ETIOLOGY OF CANCER: CARCINOGENIC AGENTS
CLINICAL ASPECTS OF NEOPLASIA

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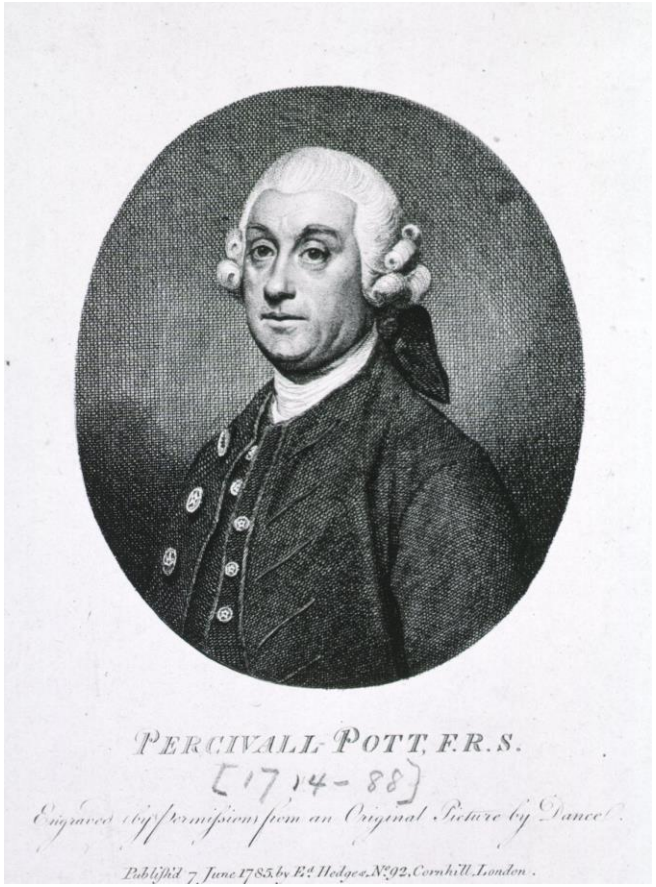
Three classes of carcinogenic agents have been identified:

- **Chemicals.**
- **Radiant energy.**
- **Microbial products.**

Carcinogenic agents inflict genetic damage;

& carcinogenesis is a multistep process resulting from the accumulation of multiple **genetic alterations** that give rise to the transformed phenotype and all of the associated hallmarks



CHEMICAL CARCINOGENS

MAJOR CHEMICAL CARCINOGENS

A. *Direct-Acting Agents:*

- requires no metabolic conversion to become carcinogenic.
- Weak carcinogens, some of them are cancer chemotherapy drugs, e.g., (alkylating agents).
- also Acylating Agents.
- Risk for induced cancer is low, ..Leukemias

MAJOR CHEMICAL CARCINOGENS

B. Indirect-Acting Agents :

- chemicals that require metabolic conversion to an ultimate carcinogen

Polycyclic Hydrocarbons:

One of the most potent indirect carcinogens. created with burning of fossil fuels, plant, and animal material.

Benzo[a]pyrene and other carcinogens formed during tobacco smoking: lung cancer

Aromatic Amines, Amides, Azo Dyes:

β-naphthylamine → a 50-fold increased incidence of bladder cancers in heavily exposed workers in the aniline dye and rubber industries.

Natural Plant and Microbial Products

Like Aflatoxin B1, produced by some strains of Aspergillus, grows on improperly stored grains and nuts. Food contaminant >> hepatocellular carcinoma

