BIOMEDICAL IMPORTANCE

- **Cancers** constitute the **second most common cause of death**, after cardiovascular disease, in many countries
- Humans of all ages develop cancer, and a wide variety of organs are affected
- Worldwide, the main types of cancer accounting for mortality are those involving **lung,stomach,colon,rectum,liver and breast**
- Other type of cancers that lead to death include **cervical,esophageal and prostate cancer**
- The **incidence** of many cancers **increases with age**

SOME GENERAL COMMENTS ON NEOPLASM

Tumor

- **Cellular mass** formed due to **uncontrolled proliferation of cells** is called a tumor

Benign Tumors

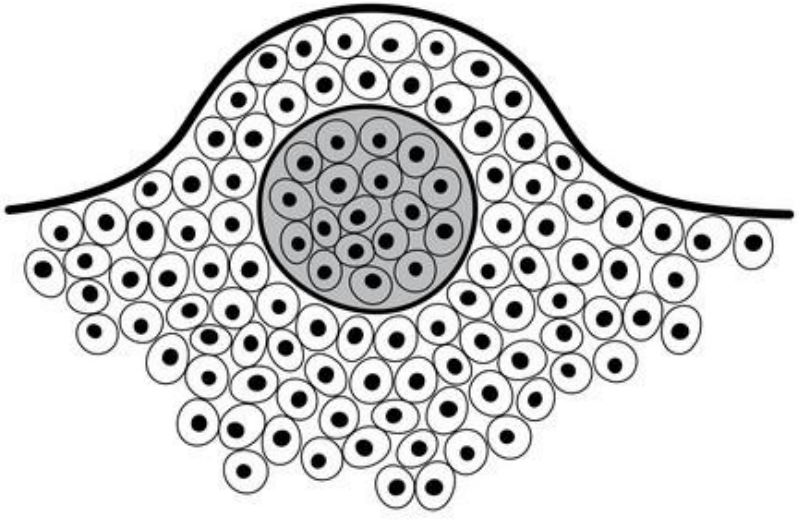
- Grow very slowly
- Remain **localized** with **well defined boundary**
- Do not invade the surrounding tissues
- Do not spread to distant organs
- Generally harmless, bad effects ,if any ,are due to pressure effects on surrounding tissues
- Once removed, they do not recur

Malignant Tumors

- Grow rapidly
- **Spread and invade the surrounding tissues as well as distant organs**
- Have great propensity for recurrence even after removal

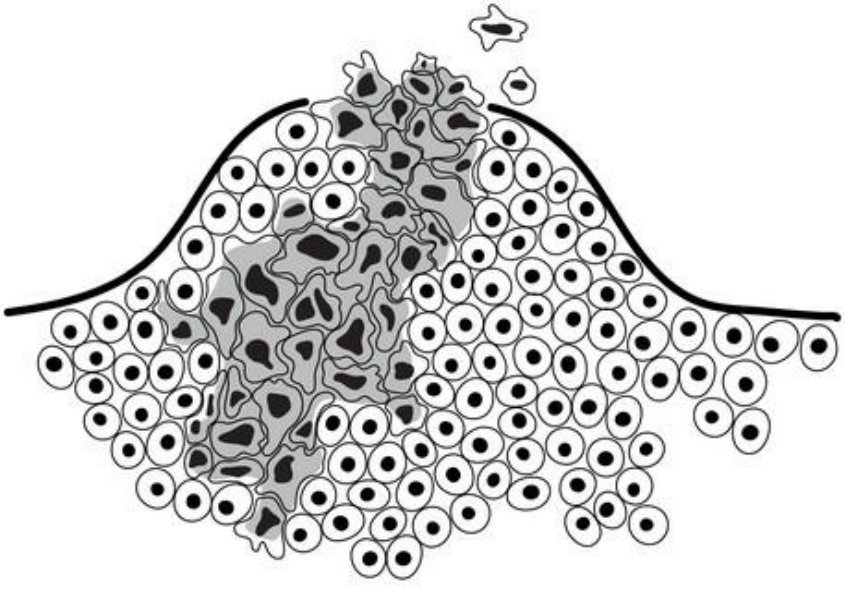
Cancer

Cancer refers to malignant tumors only



Benign tumor

- Non-cancerous
- Capsulated
- Non-invasive
- Slow growing
- Do not metastasize (spread) to other parts of the body
- Cells are normal

