NEOPLASIA : 8
CLINICAL FEATURES OF TUMORS & LABORATORY DIAGNOSIS OF CANCER

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Clinical Features of Tumors

- Tumors are essentially parasites with some only causing mischief while others are catastrophic

- All tumors, even benign ones, can cause morbidity and mortality

- The following will be discussed under this heading:
- 1) the effects of a tumor on the host
- 2) the grading and clinical staging of cancer
- 3) the laboratory diagnosis of tumors

Effects of Tumor on Host

- Certainly cancers are far more threatening than benign tumors but both types can cause problems because of:
- 1) location and impingement on adjacent structures
- 2) functional activity such as hormone synthesis
- 3) bleeding and secondary infections when they ulcerate
- 4) initiation of acute symptoms caused by either rupture or infarction

Effects of Tumor on Host: Local and Hormonal Effects

- Location of a tumor may be critical as for example Pituitary adenoma. While this tumor is benign and even though a particular one may not produce hormone, a pituitary adenoma can destroy the remaining gland and cause serious endocrinopathy;
- Benign and malignant tumors of the gut may cause obstruction

- Neoplasms arising in endocrine glands may produce manifestations by elaboration of hormones
- The erosive destructive growth of cancers or the expansile pressure of a benign tumor on any surface may cause ulcerations, secondary infections and bleeding

Clinical manifestations of Cancer

- Cachexia – wasting
- anorexia
- early satiety
- weight loss
- anemia
- marked weakness
- taste alterations
- altered metabolism

- Anemia
- chronic bleeding
- malnutrition
- medical therapies
- malignancy in blood forming organs
- Administer erythropoietin

Cancer Cachexia

- Cancer patients commonly suffer progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia and anemia. This wasting syndrome is termed CACHEXIA
- The causes of cachexia are obscure but cachexia is NOT caused by the nutritional demands of the neoplasm

- Current evidence indicates that cachexia results from the action of soluble factors such as cytokines (TNF-alpha and IL-1) either produced by the tumor or the host
- Reduced food intake alone is not sufficient to explain the cachexia of malignancy

Paraneoplastic Syndromes

- Symptom complexes in cancer patients that cannot readily be explained, either by the local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose, are known as PARANEOPLASTIC SYNDROMES

- Paraneoplastic syndromes are important for three reasons:
- 1) they may represent the earliest manifestation of an occult tumor
- 2) they may represent significant clinical problems and may even be lethal
- 3) they may mimic metastatic disease and therefore confound treatment

Endocrinopathies

Cushing Syndrome	Small cell carcinoma-lung; pancreatic carcinoma; neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate ADH secretion	Small cell carcinoma-lung; intracranial neoplasms	ADH or Atrial natriuretic hormones

Hypercalcemia	Lung (sq. cell), breast, ovarian, renal carcinoma; T-cell leukemia/ lymphoma	PTH-related peptide, TGF-alpha, TNF-alpha, IL-1
Carcinoid Syndrome	Bronchial adenoma; pancreatic & gastric carcinomas	Serotonin, bradykinin, ? Histamine

Hypoglycemia	Fibrosarcoma & other sarcomas; hepatocellular carcinoma	Insulin or insulin-like substances
Polycythemia	Renal & hepatocellular carcinomas; cerebellar hemangioma	Erythropoietin

Nerve and Muscle Syndromes

Myasthenia	Bronchogenic carcinoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma	Immunologic

Dermatologic Disorders

Acanthosis nigricans	Gastric, lung & uterine carcinomas	?Immunologic, ? Secretion of epidermal growth factor
Dermato-myositis	Bronchogenic & breast carcinomas	?Immunologic

Osseous, Articular, Soft Tissue Change

Hypertrophic osteoarthropathy and clubbing of fingers	Bronchogenic carcinoma	Unknown

Vascular/Hematologic Changes

Venous thrombosis (Trousseau phenomenon)	Pancreatic & Bronchogenic carcinomas; other neoplasms	Tumor products (mucins that activate clotting)
Non-bacterial thrombotic endocarditis	Many advanced cancers	Hyper-coagulability

Anemia	Thymic neoplasms	Unknown
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

Grading and Staging of tumors

- Grading = microscopic
- Staging = clinical

- Staging is more useful.

