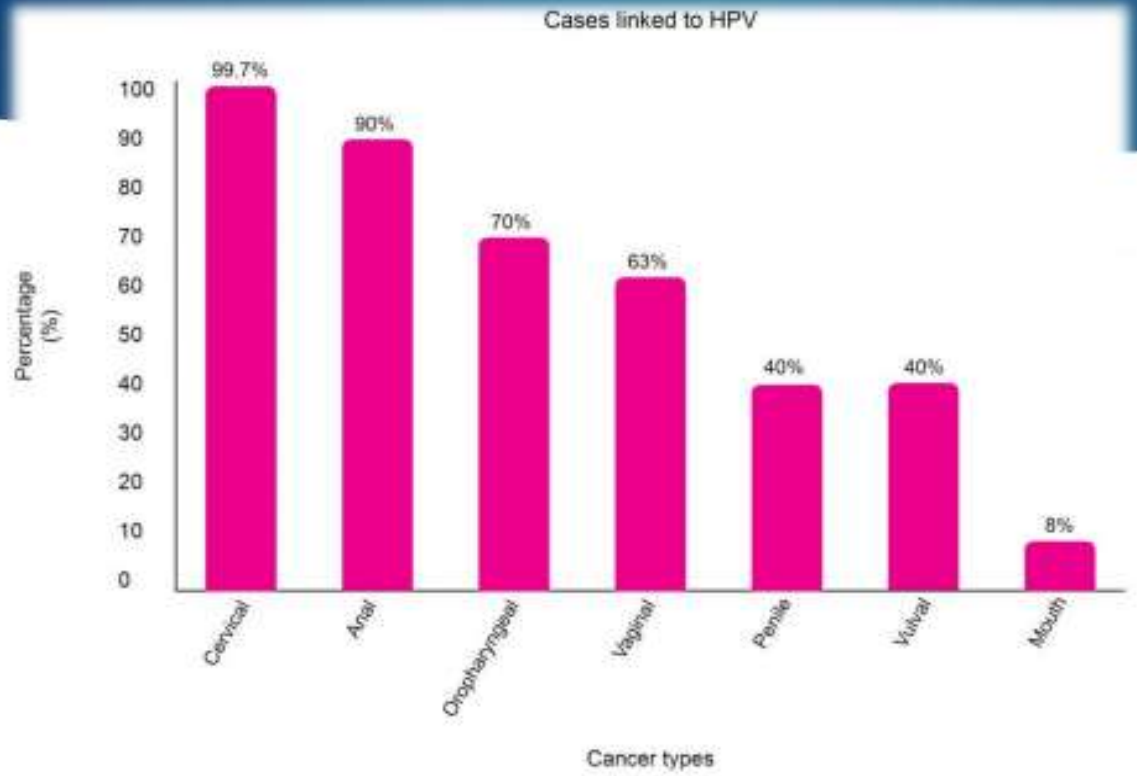
Papillomavirus are members of the family