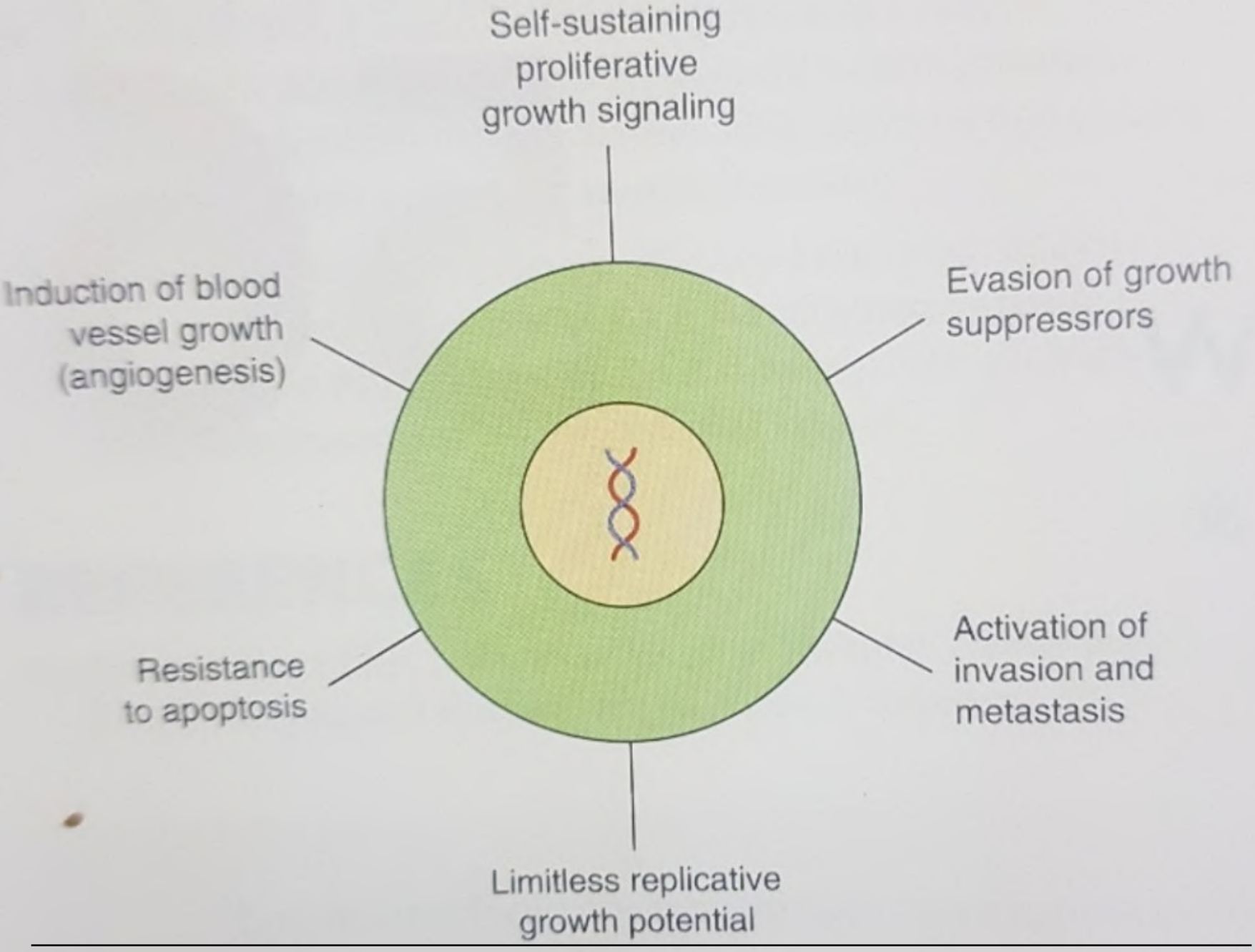


Malignant tumor

- Cancerous
- Non-capsulated
- Fast growing
- Metastasize (spread) to other parts of the body
- Cells have large, dark nuclei; may have abnormal shape

Properties of cancerous cell

- Loss of shape
- Loss of contact inhibition
- Loss of anchor support
- Diminished requirement of nutrients and growth factors
- Cancer cells become immortal



Biochemical changes in Cancer Cells

- Increased DNA replication and transcription
- Alteration in expression of cell surface molecules and cytoskeleton components
- **Increased rate of anaerobic glycolysis even in the presence of oxygen could be due to :**
- 1. cancer cell have less no of mitochondria and have an **isoenzyme hexokinase II** that does not respond to feedback inhibition
- 2.Cancer cells are also known to have different pyruvate kinase isoenzyme called **PK-2**
- 3.Despite angiogenesis solid tumors have **localized area of poor blood supply leading to anoxia**

- Mitochondria in cancerous cell produce **reactive oxygen species which can damage the DNA**
- Normal role of mitochondria in **apoptosis** may be altered due to damage
- **Alteration in antigen expression** occurs with loss of some old ones and appearance of new antigens
- Often foetal protein are expressed such as **alpha-fetoprotein or CEA**

Etiology of Cancer

- The exact etiology is not known
- No single agent or factor is responsible for causing the cancer
- Many factors are involved in causation of cancer such as **environmental, nutritional, genetic ,etc.**

DNA damage is central to the cancer development

- All cancers originate from a single cell which becomes abnormal and goes on to proliferate indefinitely to produce cancer
- Even though exact mechanisms leading to continued proliferation of a cell resulting in a tumor formation is not known in all cancers, it is established that DNA damage is seen in all cancers
- 1.A cancerous cell divides and produces only a cancerous cell
- 2.Abnormal chromosomes have been demonstrated in some cancers e.g. CML
- 3.DNA from cancer cells can transform a normal cell into malignant cell
- 4.DNA damaging agents have been shown to produce mutations leading to cancers

- Genetic damage causing cancer can be due to **acquired**, or **inherited mutations**
- Acquired mutations occur either by errors in DNA replication or DNA repair, and are termed **replication mutation**, or by exposure to **environmental mutations**
- The third major class of oncogenic mutation are termed **hereditary mutation**; inherited mutations are derived from one or both parents
- These mutations are found in specific genes (e.g. **tumor suppressor genes; DNA repair genes,cell cycle control genes**)present in germ cells
- **Spontaneous mutations**, some of which may predispose to cancer, occurs at a frequency of approximately 10^{-7} to 10^{-6} per cell per generation

- This rate increases rapidly in dividing cells which accumulate with increasing age

- **Oxidative stress**, generated as a result of enhanced production of **ROS ,**may also be a factor in increasing mutation rates

Carcinogens

- Many agents can cause cancers are called **carcinogens**

- Carcinogens could be any of the following:
- **Physical Carcinogen**
- Radiations like **X-rays,ultra-violet rays and γ-rays**
- **Chemical Carcinogen**

- **Biological Carcinogen:oncogenic viruses**

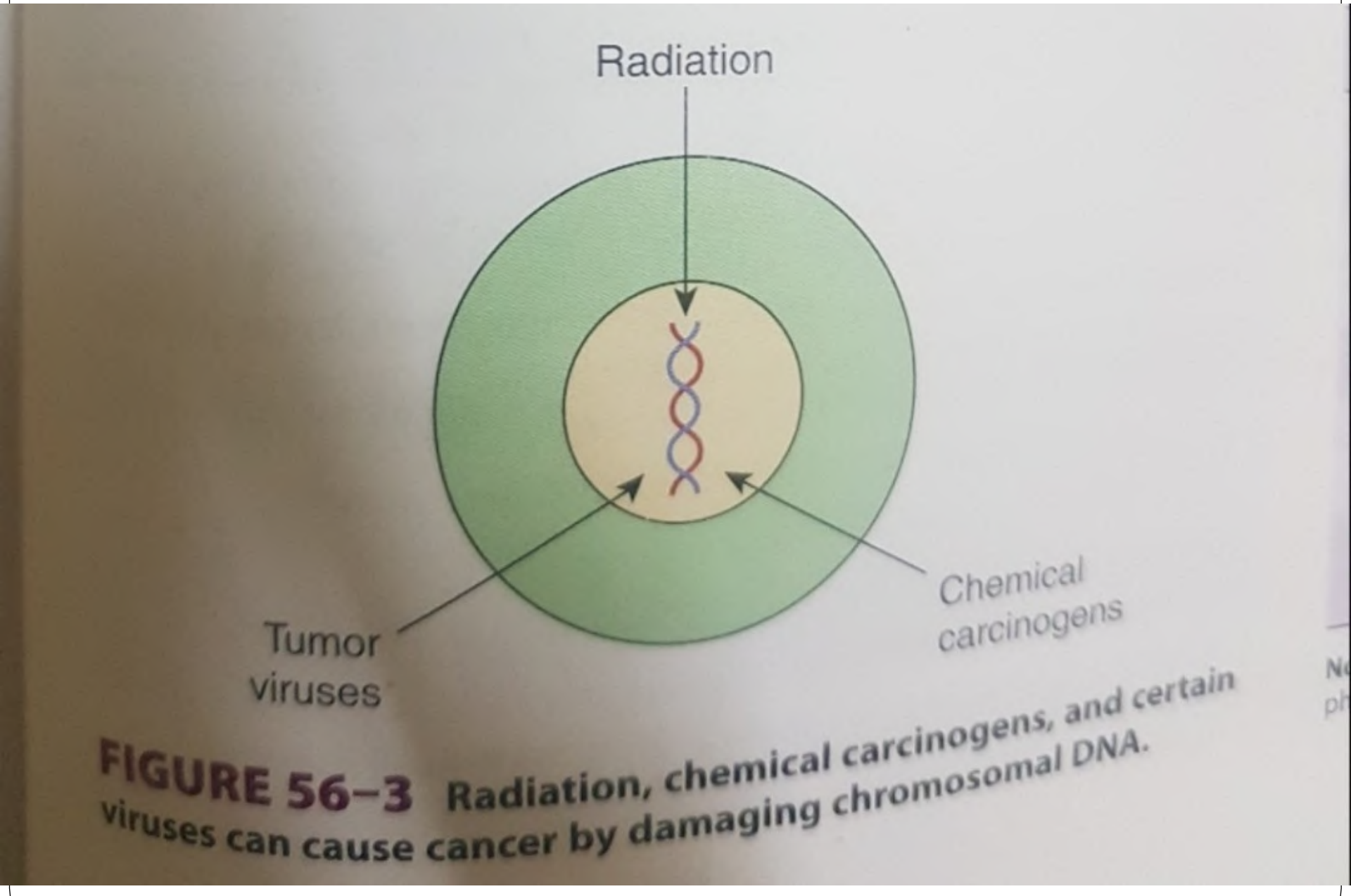


FIGURE 56–3 Radiation, chemical carcinogens, and certain viruses can cause cancer by damaging chromosomal DNA.

