Neoplasia

Neoplasia -means New growth:

Neoplasm: Greek meaning Neo- new & plasm- things formed.

A neoplasm is a growth of new cells that

- proliferates without control
- serves no useful function
- has no orderly arrangement.

Neoplastic cells are transformed cells.

In neoplastic cell growth- there is loss of responsiveness that is insensitivity to normal growth controls. They completely ignore the regulatory mechanism of normal cell growth.

Neoplastic cells like parasites compete with normal cells & tissues for their metabolic needs. They enjoy complete autonomy (self government) & steadily increase in size regardless of nutritional status of host. All neoplasms depend on host for their nutrition & blood supply. The neoplastic cells flourish while patient undergo wasting.

Neoplasm is generally referred as tumor

The study of tumor or neoplasm is called Oncology.

- A neoplasm can be divided in to Two category
- 1. Benign : A tumor is said to be benign when it remains localized, grows slowly, usually encapsulated, does not spread to other sites, can be removed surgically & do not recur when removed & does not cause death unless its location interferes with an important body function.
- 2. Malignant : A tumor which grow rapidly, not encapsulated, can invade and destroy adjacent structure, spread at distant sites, recur after excision & cause death. This is commonly called cancer.
- Cancer means a crab because cancer adhere to any part & seize very firmly like a crab.

All tumors have two basic components

1. The parenchyma : made up of transformed or neoplastic cells which determines the biological behavior of the neoplasm

2. The supporting stroma : Host derived non neoplastic stroma (Connective tissue and blood vessels) – which provide blood supply and support for the growth of parenchyma

Suffix ‘-oma’

Tumor Classification

(A)Epithelial: Tumors derived from epithelial surfaces either Squamous and glandular.

(1) Benign

(a) Papilloma- Squamous epitheliam (Non glandular)

(b) Adenoma – Glandular epithelium.

(2) Malignant

(a) Squamous cell carcinoma –Squamous epithelium

(b) Adeno carcinoma- Glandular epithelium

(B) Non-epithelial: Connective tissue (fibrous tissue, cartilage, bone, muscles)

(1) Benign: Name of tissue plus 'oma'

(2) Malignant: Indicated by term 'sarcoma'

Fibrous connective tissue:	Fibroma	Fibrosarcoma
Cartilage:	Chondroma	Chondrosarcoma
Bone :	Osteoma	Osteosarcoma
Adipose tissue (Fat Tissue):	Lipoma	Liposarcoma
Muscle (Smooth)	Leomyoma	Leomyosarcoma
Muscle (Striated)	Rhabdomyoma	Rhabdomyosarcoma

(C) Dermal cyst tumour or Dermoid: Non malignant cystic tumor which arise from embryonic defect in growth and composed of one germ layer only the ectoderm and contains teeth, hair, feathers or skin depending upon the species.

(D) Teratoma: Tumor arise from an embryonic defect in growth and is composed of two or more germ layers. It is a true tumor composed of multiple tissues. Of these two are foreign to the tissues where it is found. This may be benign or malignant. These are commonly seen in gonads.

Epithelium of the body is derived from three germ layers:

Ectoderm: Epi. of skin
Mesoderm: Renal tubular epi.
Endoderm: Intestinal epi.

Carcinoma

All these three will give rise to carcinoma but
Mesoderm can give rise to both carcinoma or sarcoma if mesenchymal tissue arise from mesoderm is involved.

Cystadenomas: Hollow cystic masses seen in ovary
Teratoma: origin from totipotential cells(Capable of differentiate into all three germ layers.)
Benign teratoma and malignant teratoma
Mixed tumour: Tumour composed of more than one type of tissue

Neoplasms (Epithelial origin)

↓---------- ↓

Benign — Malignant (suffix- carcinoma)

↓ ---------- ↓ — ↓----------↓

Squamous epi (Non glandular) — Glandular epi — Squamous epi (Non glandular) — Glandular epi

↓ — ↓ — ↓ — ↓

Papilloma — Adenoma — Sqamous cell carcinoma — Adenocarcinoma

Neoplasms of Non epithelial origin (Mesenchymal origin)

↓---------- ↓

	Benign	Malignant (suffix- sarcoma)
Fibrous C. T. tissue	Fibroma	Fibrosarcoma
Bone (Osteocytes)	Osteoma	Osteosarcoma
Cartilage(chondrocytes)	Chondroma	Chondrosarcoma
Adipose tissue-	Lipoma	Liposarcoma
Embryonal C.T. tissue	Myxoma	Myxosarcoma

NEOPLASM

HISTOGENETIC CLASSIFICATION

	Tissue of origin	Benign	Malignant
A	**Tumours of mesenchymal origin**		
(i)	**Connective tissue and derivatives**		
1.	**Fibrous connective tissue cell**	**Fibroma**	**Fibrosarcoma**
2.	**Embryonal connective tissue that produces mucin**	**Myxoma**	**Myxosarcoma**
3.	**Adipose tissue cell**	**Lipoma**	**Liposarcoma**
4.	**Chondrocytes (cartilage)**	**Chondroma**	**Chondrosarcoma**

NEOPLASM

HISTOGENETIC CLASSIFICATION

	Tissue of origin	Benign	Malignant
I	**Tumours of mesenchymal origin**		
(ii)	**Endothelial and related tissues**		
1.	Blood vessels	Haemangioma	Haemangiosarcoma
2.	Lymph vessels	Lymphangioma	Lymphangiosarcoma
3.	Mesothelium	---	Mesothelioma
4.	Meninges	Meningioma	Invasive meningioma