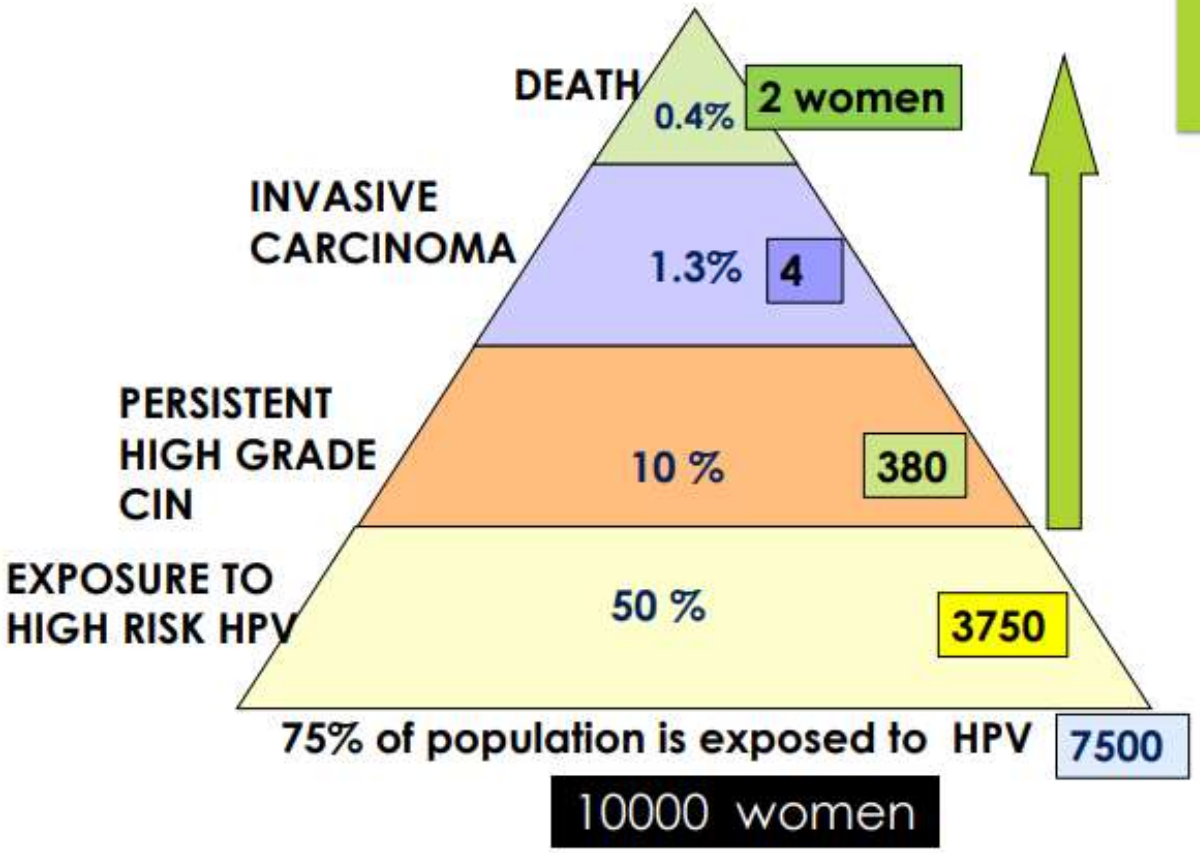
- Papillomaviridae

Double-standard DNA

Highly species specific, anatomic location specific, lesion specific virus

HPV Associated Cancers




DEATH
0.4%
2 women
INVASIVE CARCINOMA
1.3%
4
PERSISTENT HIGH GRADE CIN
10 %
380
EXPOSURE TO HIGH RISK HPV
50 %
3750
75% of population is exposed to HPV
7500
10000 women

Factors that determine progression of HPV infection

VIRAL FACTORS

- HPV type- Oncogenic Risk potential
- Viral Load- HPV DNA levels
- Time since first infection