Physical carcinogen

- Uv rays,x-rays and gamma-rays are mutagenic and carcinogenic
- Mutations in DNA,if not corrected, are thought to underlie the carcinogenic effect of radiation
- Additionally x-rays and gamma-rays can induce formation of ROS,which are also mutagenic and probably contribute to carcinogenic effects of radiation

- Exposure to UV radiation is common due to exposure to sunlight, which is its main source
- Ample evidence shows that UV radiation is linked to cancer of skin
- The risk of developing a skin cancer due to UV radiation increases with increase frequency and intensity of exposure, and decreases with increasing melanin content of skin.
- Individuals who have an inherited inability to repair DNA have increased risk of developing a malignancy

TABLE 56–1 Some Types of DNA Damage Caused by Radiation

- Formation of pyrimidine dimers
- Formation of apurinic or apyrimidinic sites by elimination of corresponding bases
- Formation of single- or double-strand breaks or cross-linking of DNA strands

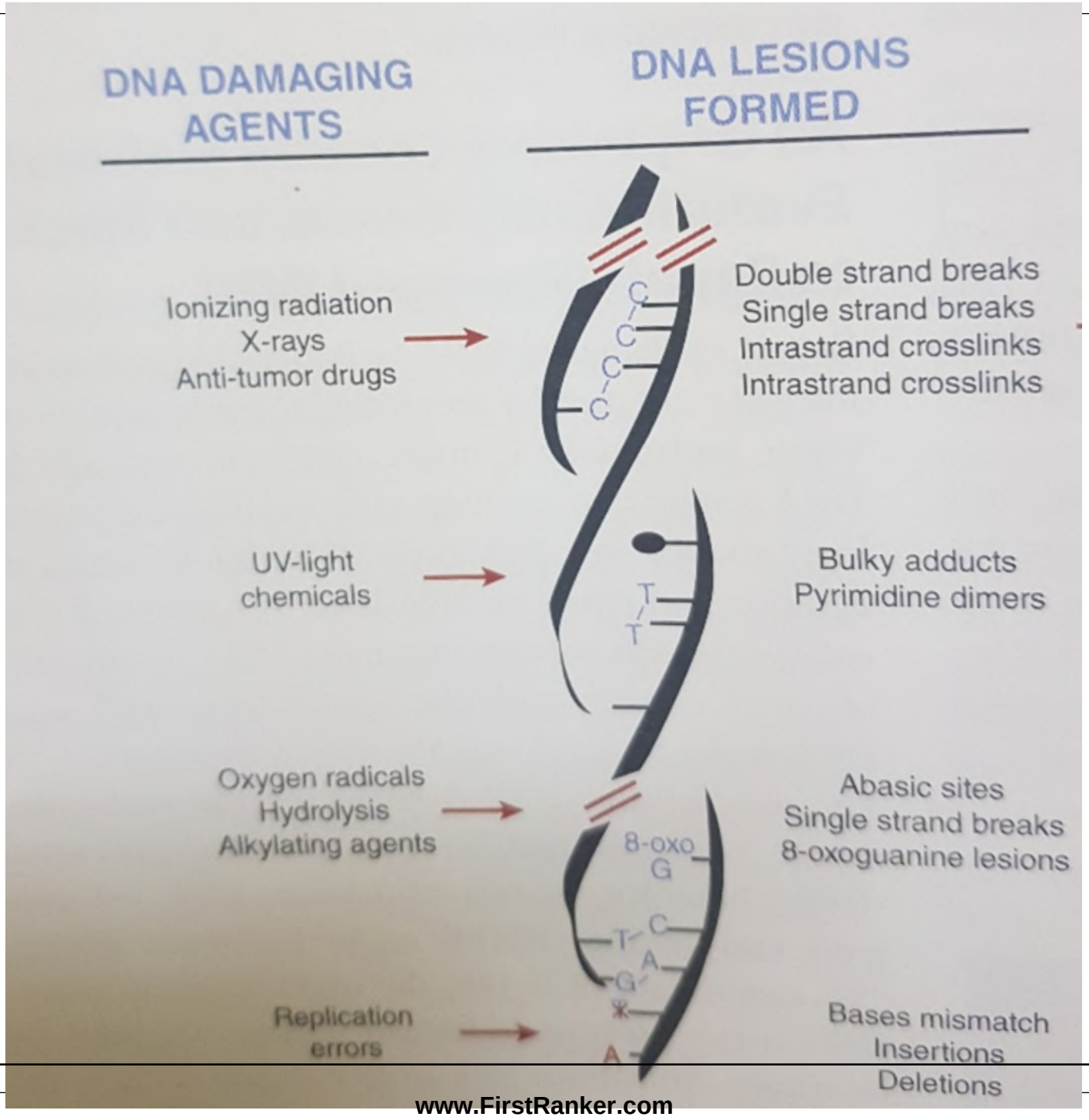


TABLE 47.2: Examples of chemical carcinogens

Chemical Nature	Name
• Polycyclic aromatic hydrocarbons	• Benzopyrenes • Dimethyl-benz-anthracene
• Aromatic amines	• 2-acetyl-amino-fluorene • N-methyl-4 amino-benzene (MAB)
• Nitrosamines	• Dimethyl-nitrosamine • Diethyl-nitrosamine
• Alkylating agents used as drugs	• Cyclophosphamide • Diethyl sulbesterol
• Food toxins	• Aflatoxins