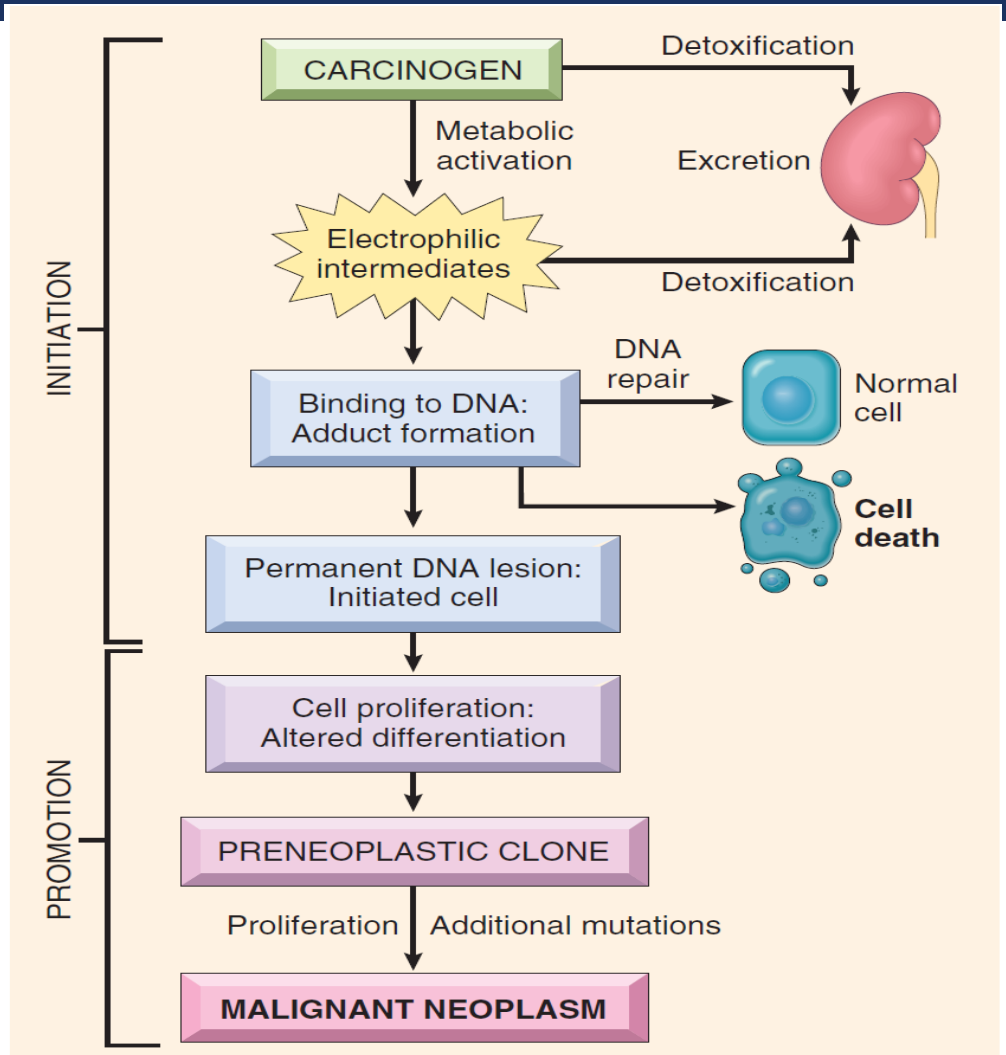
Nitrites

used as food preservatives have caused concern >> nitrosylation of amines in food >> nitrosamines formed are suspected to be carcinogenic.

MECHANISMS OF ACTION OF CHEMICAL CARCINOGENS

Chemical carcinogenesis is a two-step process:

- Initiation: Results from exposure to carcinogenic agent. Permanent DNA damage. Not sufficient alone for tumor formation
- Promotion: Induce tumor from an initiated cells. Nontumorigenic themselves. Repeated or sustained exposure to the promoter must follow the application of the mutagenic chemical.
- Tumor promoters act by stimulating cell proliferation. Increased proliferation may occur through direct effects of tumor promoters on target cells or may be secondary to tissue injury and regenerative repair



RADIATION CARCINOGENESIS

- Radiation (UV rays of sunlight, radiographs, nuclear fission, radionuclides) is an established carcinogen.
- Radiation mutagenic effects: chromosome breakage & chromosomal rearrangements, e.g., translocations & inversions.
- Doublestranded DNA breaks is the most important form of DNA damage caused by radiation.
- Natural UV radiation (Sun) can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas).

At greatest risk are fair-skinned people, living in locales that receive a great deal of sunlight. (AUS,NZL).

