# NEOPLASIA : 6
# MICROBIAL CARCINOGENESIS

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# Viral Oncogenesis

- Viruses contribute to the pathogenesis of human malignancies through the integration of viral genetic elements into the host DNA. These new genes are expressed by the host; they may affect cell growth or division, or disrupt normal host genes required for control of cell growth and division.
- Alternatively, viral infection may result in immune dysfunction, leading to decreased immune surveillance for early tumors.

## Oncogenic DNA Viruses :

- Human Papilloma virus(HPV)
- Epstein-Barr virus(EBV)
- Hepatitis B virus(HBV)
- Kaposi Sarcoma virus (KSV)
- Merkel cell polyomavirus(MCV)

## Oncogenic RNA Viruses :

- Human T-Cell Leukemia Virus Type-1(HTLV-1)

# DNA ONCOGENIC VIRUSES

- Genomes of oncogenic DNA viruses integrate into & form stable associations with host cell genome
- Virus unable to complete its replicative cycle
- So, virus remain in a latent state for years

Early genes those that are transcribed early in the viral life cycle are important for transformation..

# Human Papilloma Virus

- 70 types
- Types 16,18,31 – Cervical carcinoma , severe dysplasia, Ca in situ ( Oral & Laryngeal ca)
- Types 1,2,4,7 –Benign squamous papilloma
- Types 6,11 – Low malignant potential wart cervical ca & genital warts

- E6 & E7 Overexpression of viral oncoproteins
- E6 binds P53 and causes increased telomerase expression
- E7 binds RB promoting cell cycle progression and inactivates CDK Inhibitors P21 & P27
- E7-interfere with P53 transcriptional activity & also inactivate P21

To summarise, High risk HPV express oncogenic proteins that

- Inactivates tumor suppressor
- Activates cyclins
- Inhibits apoptosis
- Control cellular senescence

- Infection with HPV acts as initiating agent & additional mutations are essential for malignant transformation.