Chemical Carcinogen

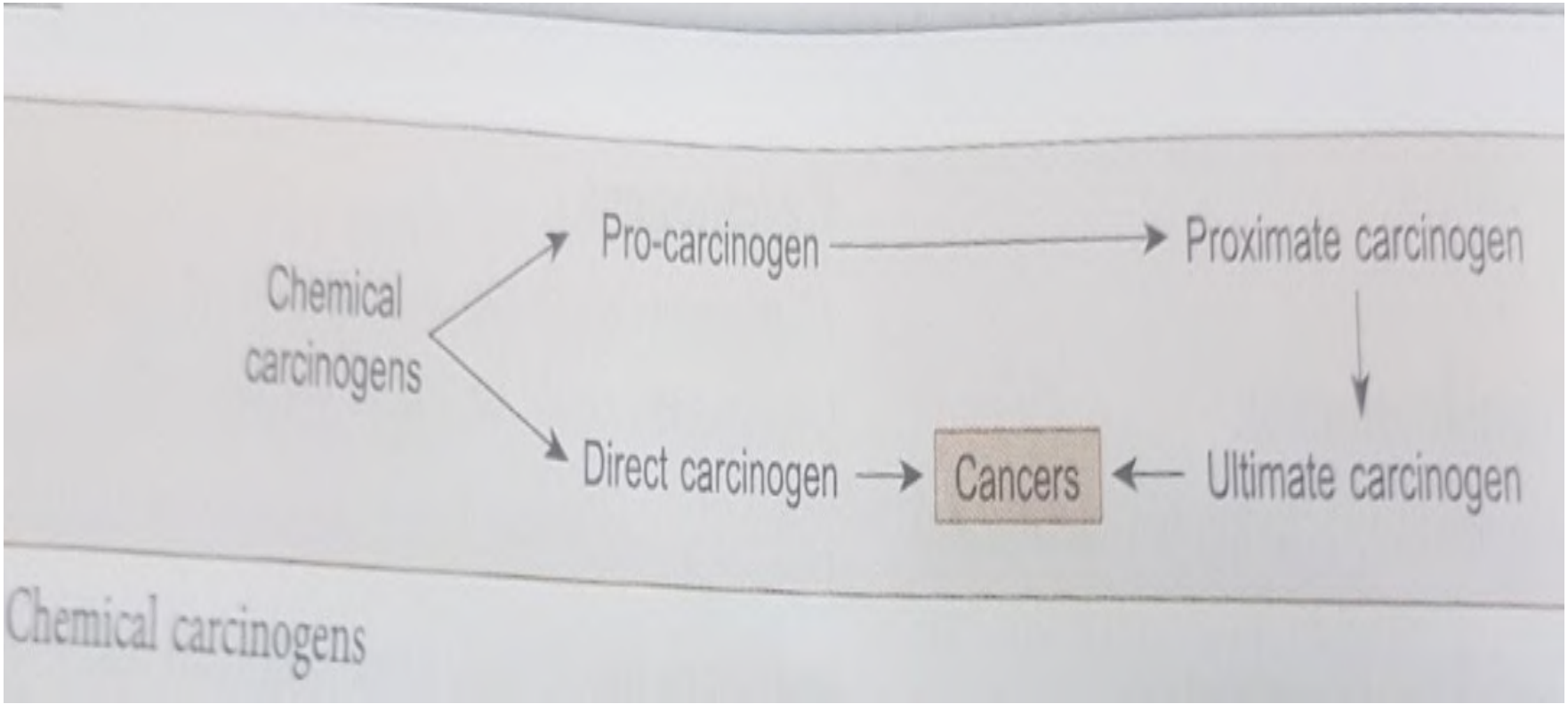
- The process by which chemical substances produce cancers is called chemical carcinogenesis
- Both inorganic and organic molecules may be carcinogenic

Direct carcinogens

- Those chemical carcinogens which are highly reactive and interact easily with target molecule like DNA to produce cancers are called direct carcinogens
- They do not undergo any modification in the body in order to cause cancer
- For example,met-chlorethamine and beta-propionolactone are direct carcinogen

Pro-carcinogens and Proximate carcinogens

- Pro-carcinogens are the chemicals which as such are not reactive and require prior metabolism to become reactive and produce an ultimate carcinogen which result in cancer
- The intermediates formed in between are called proximate carcinogens
- Examples : A pro-carcinogen 2 acetylamino fluorine is converted in to ultimate carcinogen i.e sulphate ester of N-hydroxy-AAF by undergoing chemical reactions in the body
- Most ultimate carcinogens are electrophiles and attack electron rich nucleophilic molecules like DNA,RNA,proteins etc



Stages of Chemical Carcinogenesis

- **Initiation** is the stage which produces the irreversible change in the genome of the cell resulting in one or more mutation
- Such a cell is predisposed or primed to become a cancerous cell but is yet not a cancerous cell

Promotion

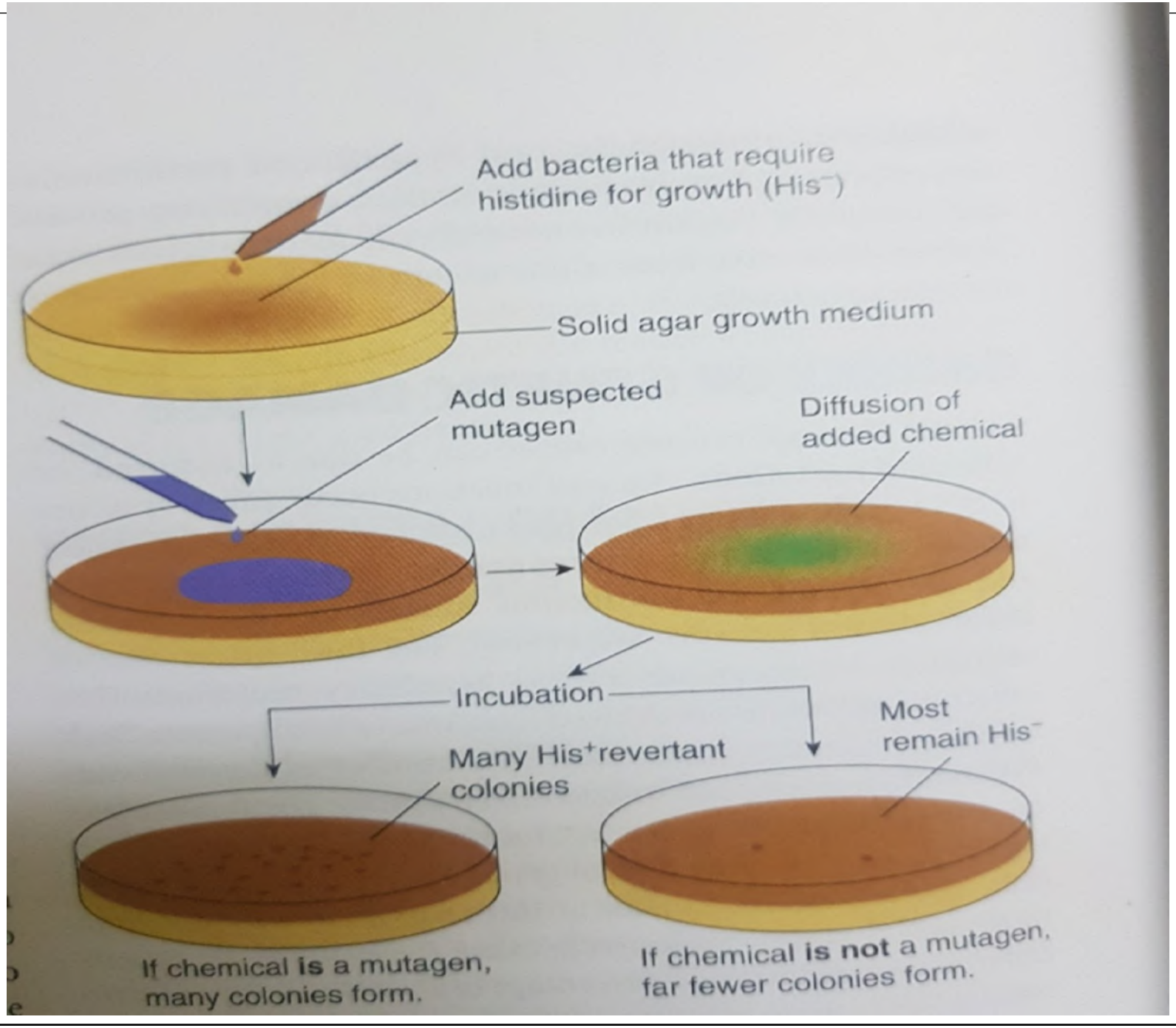
- After initiation, cell undergoes the stage of promotion in which the cell division and malignant transformation of initiated cells is induced
- Most promoting agents act by altering the signal transduction and gene expression
- Either of two processes is incapable of producing malignant transformation