HOST FACTORS

- Immunological
- Hormonal
- Nutritional- Vitamin deficiencies
- Smoking

ENVIRONMENTAL FACTORS

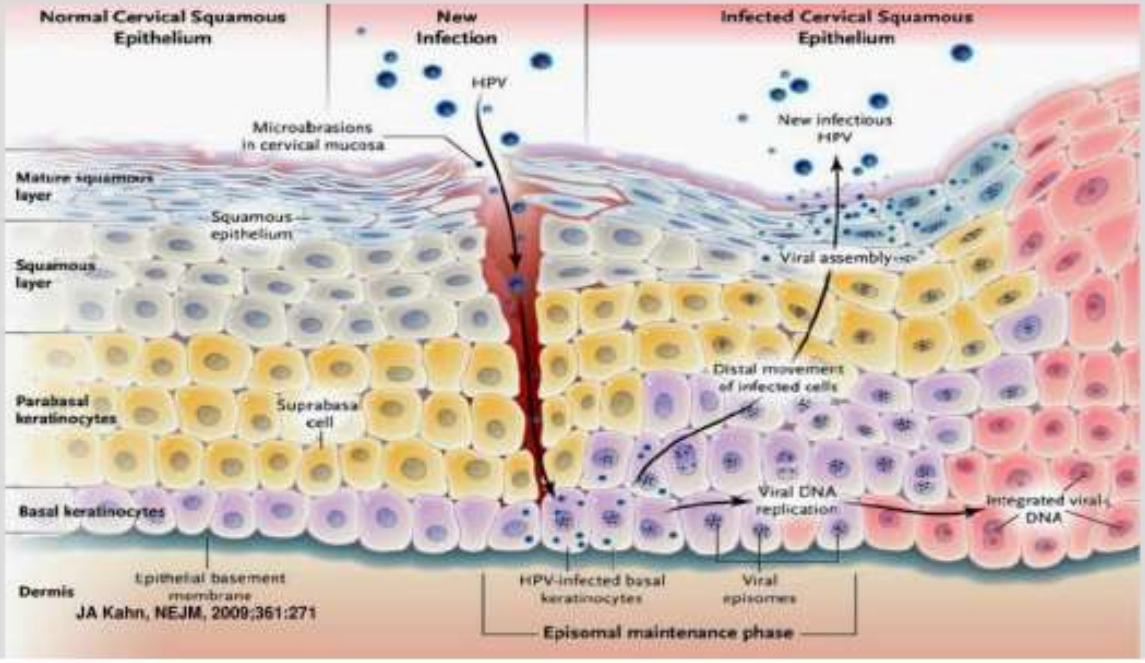
- Co-existing Infections- Microbiome