NEOPLASM

HISTOGENETIC CLASSIFICATION

	Tissue of origin	Benign	Malignant
I	**Tumours of mesenchymal origin**		
(iii)	**Tumours of haemopoietic cells**		
1.	**Lymphoid cells**	**-- Lymphoma**	**Lymphoid leukemia Lymphosarcoma**
2.	**Myeloid cell**	**--**	**Myeloid leukemia**
3.	**Plasma cell**	**---**	**Multiple Myeloma**
(iv)	**Tumours of Muscle**		
1	**Smooth**	**Leiomyoma**	**Leiomyosarcoma**
2	**Striated**	**Rhabdomyoma**	**Rhabdomyosarcoma**

NEOPLASM

HISTOGENETIC CLASSIFICATION

	Tissue of origin	Benign	Malignant
B	**Tumours of nervous tissue**		
1.	**Glia**	**--**	**Glioma, Gliosarcoma**
2.	**Neuron**	**Neuroma**	**Neuroblastoma**

NEOPLASM

HISTOGENETIC CLASSIFICATION

	Tissue of origin	Benign	Malignant
C	**Tumours of epithelial origin**		
1.	**Stratified squamous**	**Papilloma**	**Squamous cell carcinoma or epidermoid carcinoma**
2.	**Basal cell of the skin (Stratum germinativum)**	**--**	**Basal cell carcinoma**
3.	**Glandular epithelium**	**Adenoma**	**Adenocarcinoma**
4.	**Neuroectoderm (melanocyte)**	**Melanoma**	**Malignant melanoma**
5.	**Urinary Tract Epithelium**	**Transitional cell papilloma**	**Transitional cell carcinoma**
6.	**Testicular epithelium**	**--**	**Seminoma**

MACROSCOPIC APPEARANCE

Neoplasm have no definite size, shape, color, or consistency.

- **Size**
  - **One mm diameter to several centimeter**
- **Weight**
  - **Few milligram to several kg**
  - **60 kg or more**
  - **Tumour may be larger than the host (mice)**

- Shape
  - Round, elliptical or multilobulated
  - Slowly growing tumour – spherical or pedunculated
    - Rapidly growing tumour – irregular or multi-lobulated

Colour

Grayish white, yellow, red, brown or black

Fatty tissue -Yellow

Haemorrhage or congestion - Pink or red in colour

Melanoma or melanosarcoma - Black colour

Haemoglobin - Brown colour

Consistency

- **Tumour of bone**
  - Hard
  - Connective tissue tumours
    - Firm
    - Dense : Sclerotic or fibrotic
    - Scirrhous : abundant fibrous stroma
  - Soft and friable tumour -- encephaloid
    - Soft and liquefied due to deg. Suppu. And necrosis
    - Watery -- due to edema
    - Slimy – tumour contain mucin

Microscopic appearance

The appearance of neoplastic cells vary with the degree of malignancy of tumor

The more the tumor benign in nature: More the cells resemble the adult cell type

The more the tumor malignant: More the cells resemble immature or embryonal cell type

ANAPLASIA: When tumour cell become malignant, it reverts more to the embryonal type and this reversion is called anaplasia.

Anaplasia is a characteristic of malignant tumor

Anaplasia means lack of differentation & reversion of cells to its embryonic type.

Characteristic of anaplasia

- 1. Hyperchromasia and enlargement of nucleus
  - The nuclear-cytoplasmic ratio may be decreased (Normally it is 1:4 or 1:6 & reduced to 1: 1
  - Nuclei vary in size, shape and reveal odd or unusual forms.
- 2. Enlargement of nucleolus.
- 3. Increased number of mitotic figures: This is because of rapid multiplication of cells.
- 4. Giant cells
  - Cell much larger than neighboring cells.
  - Possess either one very big or several nuclei.
  - The nucleus is dividing more rapidly than the cytoplasm and results in multiple nuclei. (Tumour giant cell)
- 5. Hyperchromasia of the cell
  - More anaplastic cell – more intensity of haematoxylin stain
- 6. Embryonal type cell: Loss of growth control mechanism. The anaplastic cells loses its resemblance to the cells from which they are originated & appear as undifferentiated embryonal cell type.

Characteristics of Benign & Malignant Tumors

Benign & Malignant neoplasms can be differentiated based on following characteristics.

1. Differentiation and anaplasia
2. Rate of growth
3. Local invasion
4. Metastasis

1. Differentiation and anaplasia

- ✓It refers only to paranchymal cells
- ✓Differentiation means the extent to which they resemble the normal cells both morphologically and functionally.
- ✓Benign neoplasm:
  - ▪ Are composed of well differentiated cells
  - ▪ Closely resemble normal cells
  - ▪ Lipoma made up of mature fat cells and Chondroma of mature cartilage cells
  - ▪Mitosis are extremely small in number and are of normal configuration.

Malignant neoplasm:

- Malignant neoplasms show wide range of differentiation of paranchymal cells from well differentiated to completely undifferentiated.
- Undifferentiated cells are called anaplastic cells.
- Anaplasia is the characteristic feature of malignancy.
- Anaplasia (Ana = backward +plasma = a thing formed) means to form backward
- Anaplastic cells show marked pleomorphism that is marked variation in size & shape
- The nuclei are extremely hyper chromic and large
- The nuclear cytoplasmic ratio may be 1:1
- Giant cells may be formed
- Anaplastic nuclei vary in size and shape and show odd or abnormal form
- The chromatin is coarse and clumped, nucleoli may be extremely large
- Mitosis are numerous and atypical.