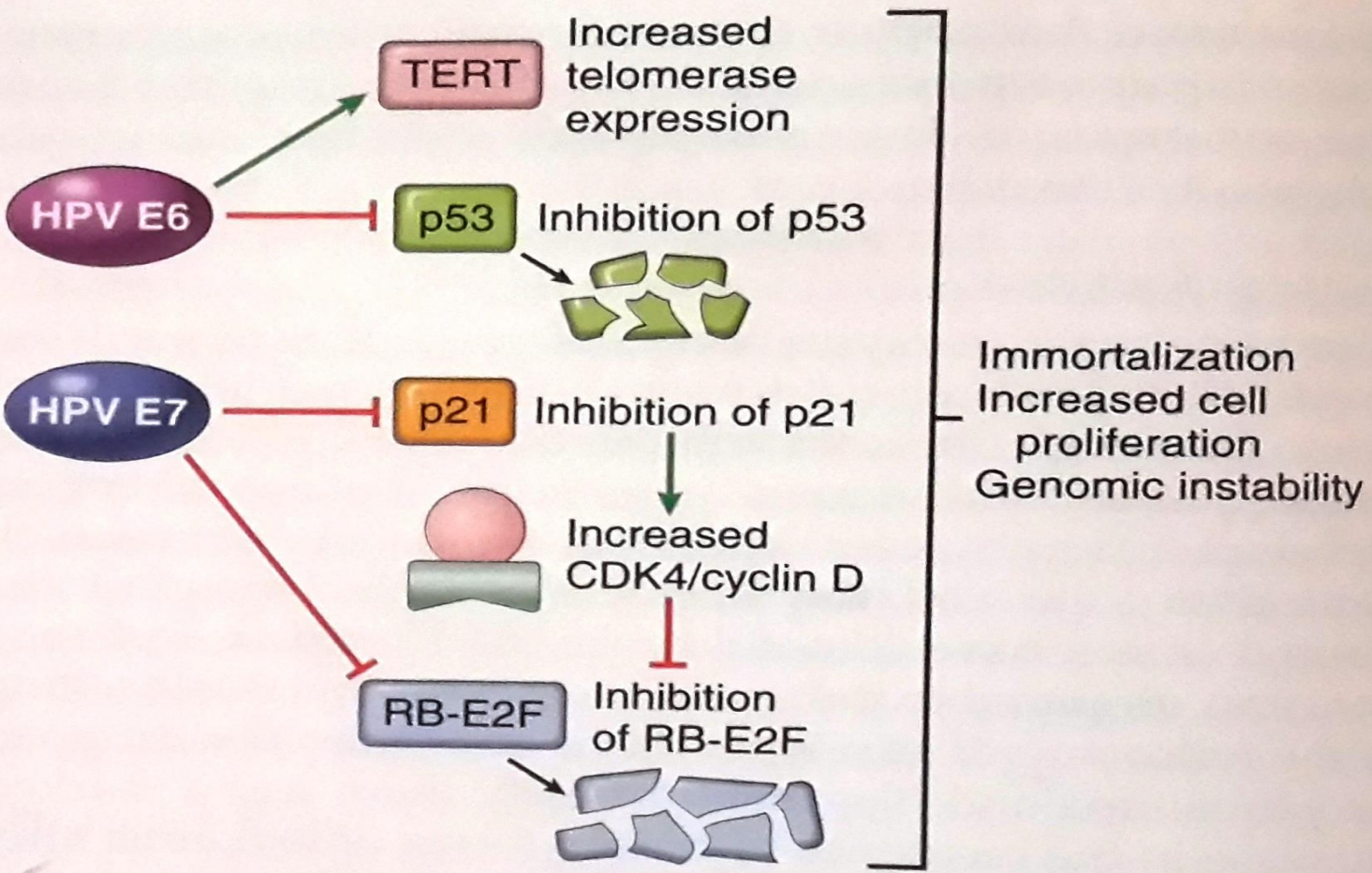
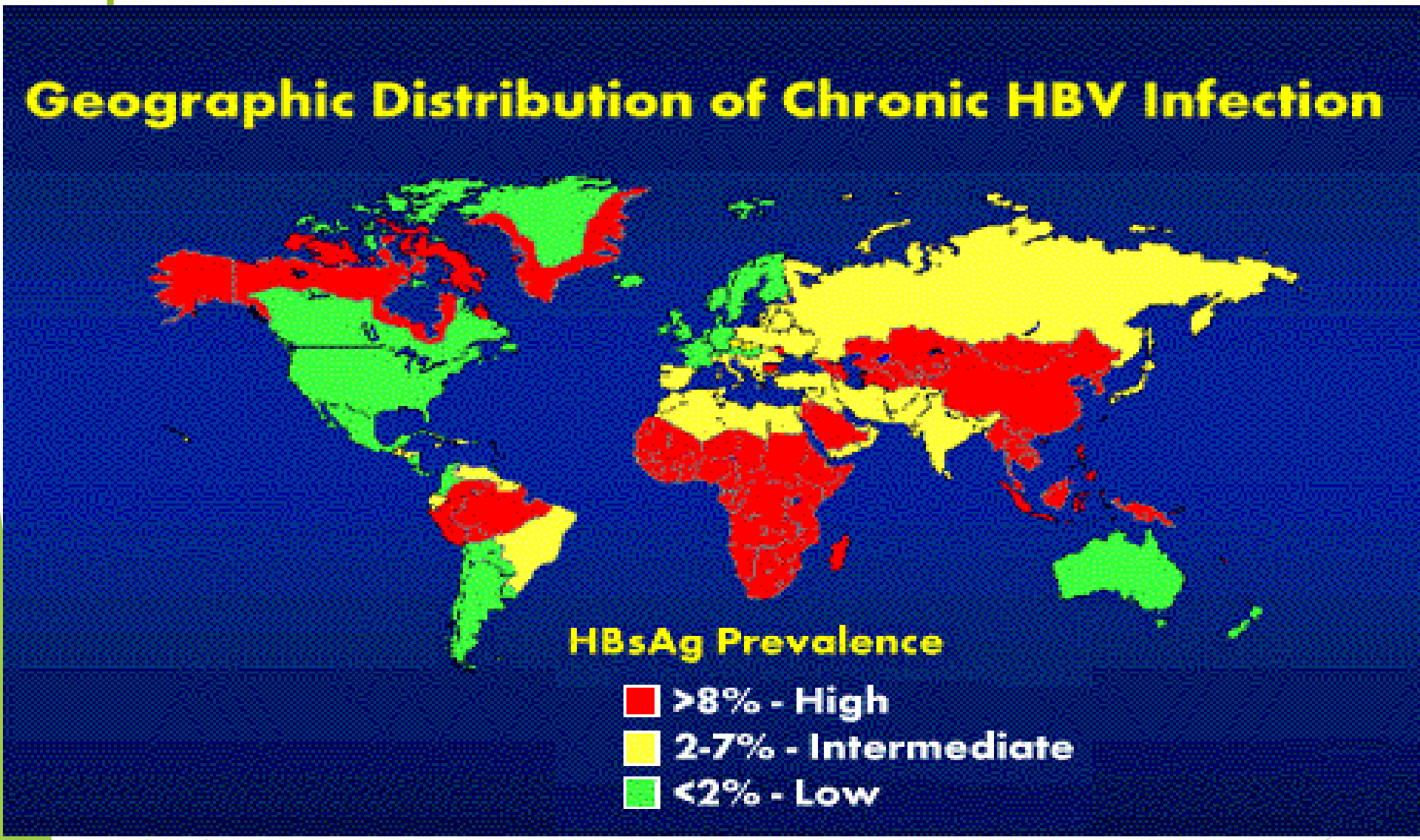



**Figure 7-45** Transforming effects of HPV E6 and E7 proteins. The net effect of HPV E6 and E7 proteins is to immortalize cells and remove the restraints on cell proliferation (see Fig. 7-29). TERC, telomerase catalytic subunit. (Modified from Münger K, Howley PM: Human papillomavirus immortalization and transformation functions. Virus Res 2002;89:213-228.)