Classification of HPV on the basis of their oncogenic risk

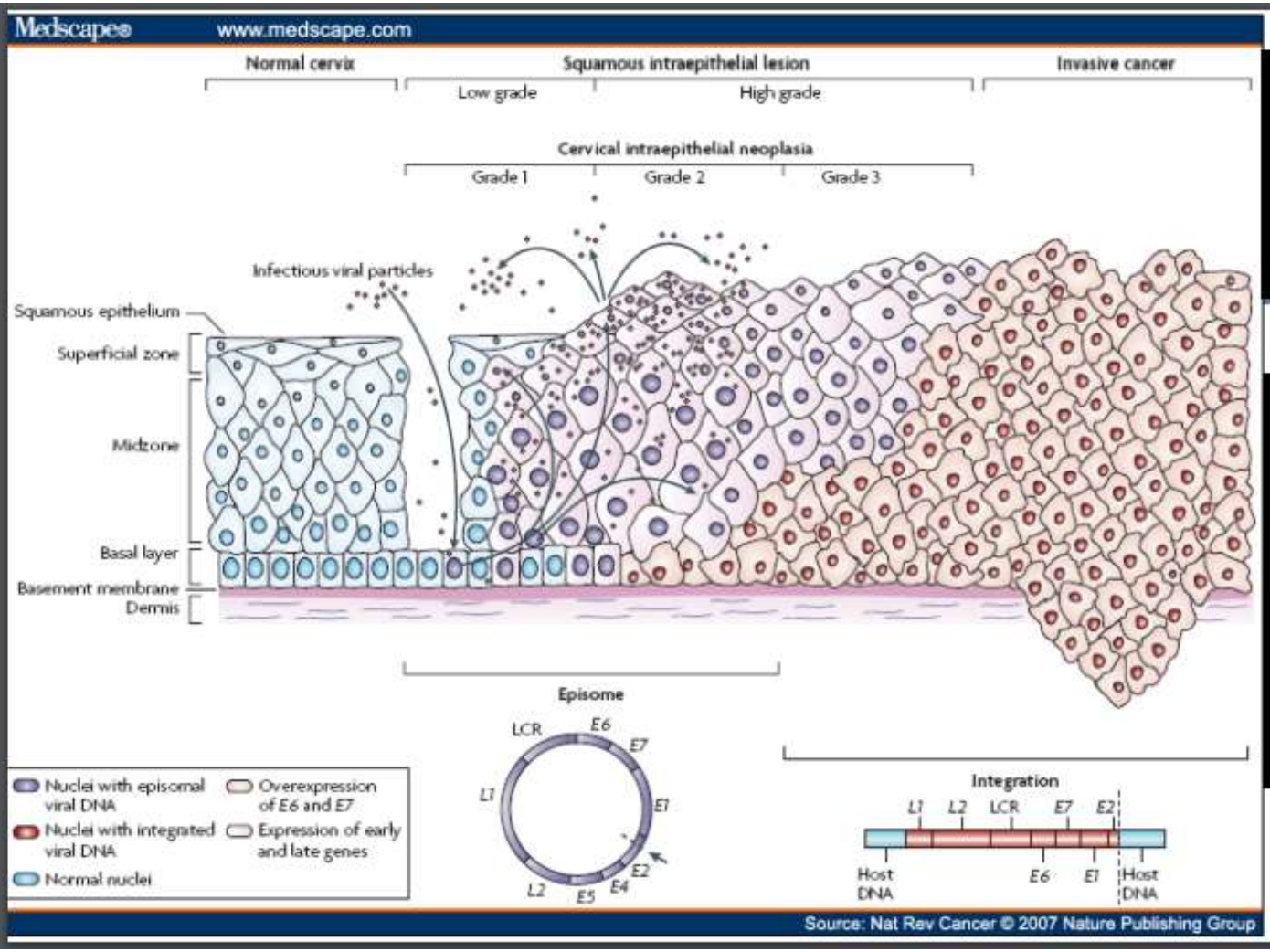
Low risk	**6,11,42,43,44,53**
High risk	**16,18,31,33,35,39,45,51,52,56,58,59,66**
Unclear risk	**26,68,73,82**