- Examples : **Benzopyrine and croton oil**
- Benzopyrene is a known **chemical carcinogen** which **acts as an initiating agent**
- However, if it is painted once on the skin of an animal it does not lead to cancers in animal but to the initiation of carcinogenesis
- However ,**if croton oil is applied several times after benzopyrene ,often the animal develops tumors**
- It is known that croton oil alone is also not capable of causing tumor
- So **croton oil is a promoting agent** containing **phorbolesters** which act through protein kinase C and influence in the cell signalling

- The exact mechanism of how promotors lead the initiated cell in to tumour forming cell remains unknown
- Most direct carcinogens **act as initiating as well as promoting agent**
- While some act only as promoting agent e.g. **saccharine,phenobrabitone or phenobarbital**

Ames assay

- Chemical carcinogens can be identified by testing for their ability to induce mutation
- A simple way to do this is by using the **Ames assay**
- This relatively simple test, which detects mutations in the bacterium **salmonella typhimurium** caused by chemicals,has proven very valuable for **screening purposes**
- A refinement of the Ames test is to add **an aliquot of mammalian ER** to assay, to make it possible to **identify procarcinogens**



Biological: Oncogenic Viruses

- Both DNA and RNA viruses have been identified as being able to cause cancers in humans
- In general, **the genetic material of viruses is incorporated in to genome of host cell**
- In RNA viruses, only retroviruses can cause cancer because they have **reverse transcriptase enzyme** by which RNA genome of the virus can be converted in to **cDNA** which is then incorporated in to host genome
- Such integration of viral DNA to host DNA results in various effect such as **deregulation of cell cycle**, **inhibition of apoptosis** and **abnormalities of cell-signaling pathways** resulting in cancers

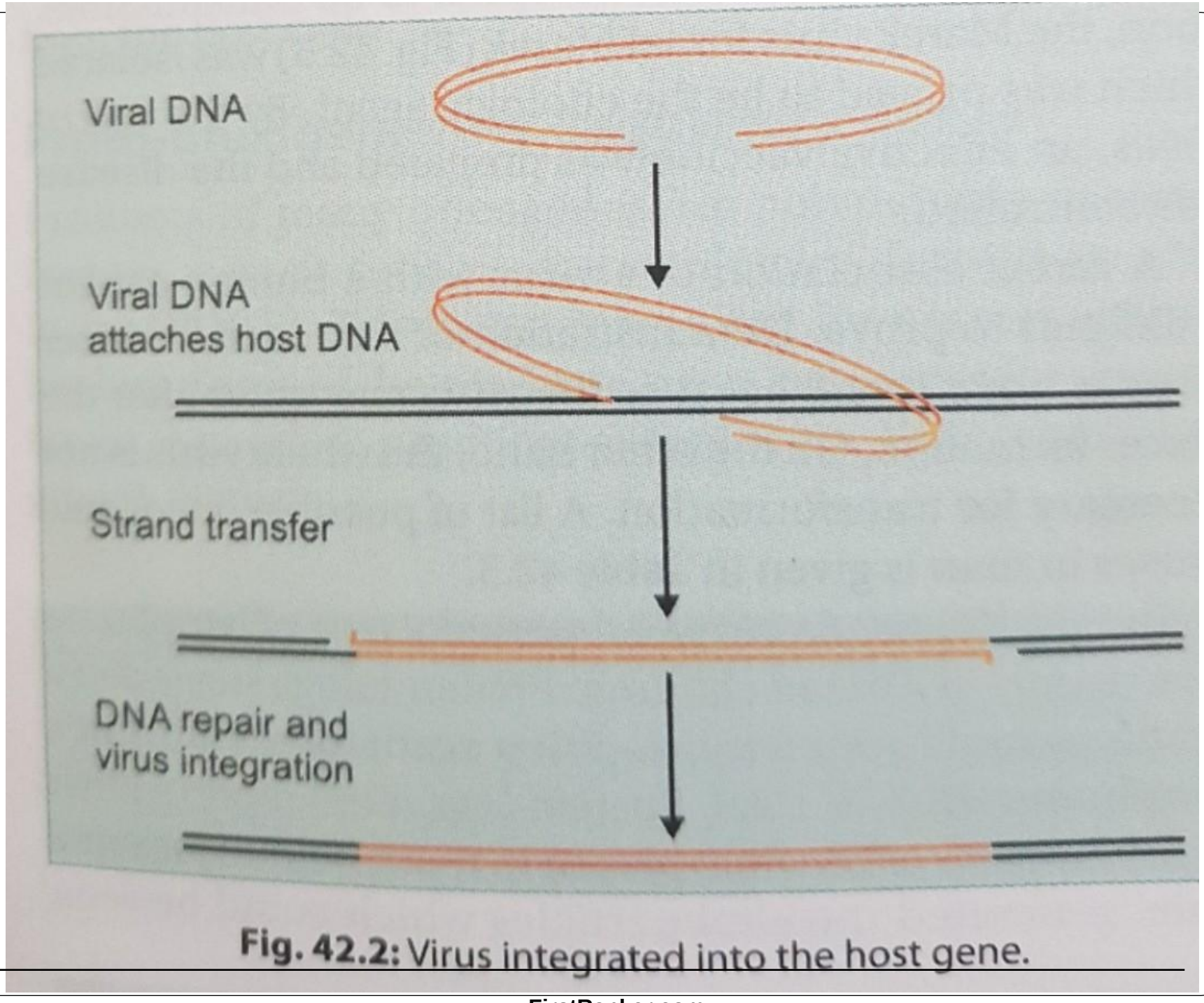


Fig. 42.2: Virus integrated into the host gene.