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

# Hepatitis B virus




www.safetyline.wa.gov.au
/.../ l81_02.asp

# HEPATITIS B VIRUS

Hepadena virus family

Far East & Africa – HCC

Chronic liver injury

↓

Regenerative hyperplasia

↓

Genetic changes

↓

Environmental or dietary aflatoxins

↓

HBV encodes HBx protein

↓

Activation of growth promoting genes

↓

HBx binds to P53 interfere in growth suppressing acting

↓

HCC

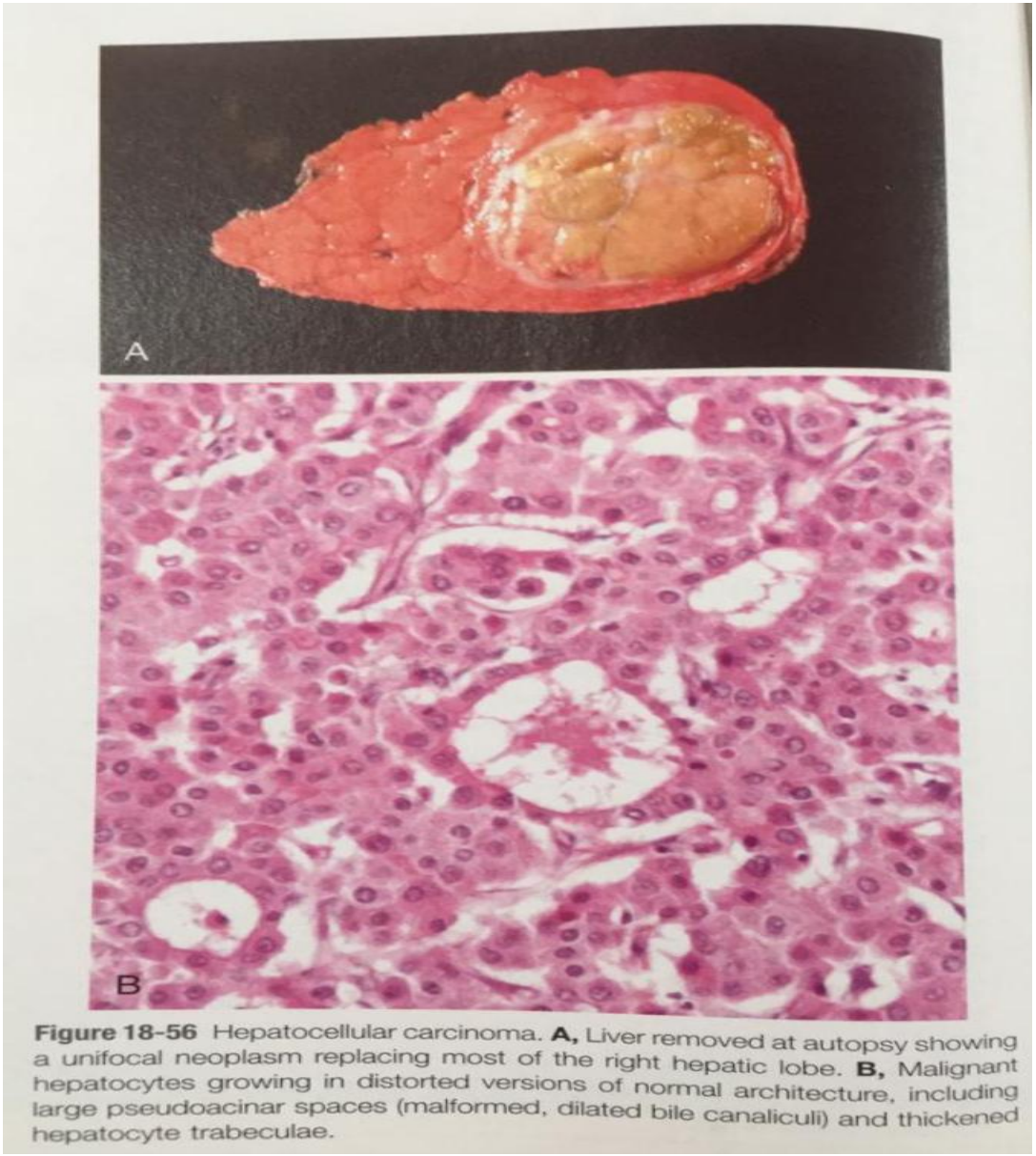



**Figure 18-56** Hepatocellular carcinoma. **A,** Liver removed at autopsy showing a unifocal neoplasm replacing most of the right hepatic lobe. **B,** Malignant hepatocytes growing in distorted versions of normal architecture, including large pseudoacinar spaces (malformed, dilated bile canaliculi) and thickened hepatocyte trabeculae.

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

# HCV Virus

- Non DNA virus
- HCV- Chronic liver injury

Cell Regeneration

Mitotically active liver cells

Altered environment

Genetic instability

Cancer development

# Epstein-Barr virus

Cause infectious mononucleosis;

associated with:

Burkitt lymphoma (endemic; childhood tumor - parts of Africa and New Guinea);

B cell lymphoma in immunosuppressed persons,

Nasopharyngeal carcinoma

Hodgkin Lymphoma

EBV infects asymptomatically almost all adults worldwide

EBV infects epithelial cell of oropharynx & B lymphocyte

- Burkitt Lymphoma- Neoplasm of B lymphocyte.
- Most common childhood tumor in central

  Africa & New Guinea  genetic & environmental factors

*More than 90 % of African tumor carry EBV genome

*100 % Pt. have increased  antibody  titers against viral capsid antigen

*Serum antibody time against viral capsid antigens correlated well with risk of developing tumor

- Virus genome entry into

  B- Lymphocyte via –CD21

  ⬇

  B-cell immortalized

  ⬇

- LMP-1 (Latent membrane protein -1)

  Binds to & activates a signalling molecule that activated by CD40 receptor on B- cell

  ⬇

B- cell survival & proliferation(Immortal B cells)

Translocation t(8 ;14 )

↓

Dysregulated expression of c- MYC oncogene

↓

Activation of MYC oncogene

↓

Other mutations

↓

Decreased recognition of cell by cytotoxic T cell

↓

Tumor progression mutation P53 or inhibitory pathway

Immunosuppressive pt. ,Pt. On Immunosuppression therapy or Aids Pt. - B cell lymphoma in lymphoid tissue or CNS lymphoma

- EBV infection is controlled by immune system
- Infected individuals remain asymptomatic or develop self- limited infectious mononucleosis
- In Africa- cofactor chronic malaria-favour sustained proliferation of B- cell