- Grading is based on the microscopic features of the cells which compose a tumor and is specific for the tumor type.
- Staging is based on clinical, radiological, and surgical criteria, such as, tumor size, involvement of regional lymph nodes, and presence of metastases. Staging usually has more prognostic value.

GRADING of a cancer is based on the degree of differentiation of the tumor cells and the number of mitoses within the tumor as presumed correlates of the neoplasm's aggressiveness

Cancers are classified as grades I to IV with increasing anaplasia

Grading system for breast cancer

Tubules		Pleomorphism		Mitoses	
lots of tubules	1	small, uniform cells	1	0-9 mitoses/10 hpf	1
some tubules	2	larger, less uniform cells	2	10-19 mitoses/10 hpf	2
rare tubules	3	markedly pleomorphic cells	3	≥20 mitoses/10 hpf	3

add all points together

	Score	5y survival
Low grade	3-5	>95%
Intermediate grade	6-7	80%
High grade	8-9	60%

Grade

- The STAGING of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases
- There are two major staging systems: 1) Union International Contre Cancer (UICC) and 2) American Joint Committee (AJC) on Cancer Staging

- The UICC uses the TMN system
- T for primary tumor: T0 (in situ); T1 to T4 with increasing size
- N for regional lymph node involvement: N0(none); N1 to N3 denotes involvement of an increasing number and range of nodes
- M for metastases: M0(none); M1 and M2 indicates the presence of metastasis and number

- The AJC employs a different nomenclature and divides all cancer into stages 0 to IV, incorporating within each of these stages the size of the primary lesion as well as the presence of nodal spread and distant metastases
- The use of these systems described in consideration of specific tumors

Stages of cancer spread:

- Stage 1 – confined to site of origin
- Stage 2- cancer is locally invasive
- Stage 3 – cancer has spread to regional structures
- Stage 4- cancer has spread to distant sites

Staging TNM system

- Size of tumor – T0, T1, T2,T3
- Degree of local invasion – lymph node involvement
- Extent of spread – metastasis

Laboratory Diagnosis of Cancer

- Every year the approach to laboratory diagnosis of cancer becomes more complex, more sophisticated and more specialized
- Importance of Clinician in diagnosis: 1) clinical data; 2) adequate, representative and properly preserved specimen

- Importance of proper history e.g. healing fracture simulates osteosarcoma…
- Radiation changes simulate cancer….
- Psuedoepitheliomatous hyperplasia of skin…
- Granulation tissue (exuberant) might mimic cancer…

- adequate, representative and properly preserved specimen..
- Ill-preserved specimen-morphology spoiled by autolysis…
- Central area of tumor shows necrosis- FNAC from the area not representative…
- Testicular Biopsy in Bouin’s fluid-formalin ruins morphology…

- Sampling approaches for histologic and cytologic methods:
- 1) excision or biopsy;
- 2) fine-needle aspiration (FNAC); Bone marrow aspiration
- 3) cytologic smears- Exfoliative, Imprint, Wash…aspiration….

Diagnostic procedures

- FNA (fine needle aspiration)
- Cytological smears
- Biopsy
- Frozen sections
- Biochemical assays
- Molecular diagnosis
- Flow cytometry