2. Rate of growth

✓Benign tumors grow slowly over a period of months to years

✓Malignant tumors grow much faster, spread locally and to distant sites and eventually cause death.

- However there is wide variations.
- Some grow slowly, others rapidly.
- Most cancer take years and in human even decades to become clinically detectable.
- Rapidly growing malignant tumour contain central mass of ischemic necrosis.

3. Local invasion

- ✓Benign tumors –
  - remains localized at its site of origin.
  - ▪ It does not have capacity to infiltrate, invade, or metastasize to distant sites.
  - ▪It slowly expand and develop an enclosing fibrous capsule means benign tumors are encapsulated.
- ✓ Malignant tumour
  - ✓Grow by progressive infiltration, invasion, destruction, and penetration of the surrounding tissue
  - ✓They do not develop capsule means they are not encapsulated

4. Metastasis

The spread of malignant cells from one part of the body to another, through the blood vessels or lymphatics (as an embolus) is called metastasis.

- **The secondary growths so formed in distant organs or tissues are called metastases.**
- **It is the most characteristic feature of malignant tumors.**
- **All cancers do not have same capability to metastasize.**
- **Basal cell carcinoma and tumors of nervous system are highly invasive in their site of origin but rarely metastasize.**
- **More anaplastic and larger primary tumors have more chance of metastasis.**

Spread of Neoplasms

Malignant neoplasms spread by either

1. Haematogenous spread : Usually sarcomas are spread by this way. Lungs and liver are the most commonly involved secondary sites in such spread.

2. Lymphatic spread: Usually carcinomas are spread by this way. Lymphatic spread invariably involves the regional lymph nodes.

3. Seeding within the body cavities: This is called transplantation or implantation spread where there is transfer of tumor cells from one serous or mucous surface to another by direct contact.
   eg. Venereal granuloma (Transmissible venereal tumor) of dog where tumor cells are spread by implantation during coitus.

Comparison or Differentiating features between benign and malignant neoplasms.

	BENIGN	MALIGNANT
Macroscopic comparison		
1	Occur singly	Single or multiple
2	The shape is round, elliptical, wart-like, or pedunculated	The shape is irregular.

	BENIGN	MALIGNANT
Macroscopic comparison		
3	Encapsulation is present	Encapsulation is not present
4	The rate of growth is slow	The rate of growth is rapid
5	Degeneration and necrosis is slight	Degeneration and necrosis is extensive
6	Removal is not difficult due to encapsulation.	Removal of tumour is difficult due to invasion, metastasis and lack of encapsulation.

	BENIGN	MALIGNANT
Macroscopic comparison		
7	Metastasis is absent	Infiltration, metastasis and transplantation is present.
8	No recurrance of the tumour	The tumour tends to recur after apparent removal.
9	Death does not occur	Death occurs.

	BENIGN	MALIGNANT
Microscopic comparison		
1	Morphology of tumour is approximately normal in relation to adjacent tissues.	Morphology of tumour is abnormal in relation to adjacent tissues.
2	Minimal or no evidence of anaplasia and appear mature. Mitotic figures are few in number or may not be seen.	Marked evidence of anaplasia and lack of maturity. Mitotic figures are present and may be abundant.
3	The tumour is confined to by adjacent tissues.	The tumour is not confined by adjacent tissues. Extend beyond basement membrane.

	BENIGN	MALIGNANT
Microscopic comparison		
4	The tumour does not penetrate, or infiltrate beyond connective tissue capsule.	The tumour penetrate, or infiltrate through connective tissue capsule.
5	The tumour does not grow beyond the blood supply.	The tumour grow beyond the blood supply.
6	Degeneration and necrotic changes within the tumour are slight	Degeneration and necrotic changes within the tumour are extensive.
7	There is no invasion of blood vessels or lymphatics.	Invasion of blood vessels and lymphatic occurs.

ETIOLOGY OF CANCER

1. The Intrinsic factors
2. The extrinsic Factors

The Intrinsic factors

1. **Heredity:** Heredity plays an imp. role in appearance of neoplasm.
    - Strain of mice susceptible or resistant to tumour have been developed. High cancer strain can be produced by genetic inbreeding
    - Chickens: Strain developed that has considerable resistance to LL.
    - Human: Breast Cancer: First degree relatives are at markedly increased risk
    - Carcinogenesis involves mutation of genome: One or more such mutations may be inherited in this germ line.
    - Familial predisposition has been noted in carcinoma of breast, colon, ovary, prostate, uterus and malignant melanoma.

2. Age:

- Frequency of cancer increases with age.
- This may be due to accumulation of somatic mutations over a period of time.
- Sarcomas are more frequently observed in younger while Carcinomas are found in older animals.

3. Pigmentation:

- In White and grey horses malignant melanomas are more common.

In Hereford cattle squamous cell carcinoma of the eye is more common.

4. Sex: Incidence of tumour in genital organs is more in females

5. Tumour immunity : Both CMI and humoral immunity have anti-tumour activity

Extrinsic causes

Large number of carcinogenic agents have shown to induce neoplastic transformation in vitro as well as in vivo in experimental animals. These are

1. **Chemicals**
2. **Radiant energy**
3. **Chronic irritation**
4. **Hormones**
5. **Parasites**
6. **Oncogenic viruses**

Chemical carcinogens

Sir Percival Pott (1775) : First to point out that chemical agents could be carcinogenic. He attributed Scrotal skin cancer in the chimney workers (persons who clean chimneys) due to chronic exposure to soot.