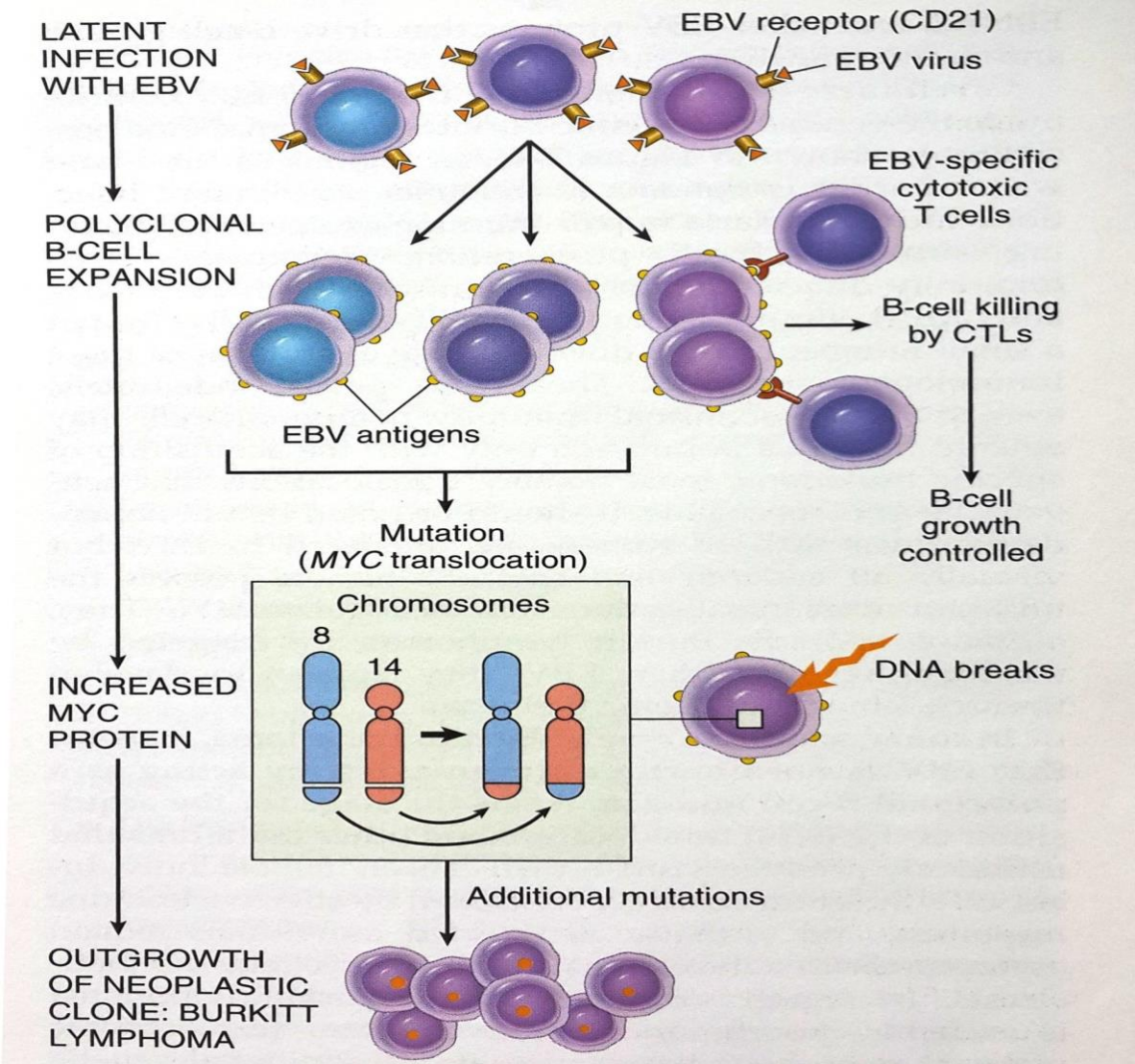



**Figure 7-46** Possible evolution of EBV-induced Burkitt lymphoma.

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

- Nasopharyngeal carcinoma- endemic in southern China & Africa
- EBV association & Nasopharyngeal ca-100 % from all parts of world
- 100 % Pt. have increased antibody titers against viral capsid antigen

# Kaposi sarcoma virus

HHV-8 virus,
common in AIDS patients
and in
transplants recipients

Agent co-infecting
homosexual men along with HIV

Soft tissue sarcoma located
below skin surface, lining of
mouth, nose or anus

# Merkel Cell Polyomavirus (MCV)

Merkel cell Cancer – aggressive skin cancer

- Merkel cells (neuroendocrine cells) found in hair follicles- basal layer of epidermis, involved in the sensation of touch

# Oncogenic RNA Viruses

**Rous sarcoma virus**


1909 Rockefeller Institute

Chicken sarcoma could be "transferred"
into a healthy chicken by grafting tumor cells.