TABLE 56–3 Some Viruses That Cause or Are Associated With Human Cancers

Virus	Genome	Cancer
Epstein-Barr virus	DNA	Burkitt lymphoma, nasopharyngeal cancer, B-cell lymphoma
Hepatitis B	DNA	Hepatocellular carcinoma
Hepatitis C	RNA	Hepatocellular carcinoma
Human herpesvirus 8 (HHV-8)	DNA	Kaposi sarcoma
Human papilloma viruses (types 16 and 18)	DNA	Cancer of the cervix
Human T-cell leukemia virus type 1	RNA	Adult T-cell leukemia

Oncogenes-Proto-oncogenes

- DNA sequence similar, but not identical ,to viral oncogenes are also present in normal cells
- These have role in cellular growth and differentiation and they are called **proto-oncogenes**
- An **oncogene** can be defined as an **altered gene**, the product of which act in a dominant manner to **accelerate cell growth or cell division**
- Oncogenes are generated by **"activation" of normal cellular proto-oncogenes,**which encode growth stimulating proteins

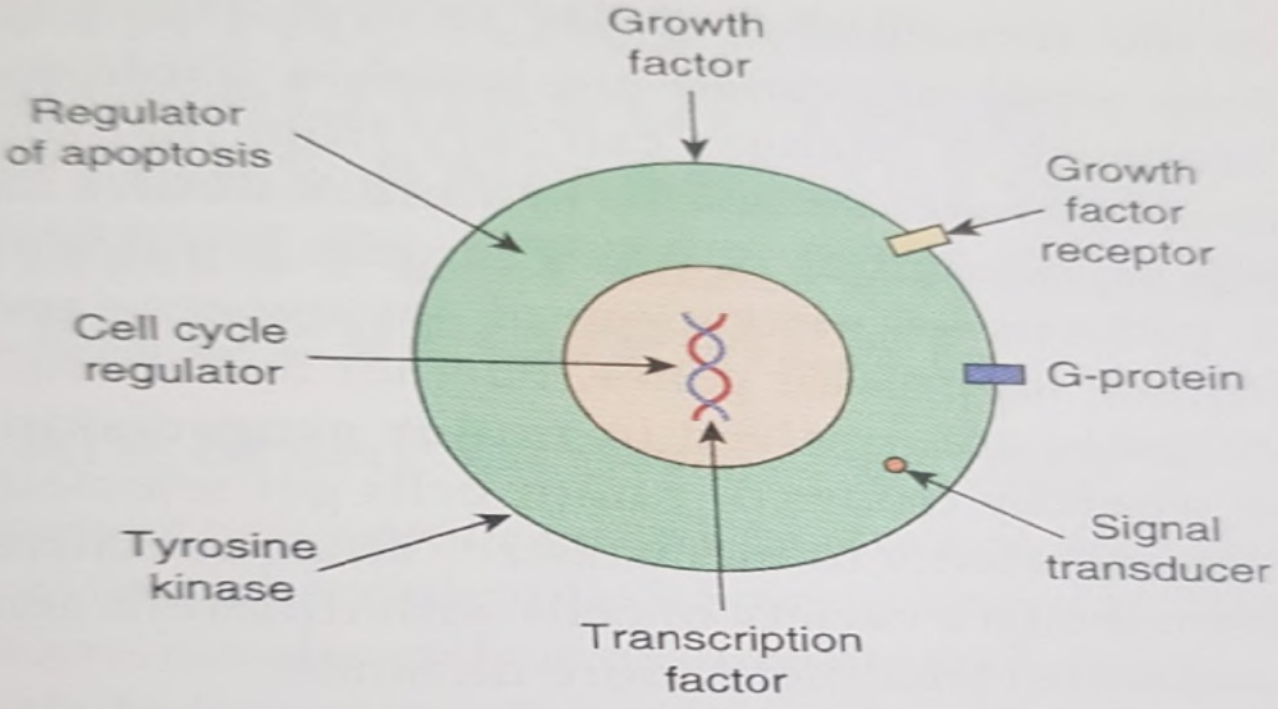


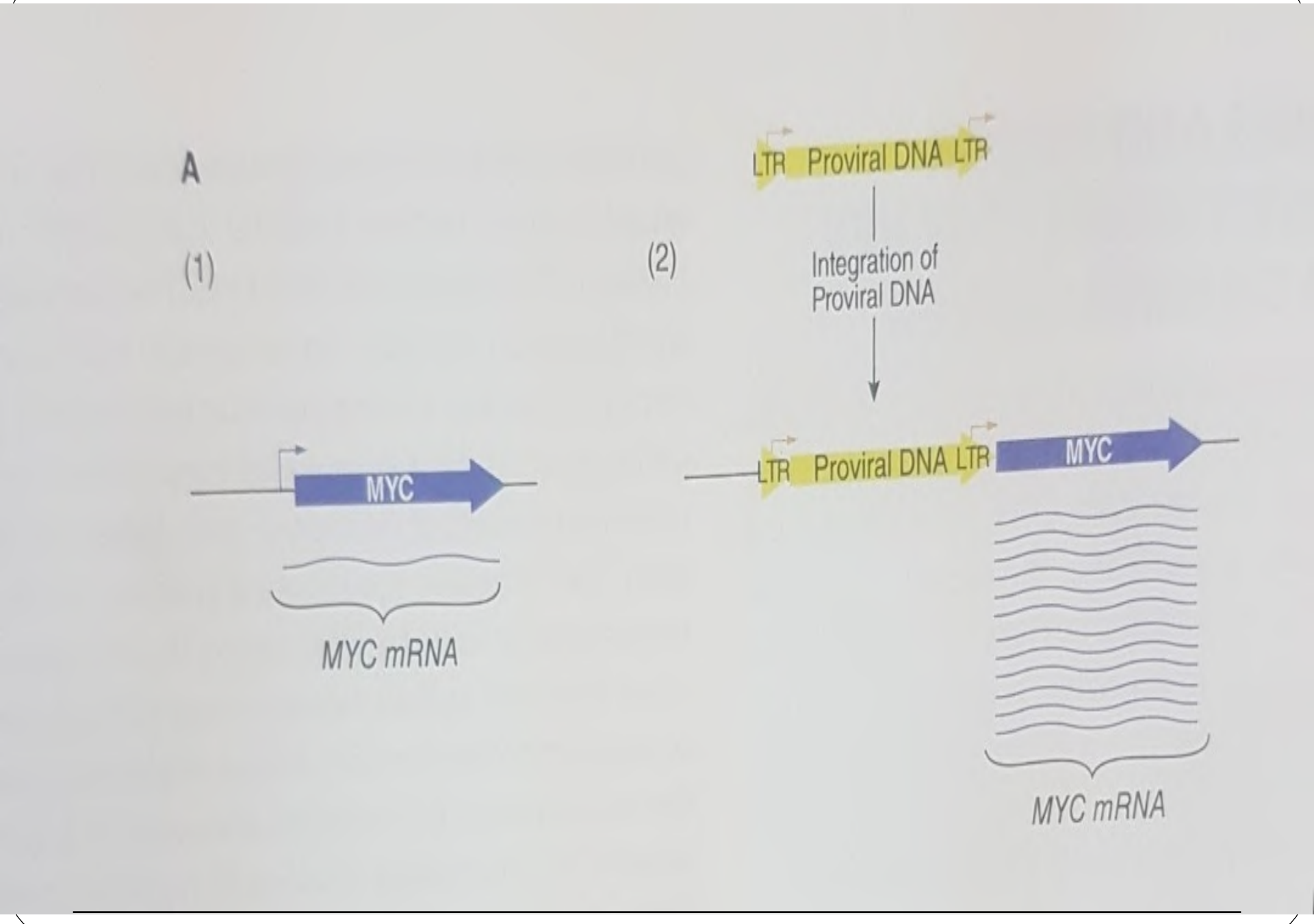
FIGURE 56–6 Examples of ways by which oncoproteins work. Shown are examples of various proteins encoded by oncogenes (oncoproteins). The proteins are listed below with the corresponding oncogene given in parentheses along with its OMIM number. A growth factor, fibroblast growth factor 3 (*INT2*,164950); a growth factor receptor, epidermal growth factor receptor [EGFR] (*HER1*, 131550); a G-protein (*H-RAS-1*, 190020); a signal transducer (*BRAF*, 164757); a transcription factor (*MYC*, 190080); a tyrosine kinase involved in cell–cell adhesion (*SRC*, 190090); a cell cycle regulator (*PRAD*, 168461); a regulator of apoptosis (*BCL2*, 151430).