HPV16 and 18 are found in approximately 80% of invasive cervical cancers worldwide.
HPV 16 alone is found in 60-70% of cases.

The HPV Life Cycle



- HPV infection is acquired by sexual contact
- Viral particles infect the basal layer of the epithelium through a breach in the epithelium.
- This breach is usually the result of inflammatory conditions
- In basal cell, it exit in two forms:
  - Non productive infection (Latent infection)
  - Productive infection

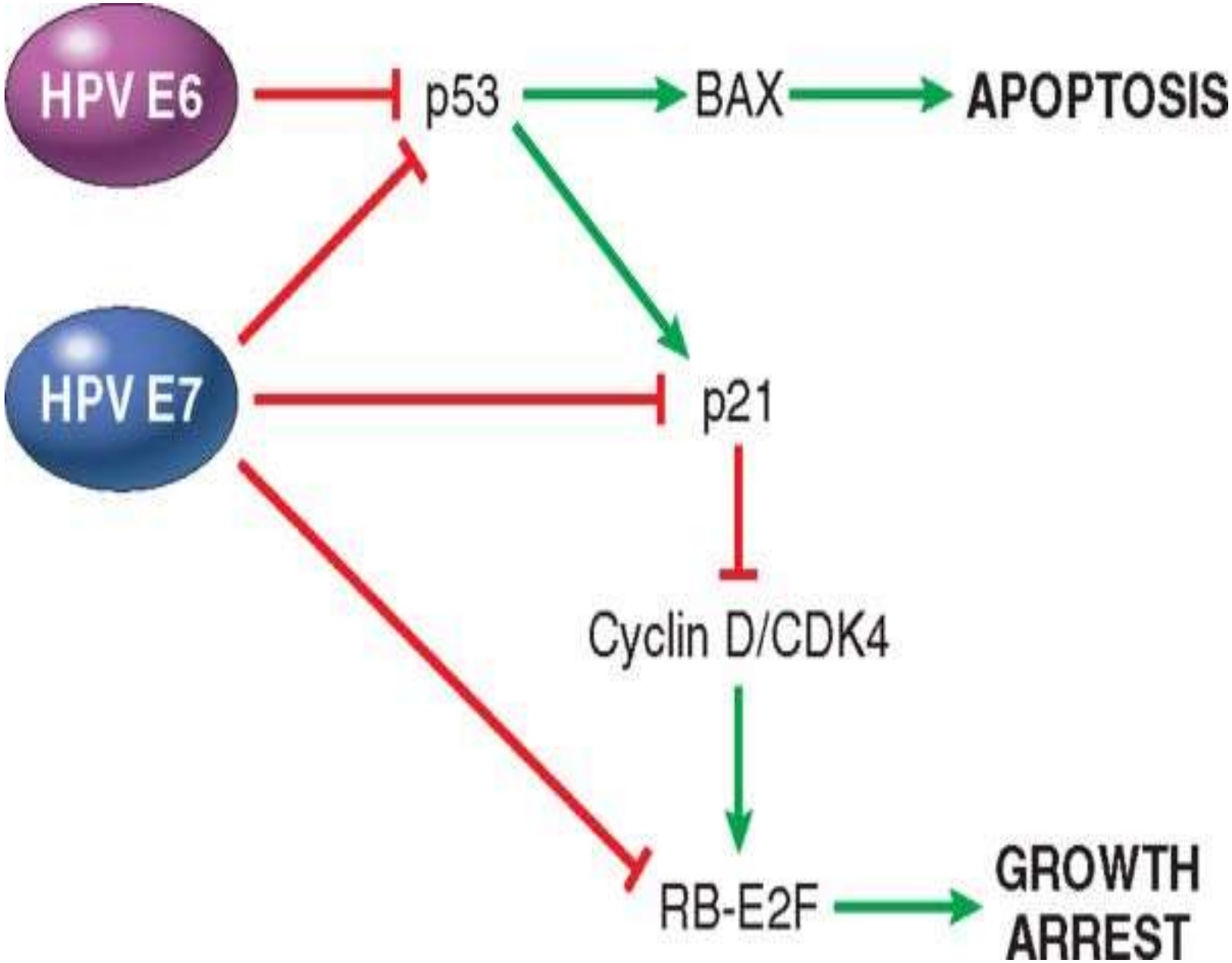


HPV induced Pathogenesis of Cervical Pre-cancer

Integration of HPV and Persistence of HPV infection are the KEY events in HPV induced Cervical carcinogenesis

Take Home Messages

- HPV is a Double stranded DNA virus belonging to the Papillomaviridae family
- HPV 16, 18, 31 are the top 3 HPV high-risk types that cause majority of carcinoma cervix
- LSIL – HPV episomal replication
- HSIL – Persistence of HR-HPV infection and Integration into cellular genome
- HSIL - True precursor of Squamous cell carcinoma cervix
- AIS- Precursor of HPV+ Adenocarcinoma cervix
- Inactivation of p53 by HPV-E6, activation of hTERT and inactivation of pRb by HPV-E7 Oncoproteins are key events
- p16 is a surrogate biomarker of HR-HPV infection
- 92-95% of Squamous cell carcinoma and 75-85% of adenocarcinoma cervix is HPV-associated