Cell-free filtrates from the tumor
also led to sarcomas in healthy chickens.
By 1914, Rous's laboratory had discovered
three distinct types of avian sarcomas.
Virus = “filterable agent”

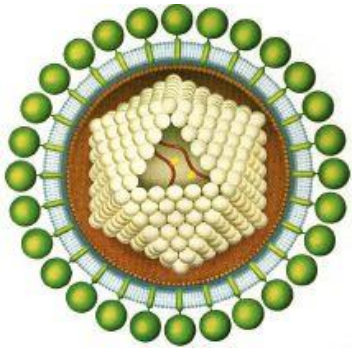
Peyton Rous

1966 –Nobel Prize
“for his discovery
of tumor-inducing viruses"

Born Baltimore
(Maryland)
1866-1970

# Human Adult T-cell leukemia viruses HTLV-1 and HTLV-2

- **HTLV-1** (human T-cell leukemia virus)



-- is sexually transmitted;

-- endemic to Japan, Caribbean

-- causes **Adult T-cell leukemia/ Lymphoma**

(Sezary T-cell leukemia);

**HTLV-2**

-- T variant of hairy cell leukemia;

-- Native American populations seroprevalence is over 50%.



www.showa.gunma-u.ac.jp/. ../bp1-4/tsld014.htm

Similar to AID HTLV-1

Tropism for CD4 +T cell

Tax region of virus → Tax protein

↓

enhances growth factor IL-2

↓

Inactives inhibitor

↓

Enhances cyclin D activation

↓

Genomic instability

↓

DNA damage

Expansion of nonmalignant polyclonal cell population due to Tax protein induces MONOCLONAL Cell population supervenes….

# 4. Bacterial and parasitic carcinogenesis

- 1. Helicobacter pylori

  Gastric adenocarcinoma

  and lymphomas

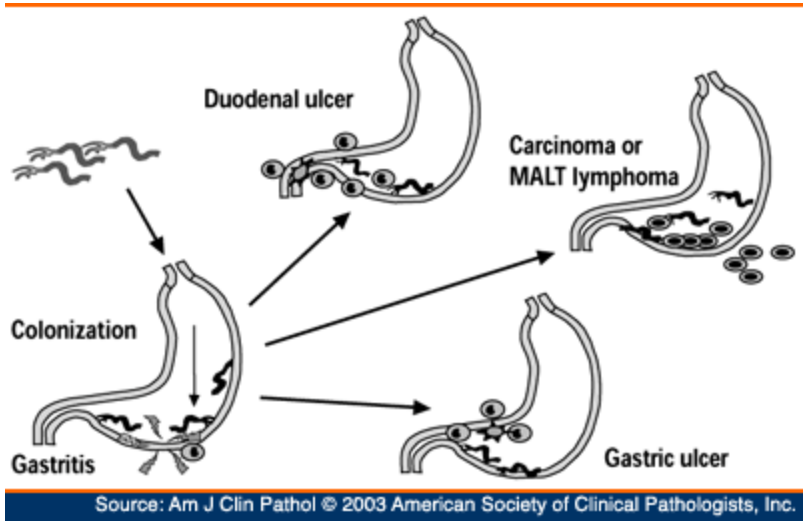
- 2. Schistosomiasis

  and bladder carcinoma

# Helicobacter pylori is linked to gastric adenocarcinoma (intestinal type) and MALToma

Both cellular and humoral immune responses are activated but the bacteria still manage to persist lifelong unless eradicated with antibiotics.

# Outcomes of H.pylori infection




Infected persons have a 2- to 6-fold increased risk of developing gastric tumor

# Helicobacter pylori

- Gastric adenocarcinoma of intestinal type
- Gastric lymphoma MALTOMA
- Cag A- cytotoxin associated gene A
- Vac A- Vacuolating toxin that causes apoptosis