Yamagiwa and Ichikawa (1915): they induced cancer in rabbit ear with repeated application of coal tar.

Kennaway and Cook: Extracted 50 grams of chemically pure carcinogen 3, 4 –benzapyrene from two tons of crude tar

Since than hundreds of chemicals have been shown to be carcinogenic in animals.

Chemical carcinogens

Two Categories:

1. Direct - acting agents : They do not require chemical transformation or metabolic conversion for producing cancer. They directly cause tumor & considered as weak carcinogens.
2. Indirect acting agents : They become active only after metabolic conversion & called as Pro carcinogens.

   Their active end products are called Ultimate carcinogens.

   Majority of the chemical carcinogens are indirect acting.

Major chemical carcinogens

1. Direct-acting carcinogens

- They do not require metabolic conversion to become carcinogenic
- They are weak carcinogens.

Alkylating agents

Anti-cancer drugs (Cyclophosphamide, chlorambucil, nitrosoureas) - These anti cancer chemotherapeutic drugs are used to cure or control or delayed recurrence of certain types of cancer but unfortunately they may later on produce second form of cancer usually leukemia.

2. Indirect-acting carcinogens (Pro carcinogens that require metabolic conversion before they are active)

i. Polycyclic and heterocyclic aromatic hydrocarbons.

1. Benzanthracene : Skin cancer and Fibro sarcoma when painted on skin or injected subcutaneously

2. Dibenzanthracene: ---------

3. 3- Methyl cholanthrene ---------Brain cancer

4. 7, 12-Dimethylbenzanthracene

5. Benzapyrene

These carcinogens are produced during combustion of tobacco and involved in lung cancer in cigarette smokers

They are also produced from animal fats in process of broiling meats and more present in smoked meat and fish.

Over 2000 substances have been counted in cigarette smoke.

ii. Aromatic amines and azo dyes

-Benzidine

-2-Naphthylamine (beta-naphthylamine): 50 folds increase the incidence of bladder carcinoma in the workers exposed to aniline dye and rubber industries.

-2-Acetylaminofluorene

-Butter yellow.

Azo dyes which were developed to color the food.

eg. Butter yellow to color margarine & scarlet red for cherries are carcinogenic

iii. Natural plant and microbial products

Aflatoxin B1: There is strong relation between dietary level of Aflatoxin B1 & Hepato cellular carcinoma (Liver cancer). Aspergillus flavus- a mould that grow on improperly stored grains & groundnuts -produce fungal metabolite called Aflatoxin B1.

iv. Miscellaneous agents

Exposure to Asbestos: associated with Lung cancer and gastrointestinal cancer in humans and animals.

Arsenic: Skin cancer

Chromium, nickel, vinyl chloride: Lung cancer

Insecticides- such as aldrin, dialdrin chlordane & fungicides are carcinogenic in animals.

Nitrosamines and nitrosamides: Gastric carcinoma

Mechanism of chemical carcinogenesis

- Chemical carcinogenesis that is production of cancer by chemical agents is divided in to two stages
- 1. Initiation of carcinogenesis- This occurs by exposure of cells to carcinogen(Poly cyclic hydrocarbons are initiators).

An initiated cell is an altered cell & can give rise to tumor. It is not a tumor cell. It is susceptible to the action of promoters. Initiation alone is not enough for tumor formation.

Initiation cause binding to DNA & permanent damage to DNA (Mutation)

2. Promotion of carcinogenesis- Promoters can induce tumors in initiated cells but they are not tumor producing by themselves.

Phorbol esters,hormones, phenols, drugs are promoters. They are not carcinogenic by themselves and do not damage the DNA. Promoters must be applied after application of carcinogenic material which act as initiator.

This initiation promotion sequence is important in chemical carcinogenesis.

Some chemicals possess the capability of both initiation & promotion. They induce tumor without added factors called complete carcinogen.

While incomplete carcinogen are capable of only initiation.

Initiation promotion sequence process leads to proliferation of mutated cells developing ultimately in to Malignant neoplasm

All direct acting and ultimate carcinogens are highly reactive electrophiles, that is they have electron deficient atoms that can react with nucleophilic (electron rich sites) in the cell.

Upon Exposure of cells to a Carcinogen

Metabolic activation

Electrophilic intermediates — Initiation

Binding to DNA

Permanent DNA lesion; initiated cells

Cell proliferation — Promotion

Neoplastic cell

- Phorbol esters
- Hormones
- Phenols
- Drugs

PROMOTERS

- Themselves are not Carcinogenic
- Not Elecrtophilic
- Do not damage DNA

- These promoters must be applied after application of the chemicals which acts as an initiator.
- Carcinogenicity of some chemical (Initiator) increased by subsequent administration of promoters
- Some chemical possess capacity of both initiation and promotion (Complete carcinogen)

Any gene can be targeted by chemical carcinogens but mutations in ras genes are common in chemically induced tumors in rodents.
Among tumor suppressor genes TP53 is an important target.
eg. Aflatoxin B1 produce characteristic mutations in TP53 gene.