+ Nonmelanoma skin cancers: total cumulative exposure to UV radiation.
+ Melanomas: intense intermittent exposure, as occurs with sunbathing.
+ UV light → forms pyrimidine dimers→ overwhelms nucleotide excision repair pathway →Failed repair →Skin Cancer

VIRAL AND MICROBIAL ONCOGENESIS

- *Oncogenic RNA Viruses:*

HTLV-1 causes *adult T-cell leukemia/lymphoma* (ATLL).

- Endemic in parts of Japan, the Caribbean basin, South America, and Africa, and sporadic elsewhere.
- HTLV-1 has tropism for CD4+ T cells, so CD4+ T cells is the major target for neoplastic transformation.
- Leukemia develops in 3-5% of the infected individuals, typically after a long latent period of 40-60 years

VIRAL AND MICROBIAL ONCOGENESIS

- *Oncogenic DNA Viruses:*

several oncogenic DNA viruses can cause tumors in animals. Five are strongly associated with human cancer.

- HPV.
- Epstein-Barr virus (EBV)
- Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8[HHV-8]).
- A polyoma virus called Merkel cell virus.
- Hepatitis B virus (HBV)

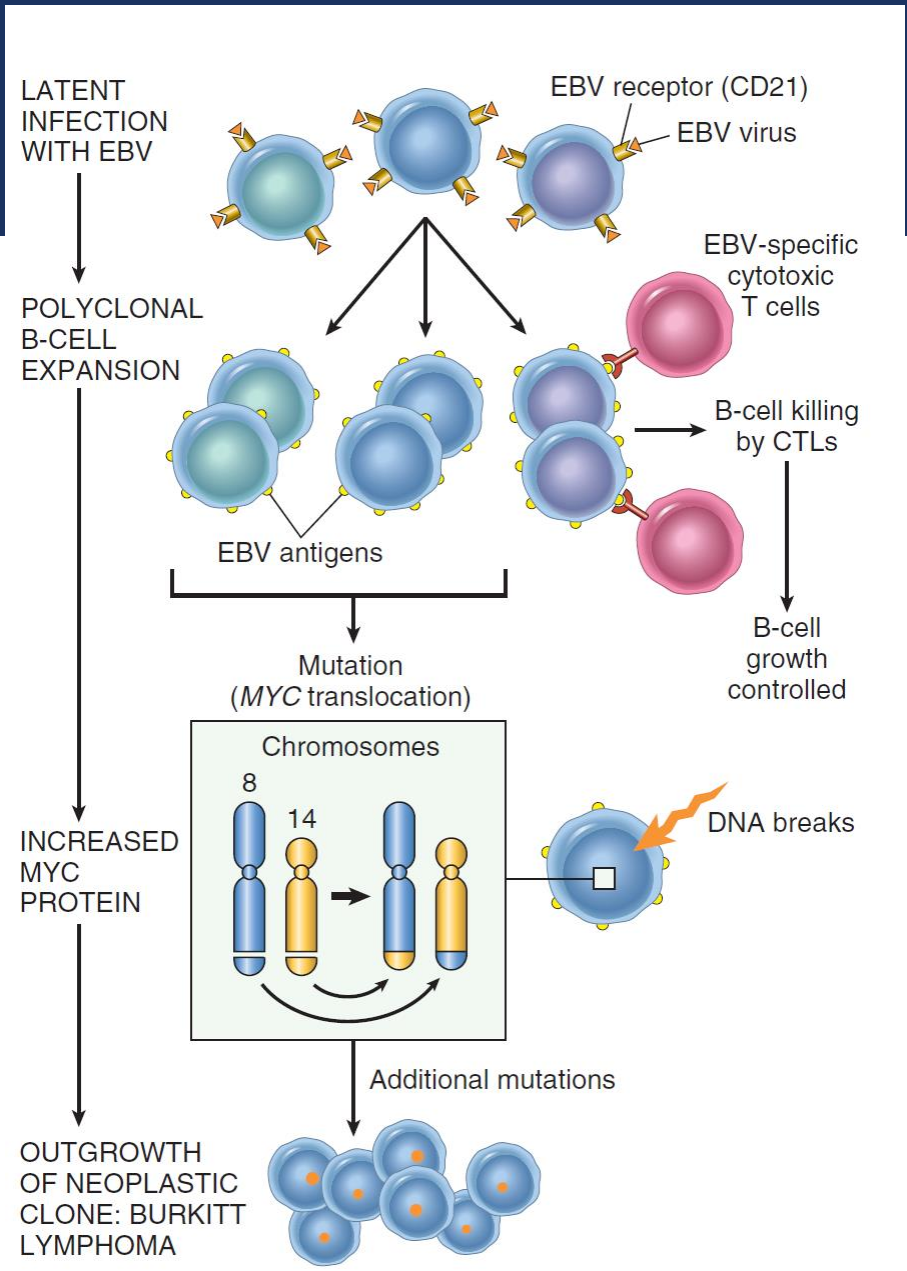
HUMAN PAPILLOMAVIRUS

Types based malignant potential of their lesions:

- Low-risk HPVs, 6 & 11: Genital warts, low malignant potential.
- High-risk HPVs, 16 & 18: several cancers, SCC of the cervix and anogenital region. In addition, ~ 20% of oropharyngeal cancers(arising in the tonsils).
- The oncogenicity of HPV is related to the expression of two viral oncoproteins, E6 and E7, which bind to the p53 and RB tumor suppressors, respectively, neutralizing their function.