chronic gastritis

↓

Multifocal atrophy with low gastric acid secretion

↓

Intestinal metaplasia

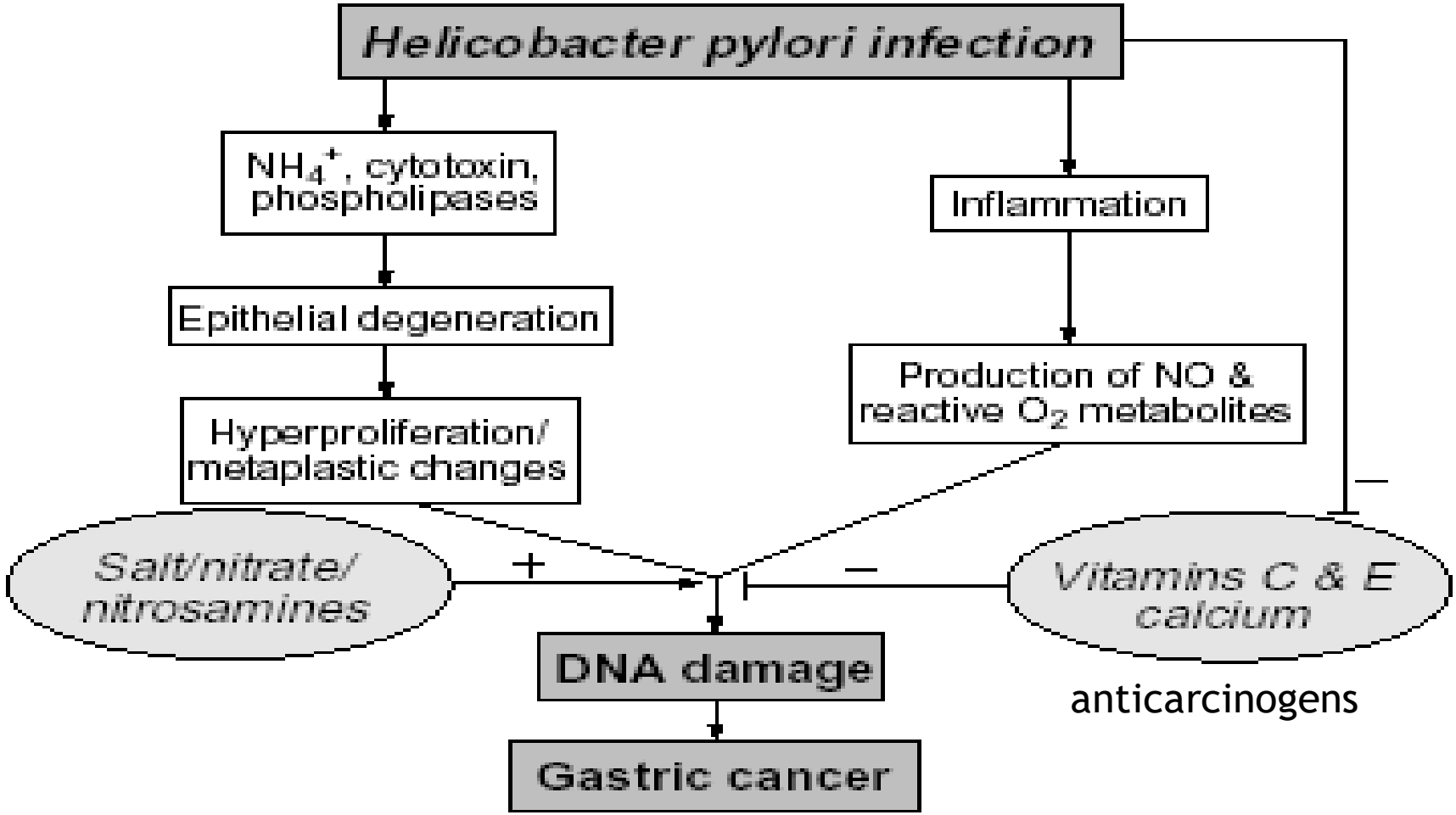
↓

Dysplasia

↓

carcinoma

# Mechanisms of gastric carcinoma induction by H.Pylori




Dr. Falguni Shah

MANFRED STOLTE, ALEXANDER MEINING " The Oncologist"

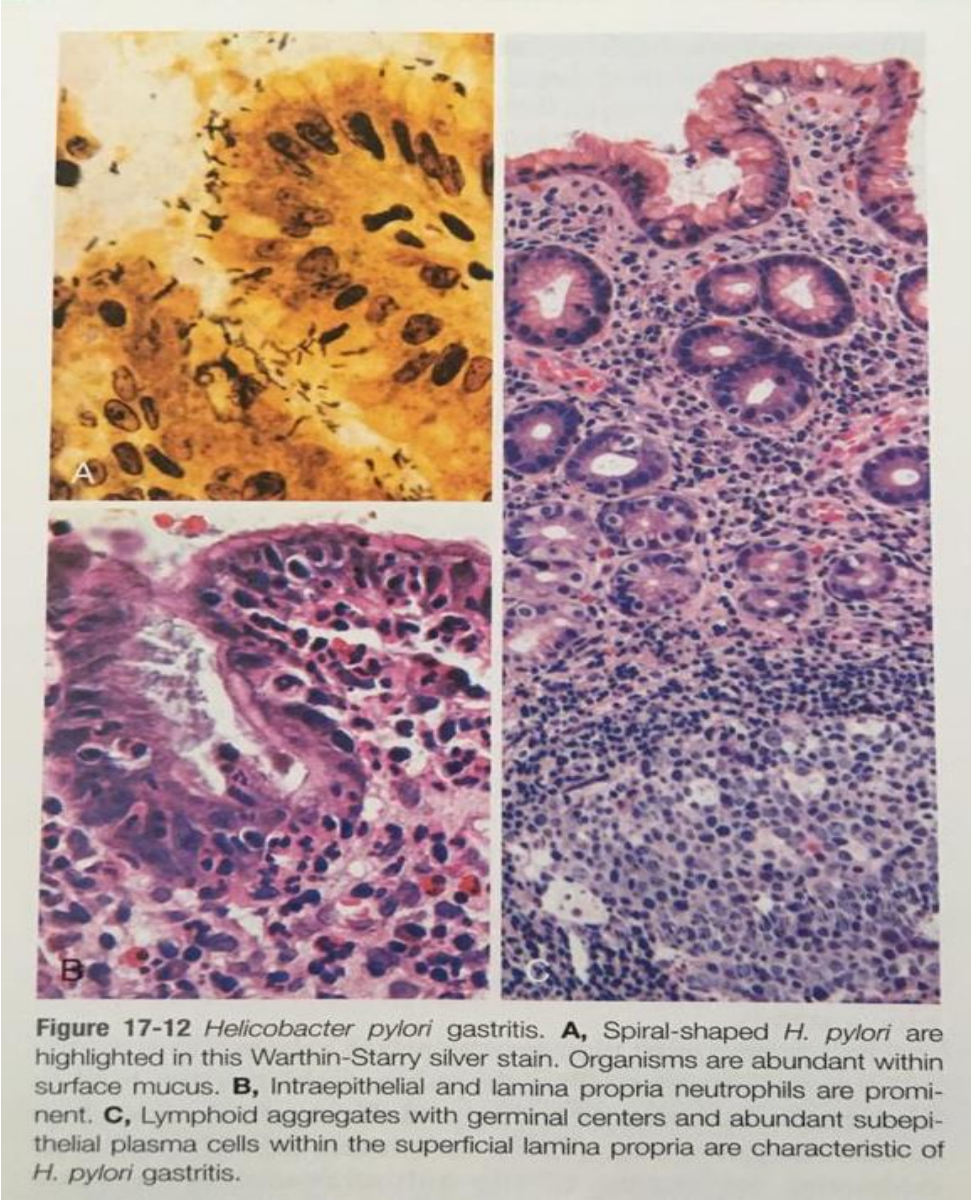



**Figure 17-12** *Helicobacter pylori* gastritis. **A,** Spiral-shaped *H. pylori* are highlighted in this Warthin-Starry silver stain. Organisms are abundant within surface mucus. **B,** Intraepithelial and lamina propria neutrophils are prominent. **C,** Lymphoid aggregates with germinal centers and abundant subepithelial plasma cells within the superficial lamina propria are characteristic of *H. pylori* gastritis.