Radiation carcinogenesis

Radiation is strongly oncogenic.
UV rays of sunlight
Electromagnetic waves: X – rays, gamma rays, protons, neutrons
Nuclear fission
Radio nuclides (species of atom)

all are established carcinogens

- **Due to effect of solar radiation incidence of skin cancer is high in cattle in Australia, USA and Africa**
- **Ocular and periocular Sq. cell carcinoma in white faced Hereford cattle (Lack of protective pigmentation in the eyelid)**
- **Carcinoma of skin in light colored Australian cattle (Photosensitization after eating certain plants)**
- **Skin cancer in X ray workers**
- **Skin cancer in fare skinned person exposed to sun light**
- **Correlation between Nuclear fission and leukemia**
- **Therapeutic irradiation also found to be carcinogenic**

- UV light has several biological effect on cell
- UV light cause DNA damage by forming pyrimidine dimers. It also cause mutations in T53 gene
- In normal persons, the altered DNA is repaired by a series of repair enzymes
- If one or more DNA repair enzymes are defective or deficient--- increased predisposition to skin cancers in sun-exposed areas of the skin
- Radiant energy causes:
  - Chromosomal breakage
  - trans locations
  - Point mutation
  - alters the protein
  - inactivates enzymes
  - injures membrane

- The radiation directly ionizes critical cellular components or
- It first reacts with water or molecular oxygen to produce free radicals that mediate damage.
- DNA is damaged inducing somatic mutations and malignant transformation occurs.

CHRONIC IRRITATION

- Incidence of Sq. cell carcinoma was more in---Scars resulting from severe burns and branding of cattle & other injuries than in normal skin. Burns often resulted in skin tumors.
- Among Kashmiri people --- abdomen skin carcinoma was frequent compare to other nationalities because they had a habit of carrying a pot filled with hot coals under their clothes during the winter to keep them warm
- Cutaneous neoplasms on feet and legs --- bare foot people
- Carcinoma of mouth --- who chew betel nut
- Horn cancer --- irritation by yolk, pairing, painting etc.

HORMONES

- Administration of massive dose of estrogenic hormones in mice induces neoplastic growth of the interstitial cells in testes.
- High estrogen levels associated with retention of milk in the mammary gland produce mammary tumors in mice.
- The dogs have high incidence of mammary tumors associated with disturbance of hormonal balance.
- Drugs such as synthetic estrogen (Stilbesterol ars established carcinogenic agent in animals.
- Similarity between Structural formula of carcinogenic hydrocarbons (Benzanthracene, cholanthrene) and hormones (Oestrogen, progesterone, testosterone, corticosteroids),
- Disordered mechanism of these hormones may lead in there transformation in carcinogenic compound.

HORMONES

- In human hormonal imbalance (endogenous estrogen excess) play a significant role in production of breast cancer.
- Ovarian tumour (that secrete estrogen) is associated with breast cancer in post –menopausal women.
- Post menopausal estrogen therapy --- increase risk of breast cancer
- In human uterine leomyomas(Fibroids) are thought to be caused by excessive estrogenic stimulation.
- Growth factors(TFG-alpha, PDGF) secreted by breast cancer cells are involved in tumour progression. Production of these growth factors are estrogen dependent.

PARASITES

- Parasites by causing chronic irritation may lead to neoplasia
- A small nematode Gongylonema neoplasticum– carcinoma of gastric mucosa -- Rat.
- Cysticurcus fasciolaris (Larval stage of cat tape worm-Taenia taeniaeformis developing in the rat liver)--- may cause sarcomas.
- Spirocerca lupi --- invade in the wall of oesophagus & may produce fibrosarcoma and osteosarcoma ---dog.
- Habronema megastoma (stomach worm)--- gastric adenoma-- horse and mules.
- Eimeria stiedae --- multiple adenoma of bile duct -- rabbit.
- Schistosoma haematobium – bladder carcinoma -- human