EPSTEIN-BARR VIRUS

- **EBV, a member of the herpesvirus family.**
- **The first virus linked to a human tumor → Burkitt lymphoma.**
- **Additionally,** EBV is implicated in the pathogenesis of lymphomas in immunosuppressed patients, Hodgkin lymphoma, uncommon T-cell and NK-cell tumors, nasopharyngeal carcinoma, a subset of gastric carcinoma, and rarely sarcomas



HEPATITIS B AND HEPATITIS C VIRUSES

- Around 70-85% of hepatocellular carcinomas worldwide are caused by HBV or HCV.
- HBV and HCV do not encode any viral oncoproteins, and has no consistent pattern of integration within the human genome in liver cells.
- The oncogenic effects of them is multifactorial, the dominant effect is immunologically mediated chronic inflammation with hepatocyte death→ regeneration→ genomic damage.

HELICOBACTER PYLORI

- **Implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.**
- the first bacterium classified as a carcinogen.
- Similar scenario to that for HBV- and HCV-induced liver cancer: increased epithelial cell proliferation due to chronic inflammation in which the inflammatory milieu contains numerous genotoxic (ROS).
- Chronic inflammation/gastritis → gastric atrophy → intestinal metaplasia of the lining cells → dysplasia → cancer.
- *H. pylori* infection leads to polyclonal B-cell proliferations and that eventually a monoclonal B-cell tumor (MALT lymphoma) emerges as a result of accumulation of mutations.