HPV E6
p53
BAX
APOPTOSIS
HPV E7
p21
Cyclin D/CDK4
RB-E2F
GROWTH
ARREST

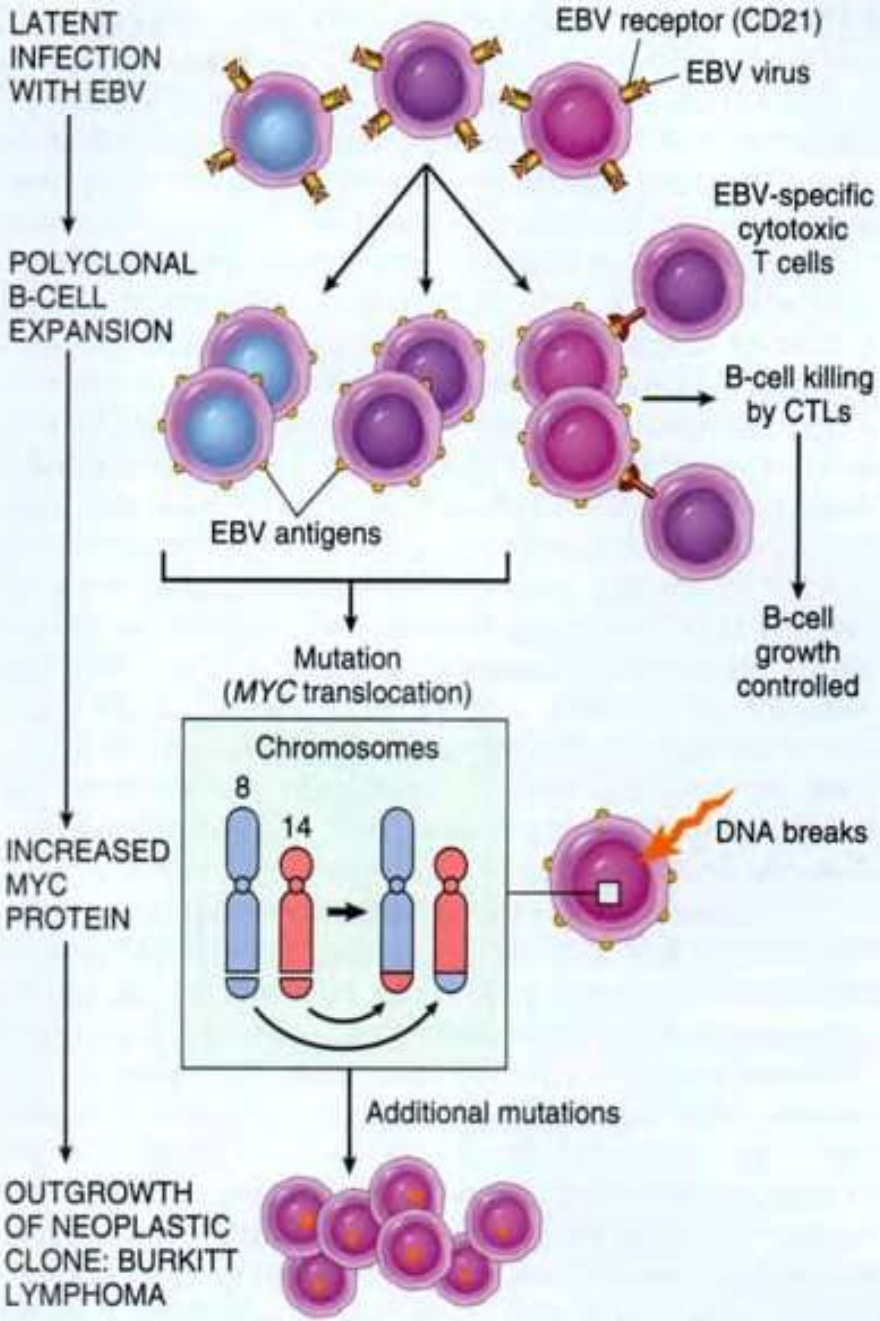


Figure 7-46 Possible evolution of EBV-induced Burkitt lymphoma.