VIRAL ONCOGENESIS

Novinsky –1876 –transplanted Venereal granuloma from one to another dog

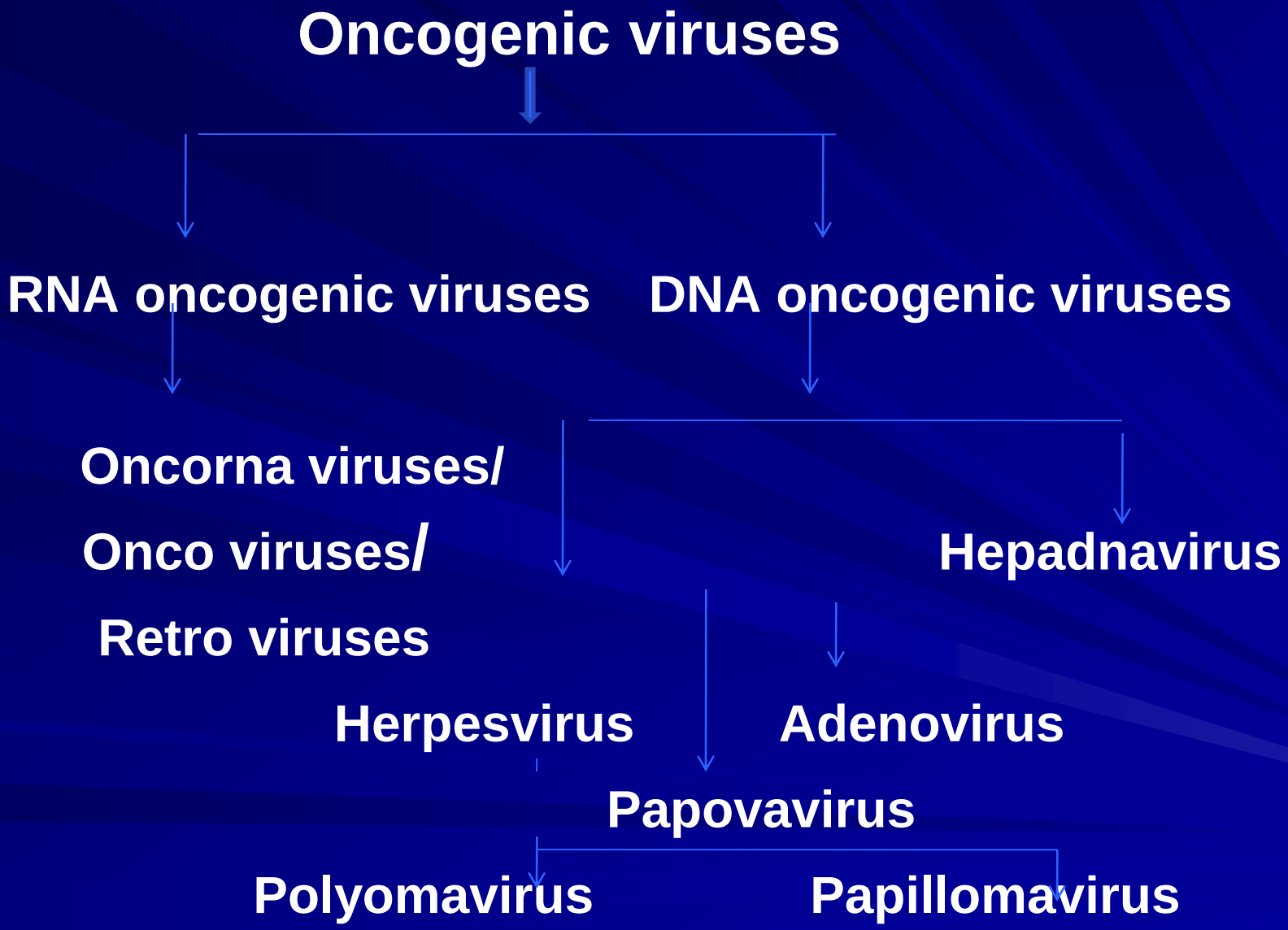
Ellerman and Bang – 1908 – were first to demonstrate an oncogenic virus in Avian leucosis

Rous – 1910 – Fowl sarcoma – Rous sarcoma virus

Shope – 1933 – Papillomas in rabbit- etiology is papilloma virus.

- Oncogenic viruses fall in to Two classes
- RNA oncogenic viruses come under Oncorna viruses or more commonly known as Retroviruses.
- DNA oncogenic viruses include members of Genus- Papovavirus, Herpes virus, Hepadna virus & Adenovirus.

CLASSIFICATION



Family	Virus	Host of origin	Associated tumours
DNA VIRUSES 1.. Papovavirus			
A Polyoma virus	Polyoma SV 40	Mouse Mouse	Various carcinoma and sarcoma Sarcoma in rodent
B. Papillomavirus	Bovine papilloma viruses (BPV) Human papilloma viruses(HPV)	Cattle, other mammals Man	Genital, alimentary and skin warts, oesophagial cancer Genital, laryngeal and skin warts(Papillomas)
2. Herpes virus	Marek's disease Epstein-Barr virus	Fowl Man	Neural Lymphoma Burkitt's lymphoma, nasopharyngeal carcinoma
3. Hepadnavirus	Hepatitis B group(HBV)	Man	Liver cancer
4. Adenovirus	Certain serotypes	New born mice,rats hamsters	Sarcoma

Family	Virus	Host of origin	Associated tumours
RNA VIRUSES(Retroviruses) 1. Rapidly transforming viruses			
Type B onco virus group.	Mouse Mammary tumour virus	Mouse	Mammary adenocarcinoma
Type C onco virus group	Feline sarcoma virus Murine sarcoma virus Rous sarcoma virus	Cat Mouse Chicken	Sarcoma Various sarcoma Various sarcoma
Alpha – retro viruses	Avian sarcoma Reticuloendotheliosis virus	Chicken Chicken	Various sarcoma Reticuloendotheliosis

Family	Virus	Host of origin	Associated tumours
2. Slowly Transforming viruses			
Alpha retrovirus	Lymphoid leukosis and Avian leukosis Feline leukemia virus Bovine leukemia virus Murine leukemia virus Primate leukemia-	Chicken Cat Cattle Mouse Monkey	Carcinoma, lymphomas and leukemias leukemia and lymphoma Leukemia and lymphoma Leukemia Leukemia in apes
Type D onco virus.	Human T cell leukemia virus 1	Man	Adult T cell leukemia lymphoma

RNA ONCOGENIC VIRUSES

- All RNA oncogenic viruses are retroviruses. They contain enzyme reverse transcriptase.- RNA dependent DNA polymerase
- This Enzyme allows transcription of viral RNA into DNA.
- The genome of animal retroviruses contain three sets of genes: gag-encodes structural core proteins and protease, pol-encodes reverse transcriptase and integrase, env – encodes envelope glycoproteins. All the three genes are required for viral replication.
- The genome of this virus consist two single stranded positive sense molecules of RNA (diploid ss RNA)

- Retro virus replication :
- Virus enters the cell through a receptor present on the cell membrane.
- Viral RNA is released in the cytoplasm under the influence of reverse transcriptase and a strand of negative viral DNA is synthesized.
- Reverse transcription then synthesizes the complementary strand of positive viral DNA.
- Both the strands get covalently linked to produce linear double stranded viral DNA called provirus or pro viral DNA.
- This pro viral DNA then migrates the nucleus and integrated into host cell DNA under the influence of enzyme integrase.
- After integration, the proviral DNA is transcribed by cell's own machinery to form viral messanger RNA and genomic RNA. This genomic RNA is incorporated in to new virions.
- The virion then comes out of cell by budding and thus the viral life cycle is completed.
- The envelope is acquired while budding through the cell membrane.