MECHANISMS OF PROTO-ONCOGENE ACTIVATION

- **At least five mechanisms are known of proto-oncogene activation**
- 1. Promoter insertion
- 2.Enhancer insertion
- 3. Chromosomal translocation
- 4. Point mutation
- 5. Gene amplification

Promotor Insertion

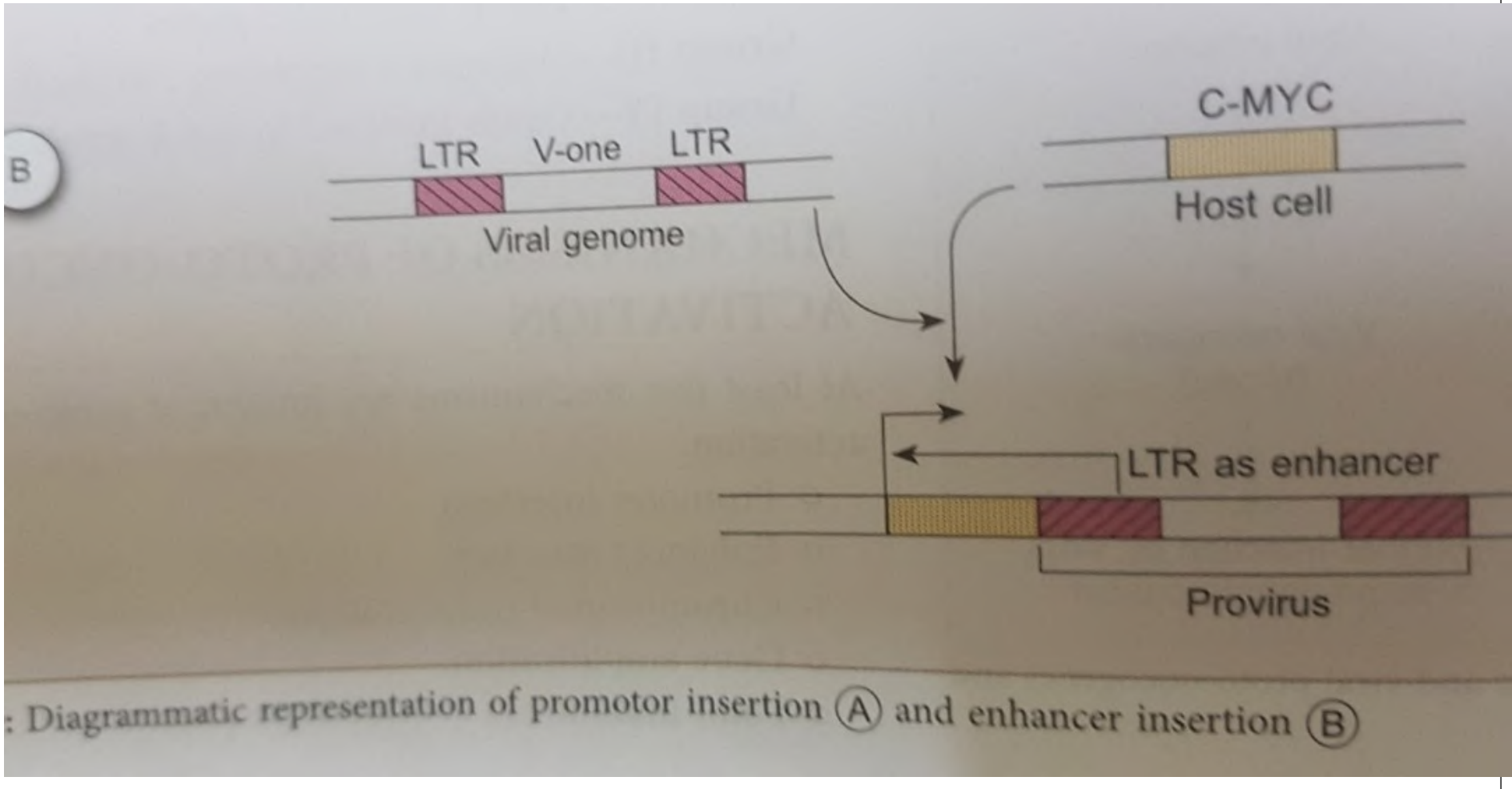
- When a retrovirus infects a host,its double stranded cDNA gets integrated in to host DNA
- This integrated cDNA is called **provirus**
- cDNA is flanked on both sides by **long terminal repeat**
- It is seen that when **chicken B-lymphocytes are infected** by **avian leukaemia virus**, provirus is integrated near the **C -MYC gene of lymphocytes**
- The LTR ,placed immediately upstream of C-MYC gene, **acts as promoter and initiates the transcription of C-MYC gene** and ultimately produces **the B-cell tumor**
- **Human colorectal cancers** also involve the **activation of C-MYC gene**



Enhancer Insertion

- It is seen that many times when a retrovirus genome, like the genome of avian leukaemia virus, is **inserted downstream of C-MYC gene**, still the activation of MYC gene transcription occurs