CLINICAL ASPECTS OF NEOPLASIA

- both malignant and benign tumors may cause problems because of

(1) location and impingement on adjacent structures

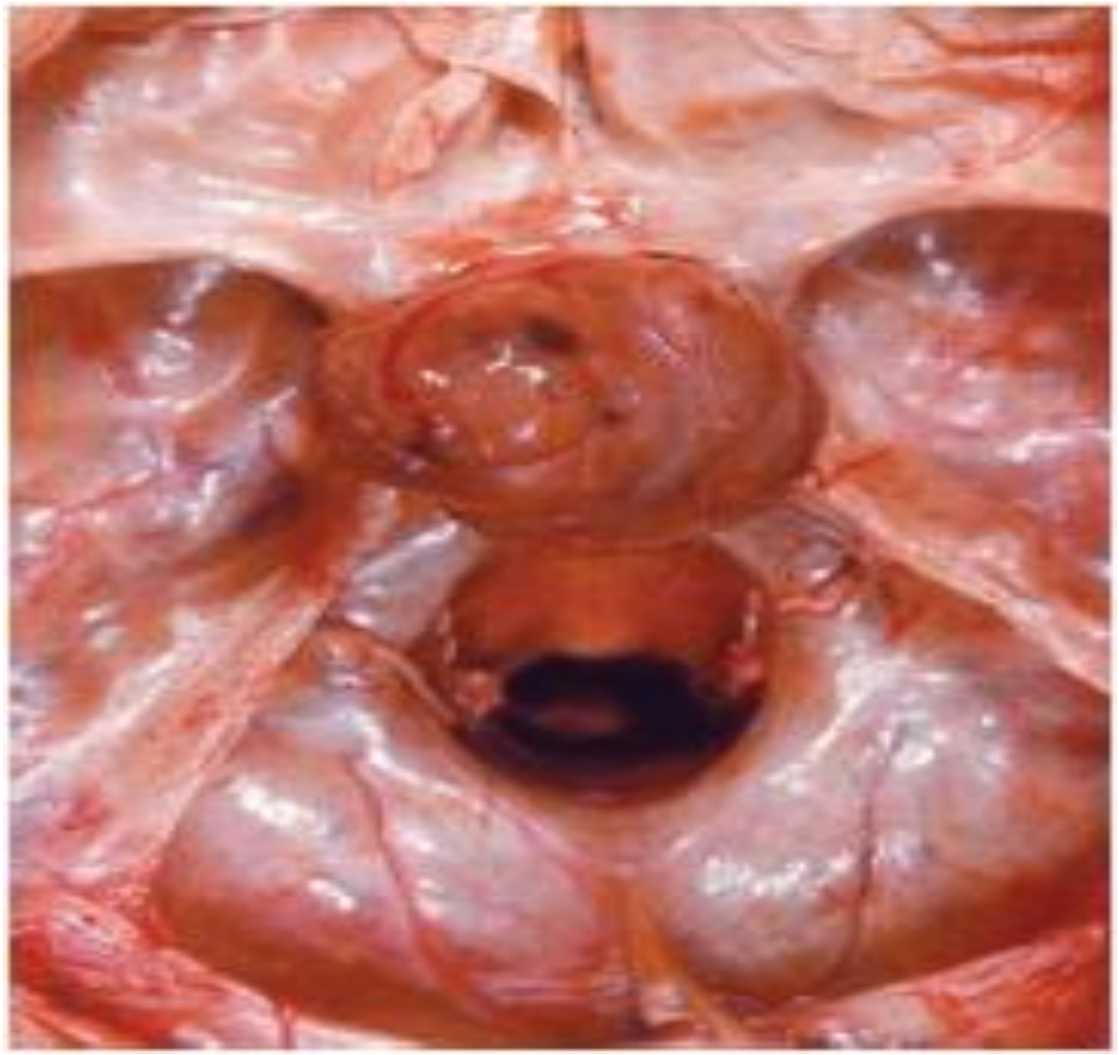
(2) functional activity such as hormone synthesis or the development of paraneoplastic syndromes

(3) bleeding and infections when the tumor ulcerates through adjacent surfaces

(4) symptoms that result from rupture or infarction.

(5) cachexia or wasting.

A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland, giving rise to hypopituitarism.



CANCER CACHEXIA

- **Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia—a condition referred to as *cachexia***
- There is some correlation between the size & extent of spread of the cancer & the severity of the cachexia.
- not caused by the nutritional demands of the tumor, current evidence indicates that it results soluble factors produced by the tumor and the host, rather than reduced food intake; TNF and cytokines.

- Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor are referred to as..

PARANEOPLASTIC SYNDROMES:

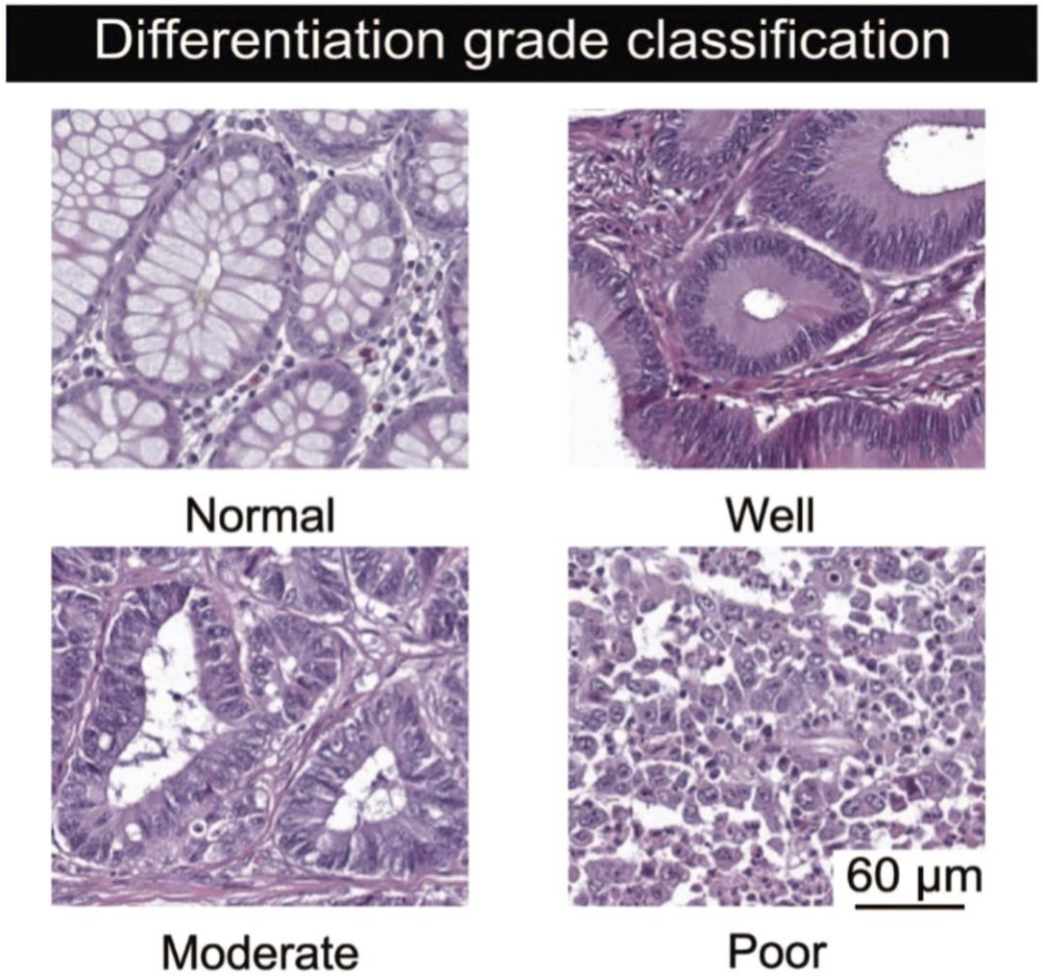
Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate anti-diuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Anti-diuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Ovarian carcinoma	Insulin or insulin-like substance
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic

GRADING AND STAGING

- Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary for arriving at an accurate **prognosis** and for comparing end results of various treatment **protocols**.
- **staging has proved to be of greater clinical value.**

GRADING

- Grading of a cancer is based on the degree of differentiation of the tumor cells and, in some cancers, the number of mitoses and the presence of certain architectural features.