Mechanism of action of RNA viruses

- Animal Retroviruses transform cells by two mechanisms
- 1. Rapidly or acutely transforming viruses– contain – viral oncogene
- 2. Slowly transforming viruses – do not contain Viral Oncogene but proviral DNA (Single stranded viral RNA is converted in to Double stranded DNA & this viral DNA is integrated in to host cell genome) is always inserted near a cellular oncogene.

Differences between proto-oncogene, oncogene and viral oncogene

Proto-oncogene- Those genes which are involved in normal cell division that is in the normal growth control pathways , are called proto oncogene. Their expression is regulated during normal regeneration and repair.

Proto oncogenes are cellular genes which are not oncogenic in physiological state

Oncogene --- Alteration in the structure and expression of proto-oncogene can convert them in to oncogene which cause uncontrolled cell growth characteristic of cancer. OR

When mutated proto oncogene results in neoplastic transformation, the affected gene is called Oncogene. Thus oncogene is a tumor producing gene.

Proto oncogenes have potential to produce tumor when they are converted to oncogene.

Viral Oncogenes -- they are not viral genes , they are copies of proto-oncogenes that got incorporated (transduced) in to viral genome during the process of viral replication in a normal cell. OR

When proto oncogenes are incorporated in to rapidly transforming retroviruses , they give rise to viral oncogenes.

Viral oncogenes are mere travelers in the viral genome imparting virus into transformed cells at the expense of the ability to replicate. Such retroviruses are unable to replicate.

Proto oncogenes are the cellular genes which are not oncogenic in the physiological state.

But on alteration on their structure or expression can give rise to cancer causing oncogenes.

This occurs when proto oncogenes are incorporated into rapidly transforming retroviruses, giving rise to viral oncogenes.

Viral oncogene is acquired originally from a host cell proto oncogene by recombinant events at some earlier time in evolution of the virus.

Mechanism of action of DNA viruses

- **Mechanism of DNA viruses causing neoplastic transformation are different as per different viruses and extremely complex but There are certain features shared by DNA viruses.**
  - **1. To be transformed by a virus, the cell must survive the infection and should not die.**
    - **Permissive: Cells in which virus replication can be completed are called permissive. Such cells cannot be transformed because they die with release of newly formed virions.**
    - **Non permissive cells: Which do not allow the virus to complete its life cycle, can be transformed into neoplastic cells.**
  - **2. With most oncogenic viruses only those portion of the genome that are transcribed early in the viral life cycle are essential for transformation.**
    - **The protein products of early genes have been identified and molecular basis of their action is examined in polyomaviruses and adenoviruses.**
  - **3. In non permissive cells, oncogenic DNA viruses form stable association with the host genome. This occurs by integration of viral DNA into chromosomes. However only those integration events that interrupt late viral genes can produce transformed cells.**

Clinicopathological effects of Neoplasia

- **Systemic effects**
  - **Cachexia OR Wasting– Progressive loss of body fat & lean body mass with profound weakness, anorexia, & anemia**
  - **Paraneoplastic Syndromes- If tumor can not easily explained by symptoms like Local or distance spread of tumour or by Secretion of hormones common to the tissue from which it arise Then it is referred to this syndrome.**

This is earliest manifestation of a hidden neoplasm. Hypercalcaemia is most common paraneoplastic syndrome.

- **Local effects**
  - **Pressure atrophy, Obstruction, Pain**

GRADING OF NEOPLASMS (Broder's grading)

Grading of neoplasm is done to have its estimate about its aggressiveness or level of malignancy

- Grade I: Well differentiated tumour (<25% anaplastic cells)
- Grade II: Moderately differentiated tumour (25-50% anaplastic cells)
- Grade III: Low differentiated tumour (50-75% anaplastic cells)
- Grade IV: Poorly differentiated tumour (>75% anaplastic cells)

STAGING OF NEOPLASMS

- The staging of cancer is based on size of primary lesion, its extent of spread to regeonal lymphnodes & the presence or absence of Metastasis
- TNM System
- T (primary tumour)
  - T0 = No evidence of tumour
  - T1 = Tumour confined to primary site
  - T2 = Tumour invades adjacent tissue

- **(N = local lymph node)**
  - N0 = No evidence of tumour
  - N1 = Regional node involvement
  - N2 = Distant node involvement

Metastasis

- **(M = distal lymph node)**
  - M0 = No evidence of metastasis
  - M1 = In same cavity/place as primary tumour
  - M2 = Distant metastasis
    - Stage I = T1, N0, M0
    - Stage II = T1, N0, /N1, M1
    - Stage III = T2, N1/N2, M2

Laboratory Diagnosis of cancer

- Clinician and Pathologist collaboration
- Specimen
  - Adequate
  - Representative
  - Properly preserved