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

- Gastric lymphoma-MALTOMAS

Chronic infection

↓

B-cell actively proliferate

↓

Genetic abnormalities

↓

t(11; 18) translocation

Initially growth dependent on immune stimulation by H.Pylori but later stages no longer requires bacteria

# MALToma

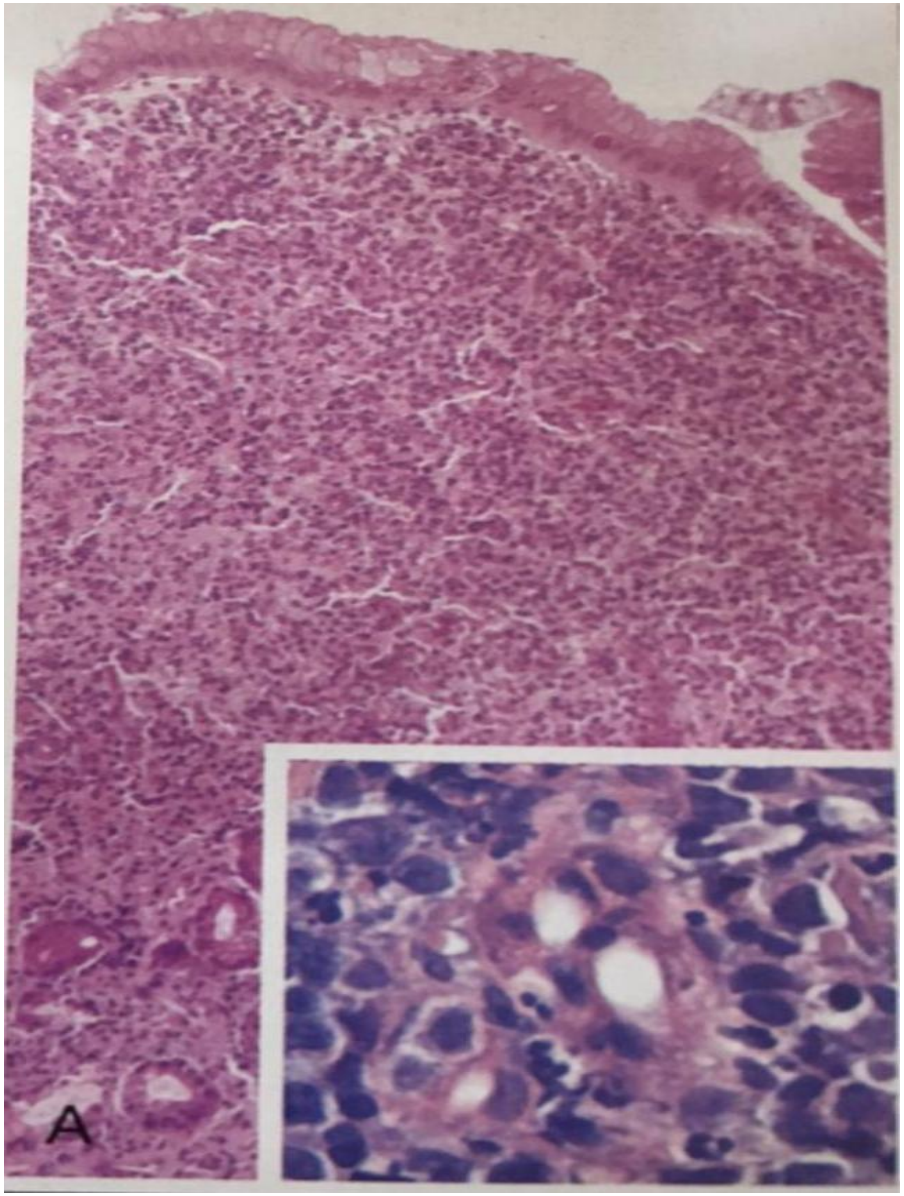



Figure courtesy reference :
Robbins & Cotran,
Pathologic Basis of Disease,
South Asia Edition, 2017

# Schistosomiasis

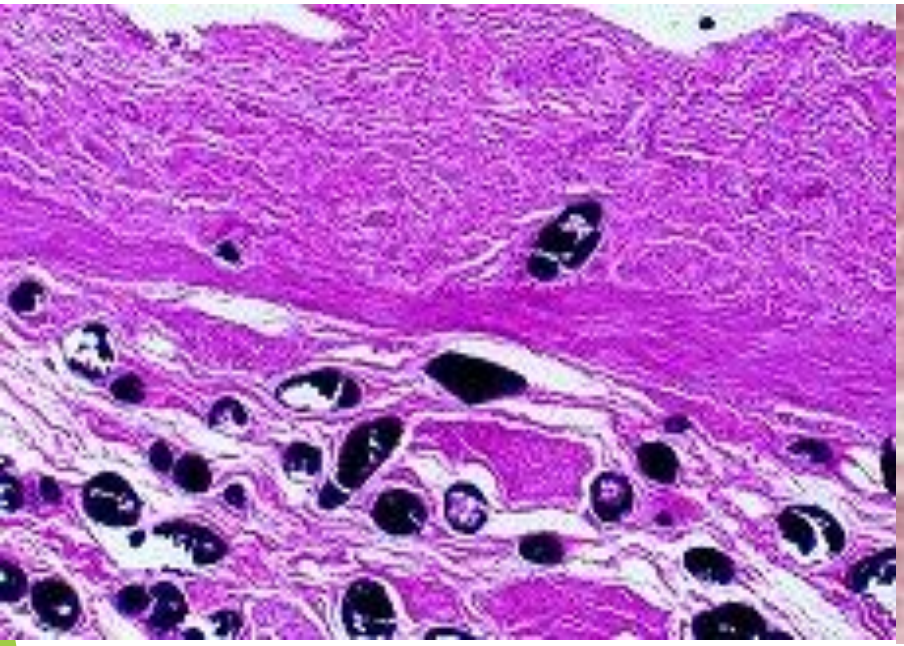
- *Schistosoma mansoni (intestinal)*
- *S haematobium (urinary)*
- *S. japonicum (intestinal)*
- *S. mekongi (intestinal)*
- *S. intercalatum (intestinal)*