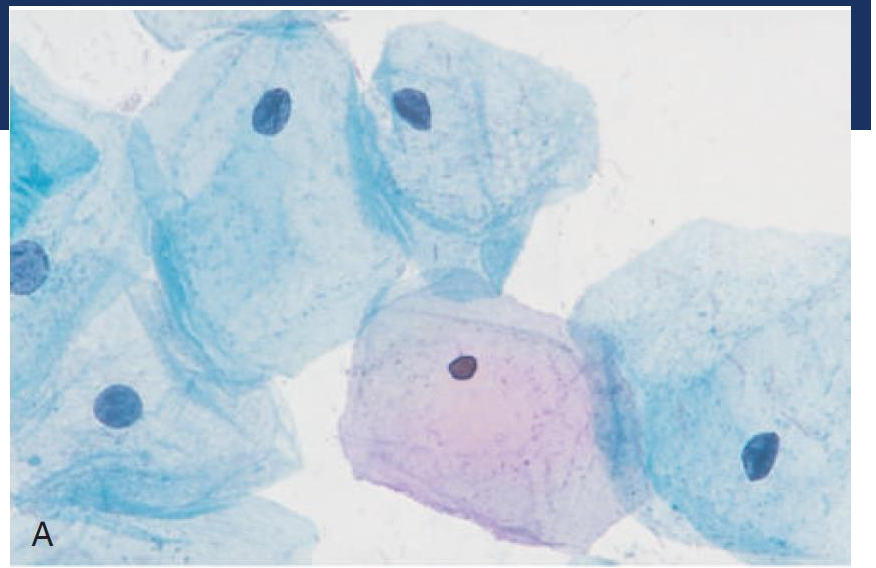
STAGING

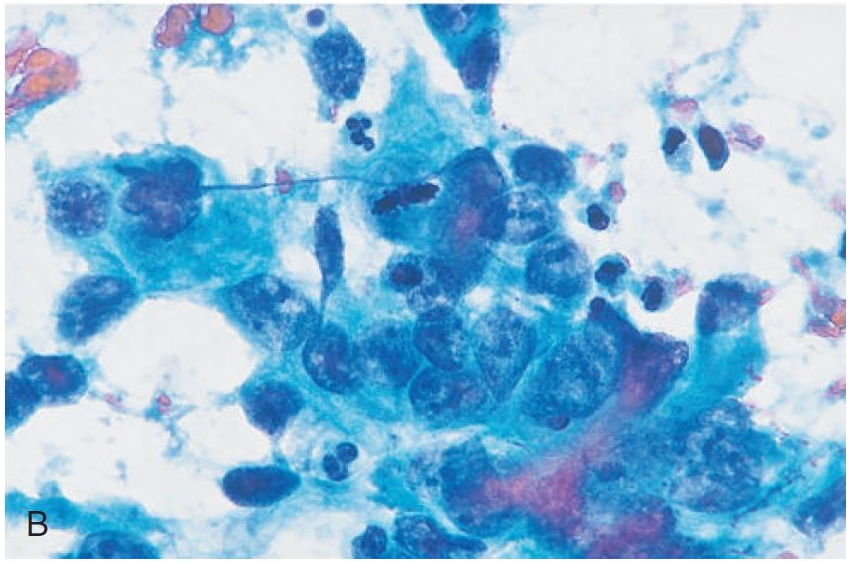
- The staging of solid cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of bloodborne metastases.
- The major staging system currently in use is the American Joint Committee on Cancer Staging.
- This system uses a classification called the TNM system—T for primary tumor, N for regional lymph node involvement, and M for metastases.
- TNM staging varies for specific forms of cancer, but there are general principles.
- The primary lesion is characterized as T1 to T4 based on increasing size.
- N0 mean no nodal involvement, whereas N1 to N3 would denote involvement of an increasing number of nodes.
- M0 signifies no distant metastases, whereas M1 or sometimes M2 reflects the presence and estimated number of metastases.

LABORATORY DIAGNOSIS OF CANCER

- Morphologic Methods:

Several sampling approaches are available, including excision or biopsy, fine-needle aspiration, and cytologic smears.