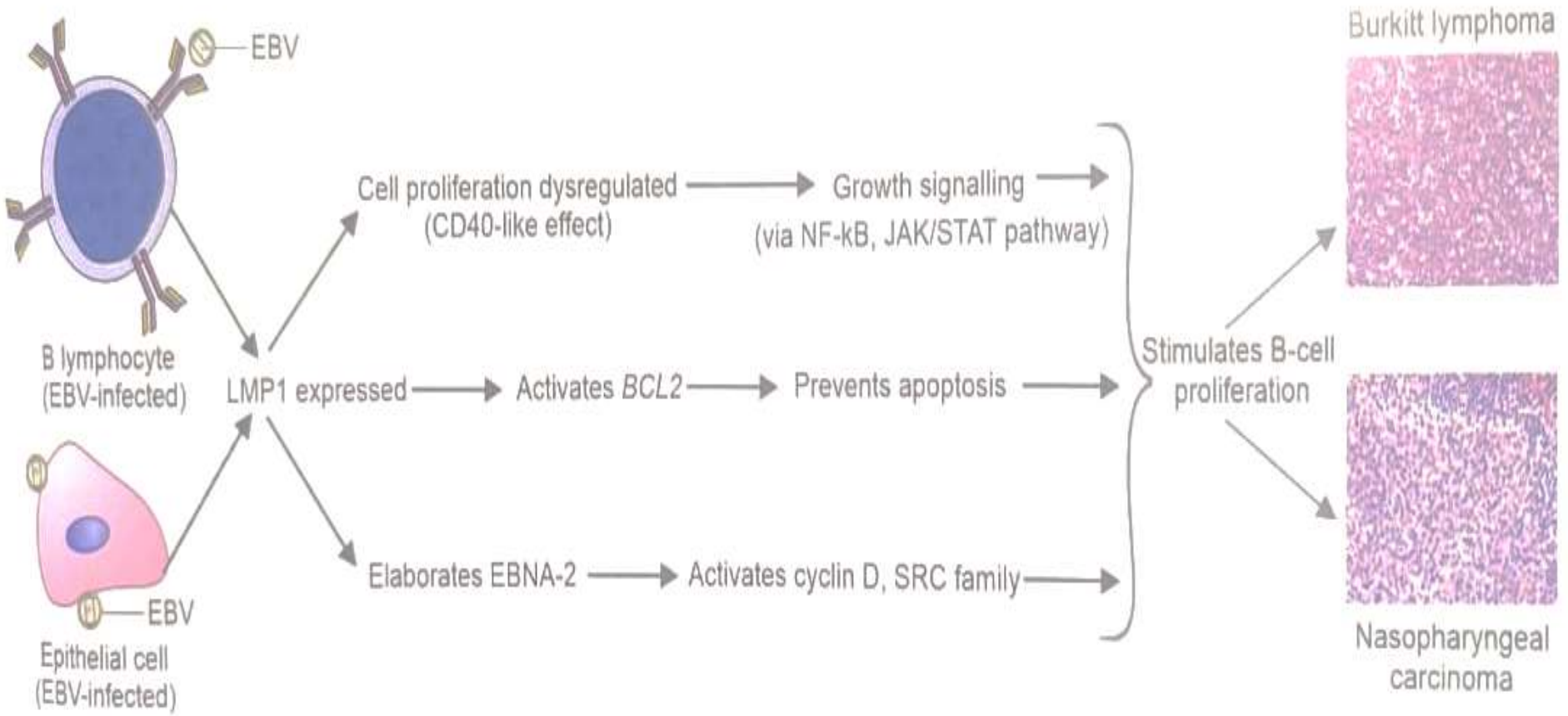


Figure 7.31 EBV-induced oncogenesis.

RNA Oncogenic Virus

Mechanism

contain reverse transcriptase enzyme (RT) which is required for reverse transcription of viral RNA to synthesize viral DNA strands.

RT is a DNA polymerase & helps to form complementary DNA that moves into host cell nucleus & get incorporated into it and may transform the cell into neoplastic cell.