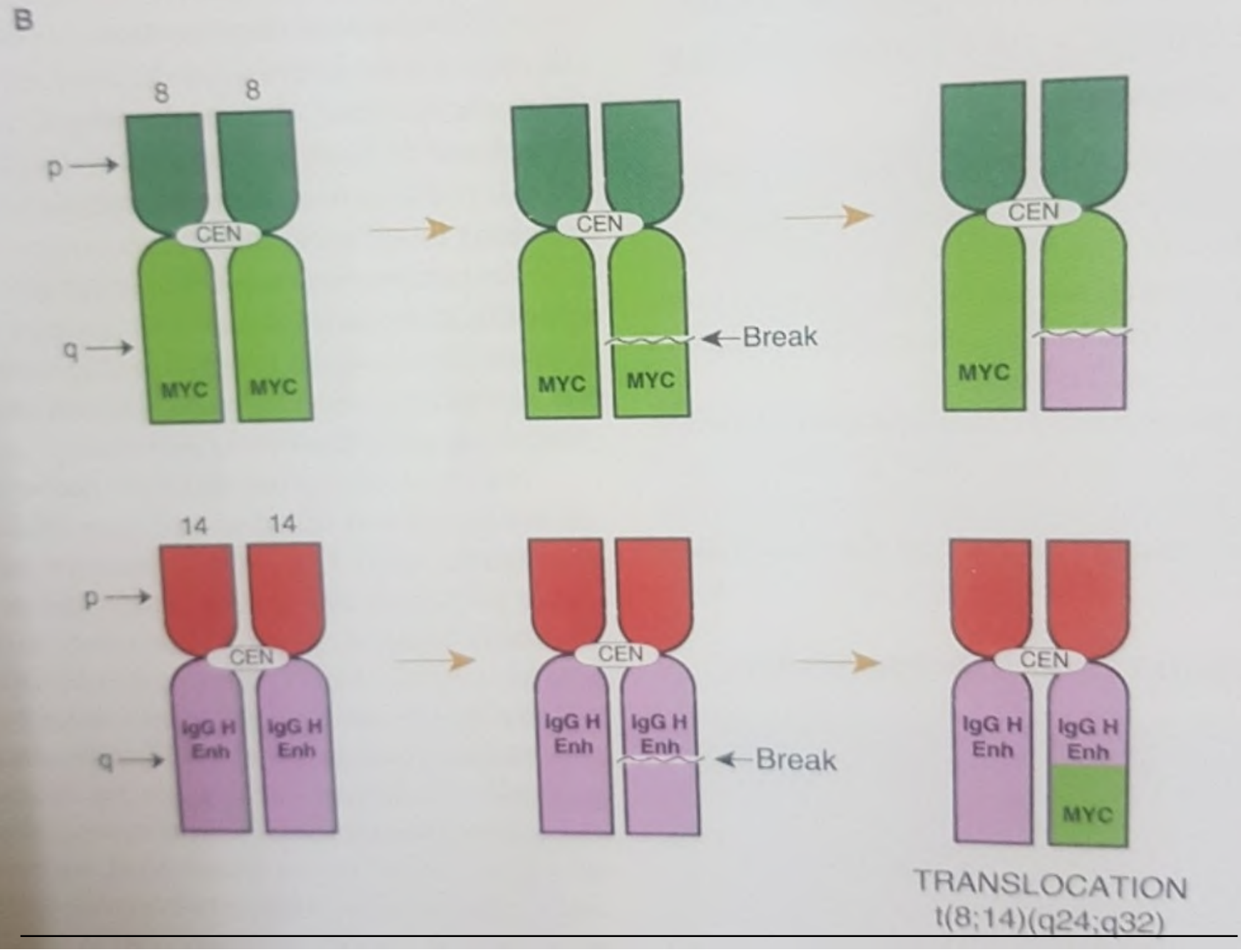
- In such a situation, **LTR of provirus act as an enhancer** and activate the transcription of C-MYC gene



: Diagrammatic representation of promotor insertion (A) and enhancer insertion (B)

Chromosomal Translocation

- Chromosomal translocation is a type of chromosomal abnormality seen in some cancers like **CML,Burkitt lymphoma** etc.
- A portion of chromosome is split off and joined to another chromosome, **resulting in activation of an oncogene at the site where insertion occurs**
- Usually there is **an exchange of a chromosomal material between both the chromosomes**, hence this is called **reciprocal translocation**



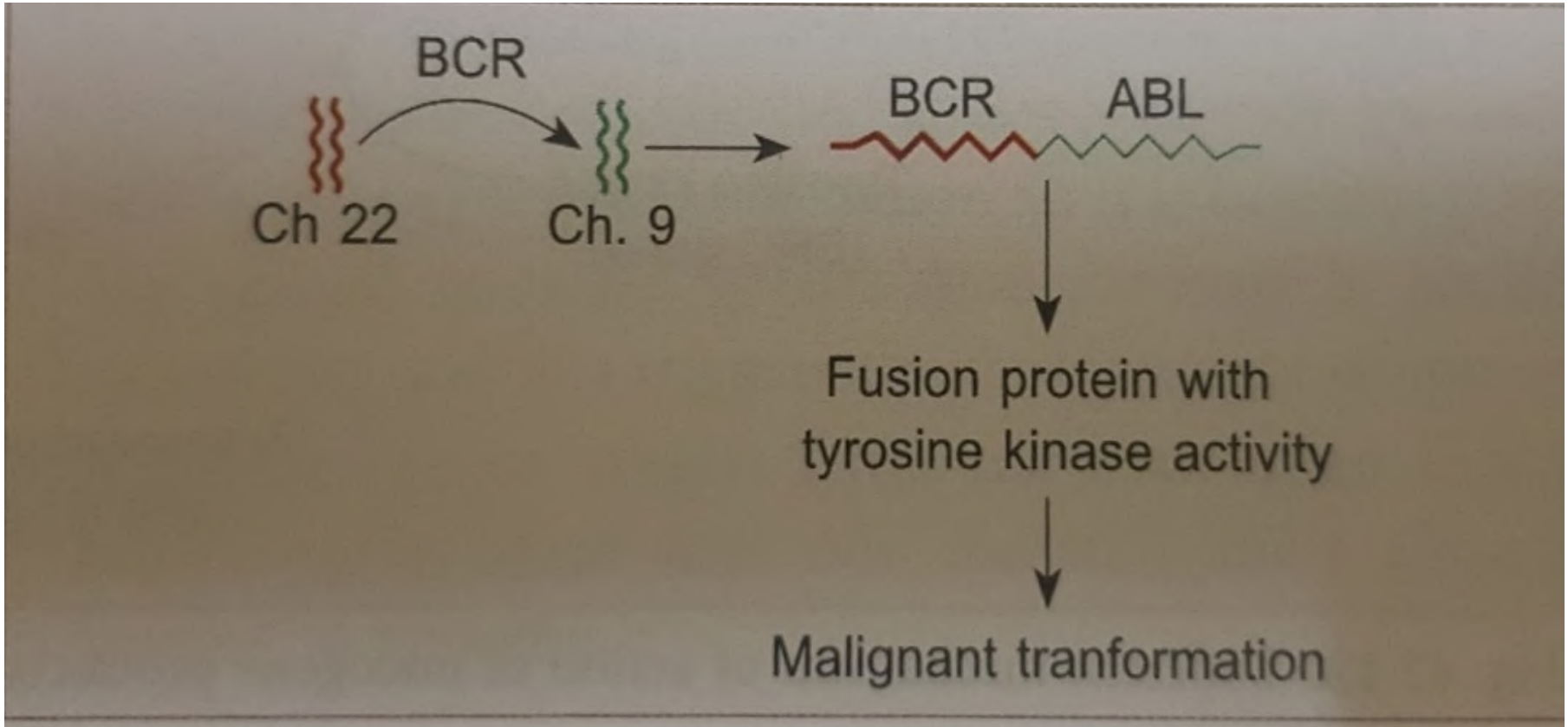


Fig. 47.10: Abnormality of Philadaphia chromosome in chronic myeloid leukaemia

Point mutation

- A classic example is a **point mutation of the RAS oncogen**
- This result in the gene product, a small of G-protein (RAS),in which **intrinsic GTPase activity of the protein is lost**
- Loss of GTPase activity of this G-protein results in **chronic stimulation of the activity of adenylyl cyclase and the MAP kinase pathway,** leading to cell proliferation and **malignant transformation**

Gene amplification

- **Abnormal multiplication of a gene occurs**, resulting in many copies and increased gene expression

- It has been shown that **gene amplification of C-RAS proto-oncogene** has a **role in a malignant transformation**

Examples of oncogenes

- **SIS** and **INT-2 genes**: These are located on chromosome 22q13.1 and 11q13 respectively and encode growth factors to stimulate growth of certain type of cells
- **FMS** and **ERB** encode receptors for colony stimulating factor and epidermal growth factor
- **SRS** and **ABL** which encodes non-receptor tyrosine kinase and are proteins involved in signal transduction
- **H-ras** and **K-ras** which encode membrane associated protein that relay growth factor