1. Histological and Cytological methods

- Biopsy
- FNAC
  - Aspiration of cells from a tumour
  - It prevent unnecessary surgery and its risk
  - By experienced hand it can be reliable, rapid and helpful
- Cytology(Papanicolaou) Smears
  - Bladder and prostate tumour and gastric carcinoma in dog
  - Identification of tumour cells in abdominal, pleural, joints and cerebrospinal fluid. (Exfoliative cytology). Neoplastic cells are less stick together & are shed in to fluid or secretions. The sheded or exfoliated cells are evaluated for features of malignanc.
- Frozen section diagnosis
- Histopathological diagnosis
- Immunocytochemistry
- Southern blot analysis
- Flow cytometry
- DNA probe analysis

2. Biochemical Assays

- Tumour associated enzymes
- Hormones
- Other tumour markers in blood

  are helpful and also useful in determining the effectiveness of therapy
- The important established tumour markers in human are
- 1. Carcino-embryonic antigen(CEA)
- 2. Alpha-foetoprotein.

  Their levels are increased in tumour state

3. Molecular Diagnosis

- 1. Polymerase chain reaction (PCR) : to differentiate between monoclonal and polyclonal (reactive)proliferations
- 2. Fluorescent in situ hybridization(FISH) technique: useful in locating translocation characteristic of many tumors.
- 3. DNA microarray analysis also called gene chip technology allows measurements of expression of several thousand genes.

Radiological diagnosis – using X-rays , Ultrasonography, C T Scanniong can also aid in detection of tumor.

Tumour immunity

Malignant transformation is associated with complex genetic alterations. Some of these may result in expression of proteins that are treated as non-self or foreign by the immune system.

Immuno surveillance that is recognition and destruction of non- self tumor cells on their appearance , by the immune system. This become imperfect or some tumor escape this mechanism.

Tumour antigens: Tumour cells differ antigenically from normal cells. They either gain or lose membrane molecules. Antigens that produce immune response have been demonstrated in many experimentally induced and in animal and human tumours. They are

1. Tumour Specific antigens- are present only on tumour cells and not on normal cells.
2. Tumour associated antigens: - are present on tumour cells as well as on some normal cells.

Tumor Specific antigens: These were demonstrated in chemically induced tumors of mice and rats. They express private or unique antigens not shared by other histologically similar tumors induced by the same chemical even in the same animal.

Tumor associated antigens: These are not specific to the individual tumor, but are shared by similar tumors in other hosts.

Both CMI & Humoral immunity can have anti tumour activity. The cells that mediate tumor immunity are

1. Cytotoxic T-cells (CD8+ T cells): They have protective role mainly against virus associated tumors.

   By recognizing MHC class 1 antigens expressed on tumour cells, cytotoxic T cells destroy the tumor cells.

   (MHC-I molecules bind to antigens derived from proteins synthesized within the cells (e.g. viral antigens, Because they are present on virtually all nucleated cells, virus infected cells can be detected and lysed)

- 2. Natural Killer cells.These are the lymphocytes capable of destroying tumour cells without prior sensitization. They provide first line of defense against tumour cells. After activation NK cells can lyse wide range of animal and human tumors. T cells and NK cells provide complementary (mutually supportive) anti tumour mechanisms.
- NK cells express surface receptors that enable to kill neoplastic or virus infected cellscan not lyse healthy nucleated cells.
- 3. Macrophases; activated macrophases show selective cytotoxicity against tumor cells. T cells, NK cells and macrophages may work together in their anti tumour activity.

- Humoral mechanism may participate in tumor cell destruction by
- i) activation of complement : here antibody bind to cell surface antigen and this causes fixation of complement to the cell surface with subsequent lysis through membrane attack complex
- ii) induction of antibody dependent cellular cytotoxicity

- ADCC- mediated by antibodies. These antibodies are targeted against target antigens on the surface of cells or tissue components.
- This form dependent upon killing through cells that bear receptors for Fc portion of Ig G. Target cells coated by antibody are destroyed without phagocytosis or complement activation

Horn Cancer

Histologically Horn cancer is squamous cell carcinoma. This is a commonly occuring tumor of Indian Zebu cattle & large horned breeds like Kankrej & Gir in Gujarat. It is most common in bullocks & rare in cows& very rare in buffaloes.

Horn cancer arises from horn core epithelium whish is simple columnar type.

The cancerous growth begins from middle or distal region of the core & progress towards base & frontal sinus.

Grossly- The tumor is pinkish in color & polyploid like cauli flower appearance. It is friable & bleeds easily.

Microscopically _- It is squamous cell carcinoma & characterised by presence of epithelial pearls. Metastasis occur in regional lymphnodes & visceral organs like heart & lung

Ethmoid Neoplasm

- The tumor arising from mucosal lining of ethmoid bone is seen in cattle & buffaloes in India in southern states of Kerala & Tamil nadu.
- The histological type is Adenocarcinoma.
- The tumor growth blocks the paranasal sinuses & nasal & pharangeal passages

Basai cell carcinoma

- Originate from Basal or germinal layer (stratum germinativum) of the epidermis & also mfrom basal cells of hair follicles,sebaceous glands & sweat glands. Usually this tumor is locally invasive in the dermis & does not metastatise. This is also called Rodent ulcer because of its gross appearance. The tumor ulcerate on the skin ulcerations are characterised by pearly border as it gnawed by rodent.