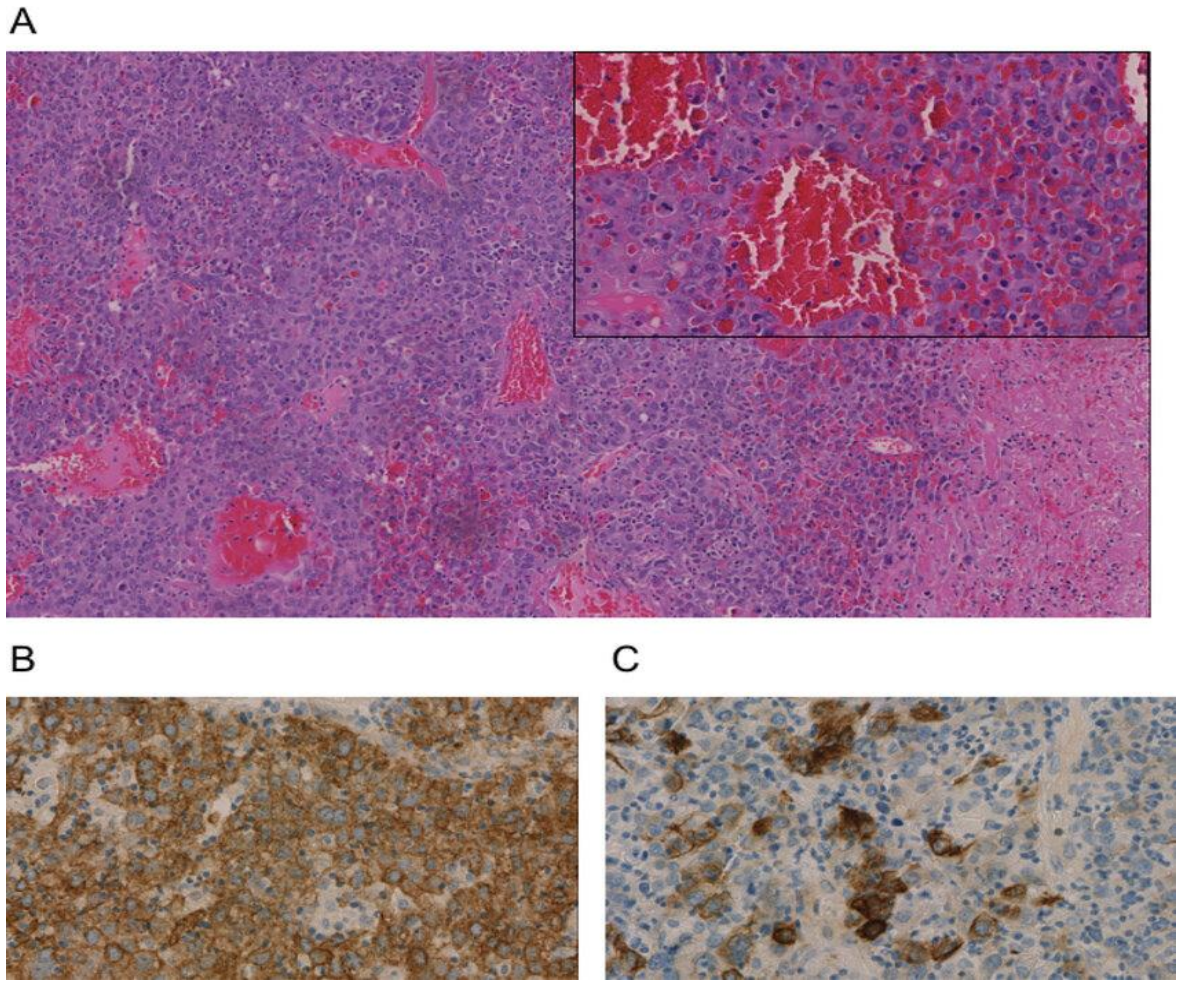


LABORATORY DIAGNOSIS OF CANCER

- Immunohistochemistry :

Offers a powerful adjunct to routine histologic examination.

Allow categorization of undifferentiated tumor using immun-based process and Ab(s) for a specific cellular protein.



LABORATORY DIAGNOSIS OF CANCER

- Tumor Markers :

Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood *cannot be utilized for definitive diagnosis of cancer*; however,they are used with varying success as screening tests and have utility in monitoring the response to therapy or detecting disease recurrence.

PSA	prostatic adenocarcinoma.
CEA	colon, pancreas, stomach, and breast Ca.
AFB	hepatocellular carcinomas, yolk sac remnants in the gonads

LABORATORY DIAGNOSIS OF CANCER

Molecular Diagnosis :

An increasing number of molecular techniques are being used for the diagnosis of tumors and for predicting their behavior.

1. Diagnosis of malignancy:

PCR-based detection of BCR-ABL transcripts can confirm the diagnosis of chronic myeloid leukemia .

2. Prognosis and behavior:

Certain genetic alterations are associated with a poor prognosis, e.g HER2 and NMYC, expression breast cancers and neuroblastomas, respectively.

3. Diagnosis of hereditary predisposition to cancer, e.g BRCA1