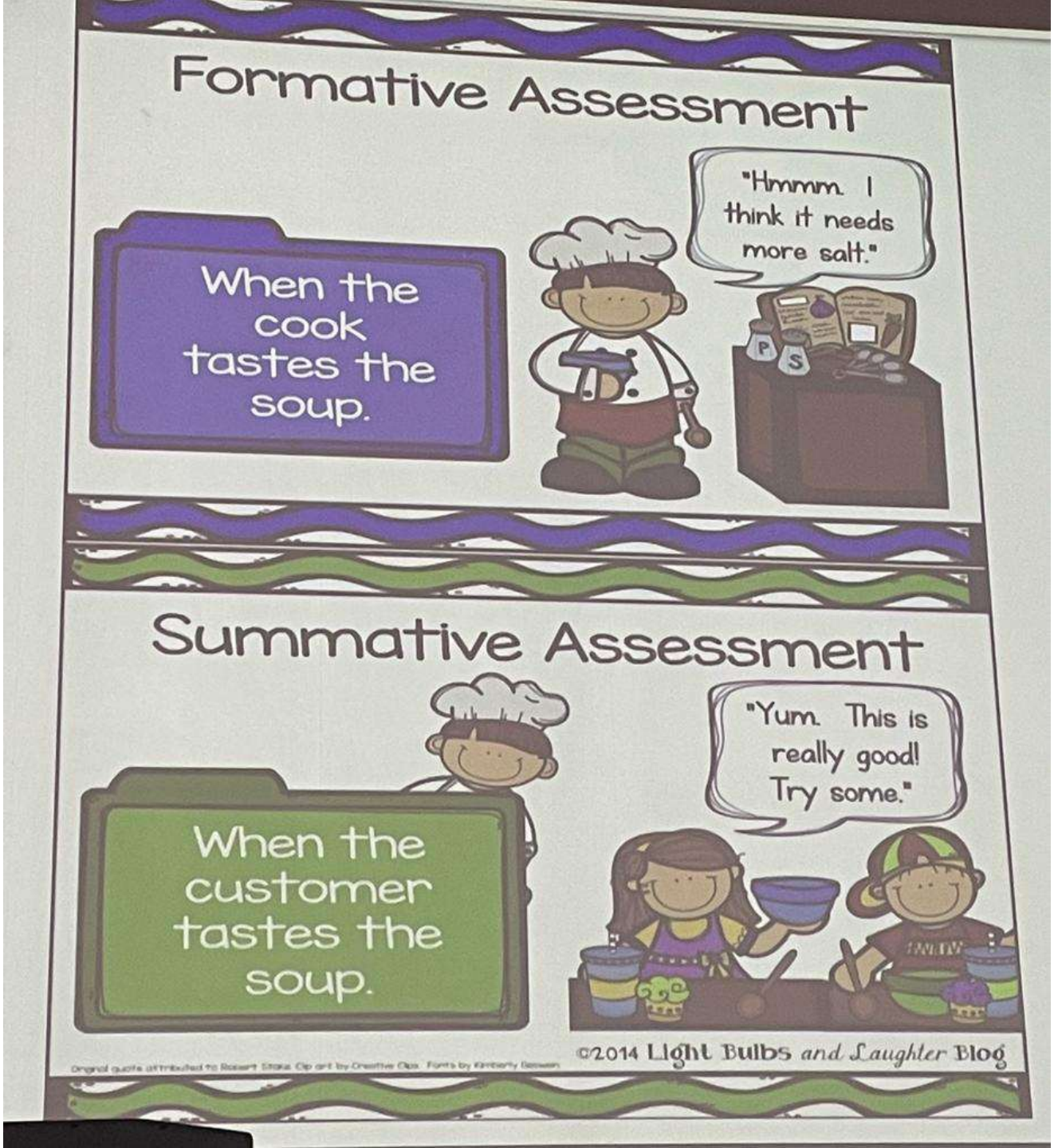
RNA VIRUS

I. Human T cell lymphocytic virus (HTLV)

a) HTLV-1 – Adult T Cell Leukemia Lymphoma

b) HTLV II – Hairy Cell Leukemia (T cell variant)

II.HCV – Hepatocellular carcinoma


Formative Assessment
When the cook tastes the soup.
"Hmmm. I think it needs more salt."
P
S
Summative Assessment
When the customer tastes the soup.
"Yum. This is really good! Try some."
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