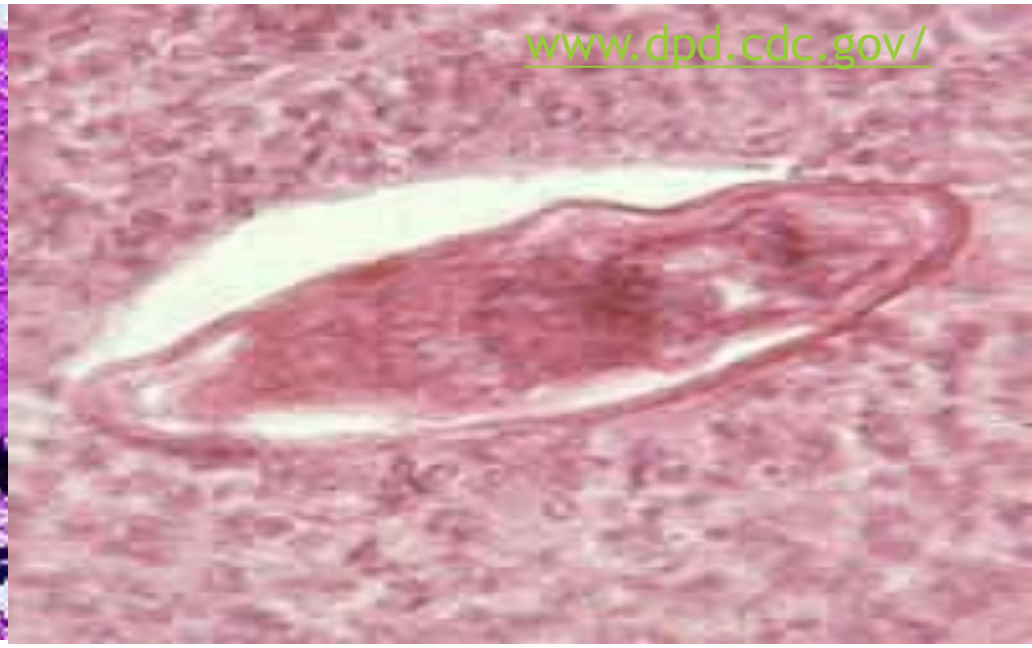
Fresh water snail is an intermediate host.

On contact with humans, the parasite burrows into the skin,
matures into another larval stage (schistosomula),
then migrates to the lungs and liver
(where it matures into the adult form).

The adult worm then migrates to the intestine, liver or bladder

# In Egypt, **schistosomiasis** linked with **cancer** is the primary cause of death among men aged 20 - 44.






Cross-section of different human tissues showing *Schistosoma* sp. eggs.

*Schistosoma* sp. in bladder and liver, respectively



http://www-micro.msb.le.ac.uk/224/Schisto.html

# 5. Inflammatory carcinogenesis

ALL Pro-inflammatory agents are tumor promoters

Anti-inflammatory agents
can reverse action of tumor promoters

Anti-inflammatory steroids (dexamethasone) and
COX inhibitors such as indomethacin etc.

**Table 7-4** Chronic Inflammatory States and Cancer

| Pathologic Condition | Associated Neoplasm(s) | Etiologic Agent |
|---|---|---|
| Asbestosis, silicosis | Mesothelioma, lung carcinoma | Asbestos fibers, silica particles |
| Inflammatory bowel disease | Colorectal carcinoma | |
| Lichen sclerosis | Vulvar squamous cell carcinoma | |
| Pancreatitis | Pancreatic carcinoma | Alcoholism, germline mutations (e.g., in the trypsinogen gene) |
| Chronic cholecystitis | Gallbladder cancer | Bile acids, bacteria, gallbladder stones |
| Reflux esophagitis, Barrett esophagus | Esophageal carcinoma | Gastric acid |
| Sjögren syndrome, Hashimoto thyroiditis | MALT lymphoma | |
| Opisthorchis, cholangitis | Cholangiocarcinoma, colon carcinoma | Liver flukes (*Opisthorchis viverrini*) |
| Gastritis/ulcers | Gastric adenocarcinoma, MALT lymphoma | *Helicobacter pylori* |
| Hepatitis | Hepatocellular carcinoma | Hepatitis B and/or C virus |
| Osteomyelitis | Carcinoma in draining sinuses | Bacterial infection |
| Chronic cervicitis | Cervical carcinoma | Human papillomavirus |
| Chronic cystitis | Bladder carcinoma | Schistosomiasis |

Adapted from Tlsty TD, Coussens LM: Tumor stroma and regulation of cancer development. Ann Rev Pathol Mech Dis 2006;1:119.



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