Pap smear with dysplasia

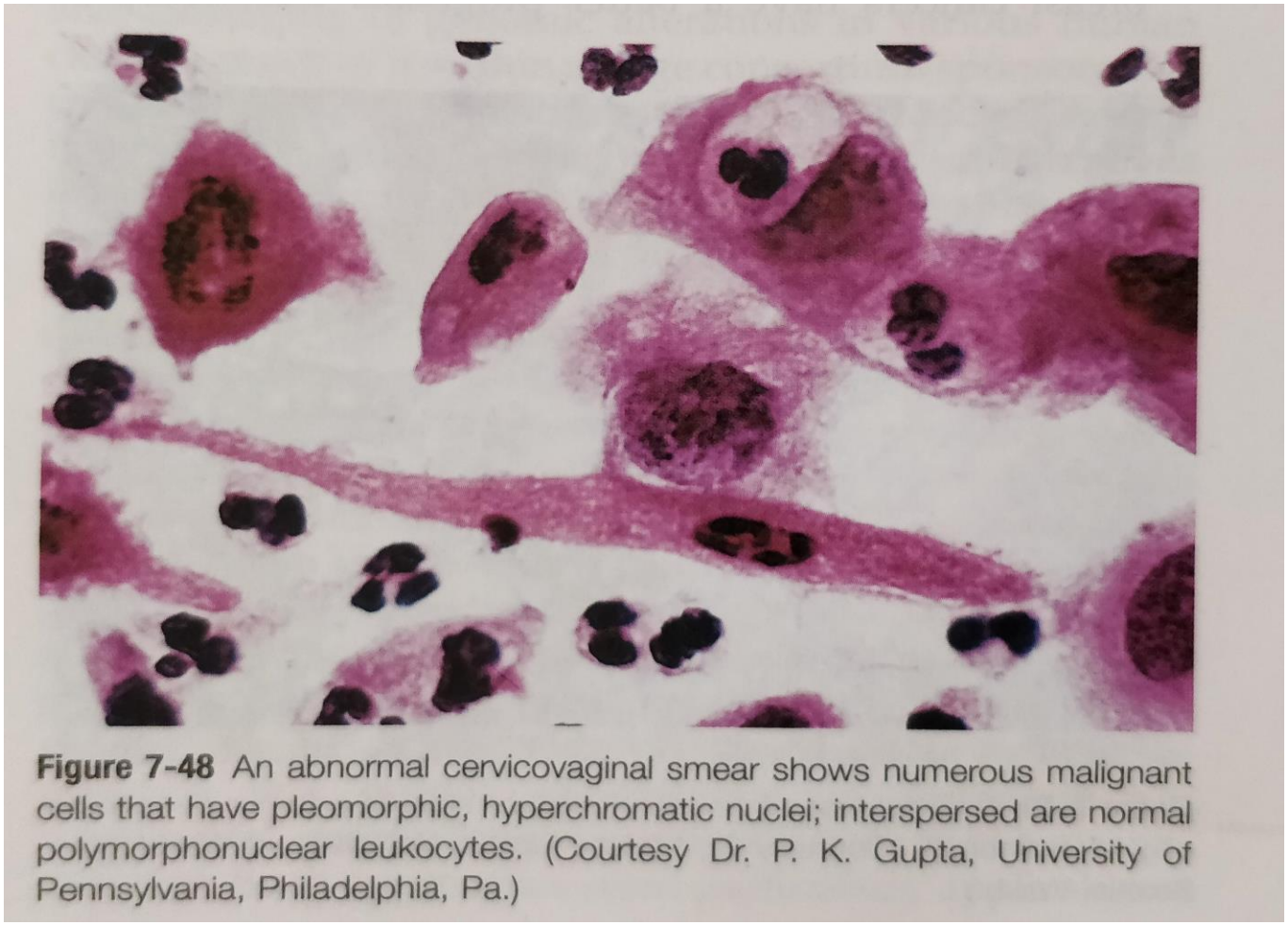


Figure 7-48 An abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

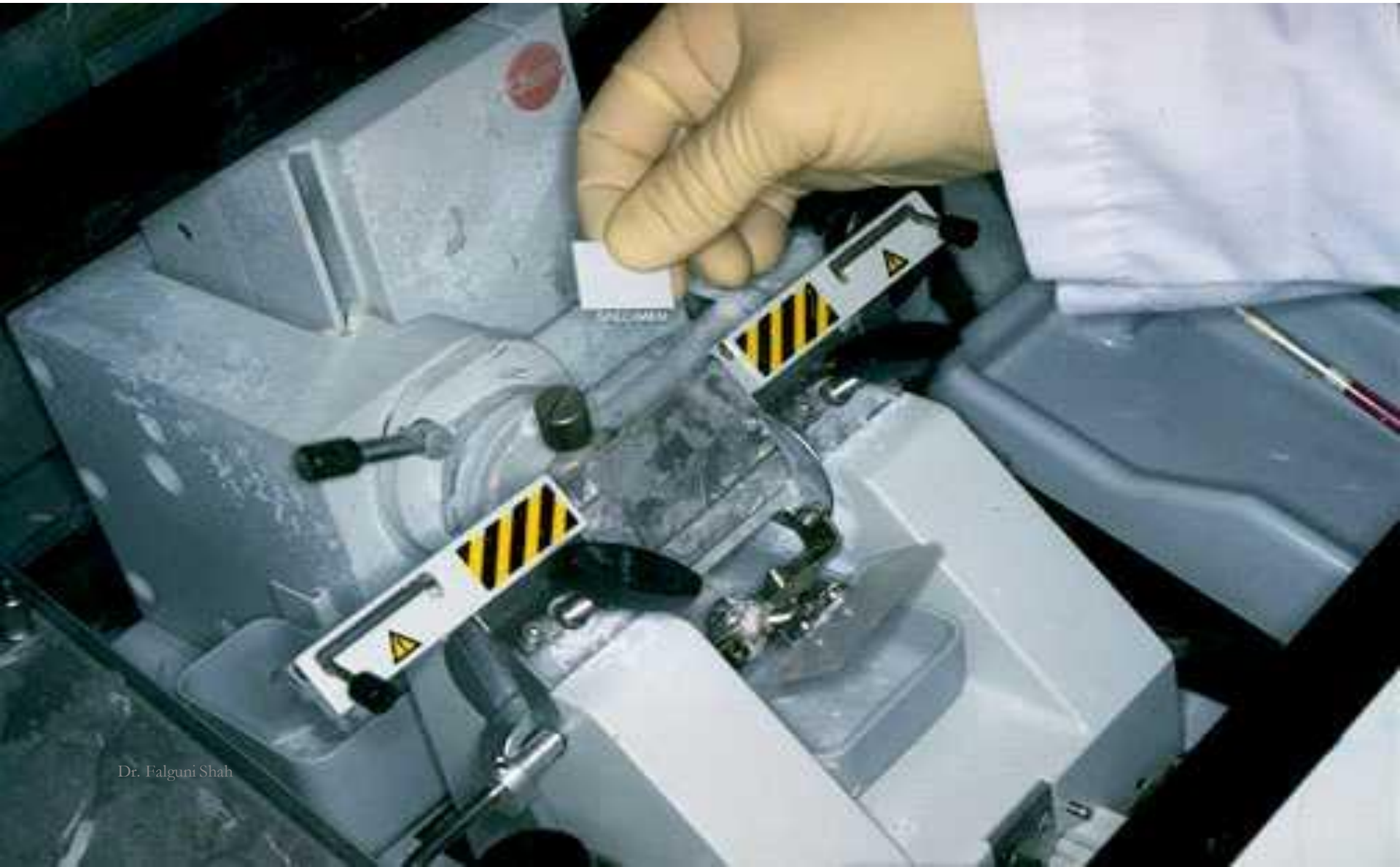
Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017

Biopsy

- Incisional
- Excisional(Importance of surgical margins)
- True –cut

- Autopsy……

Frozen section



staining a frozen section

Ancillary studies

- Immunohistochemistry
- Cytogenetics
- Flow cytometry
- Electron microscopy

Laboratory Diagnosis of Cancer

- Immunocytochemistry:

- Availability of specific monoclonal antibodies has greatly facilitated the identification of cell products or surface markers

The utility of immunohistochemistry

- 1) Categorization of undifferentiated malignant tumors; ex. keratin in tumors of epithelial origin
- 2) Categorization of leukemias and lymphomas; ex. classification of T and B cell tumors
- 3) Determination of site of origin of metastatic tumors; ex. prostate-specific antigen in a tumor
- 4) Detection of molecules that have prognostic or therapeutic significance; ex. detection of hormone (estrogen and/or progesterone) receptors in breast cancer cells

AFP stain on a yolk sac tumor

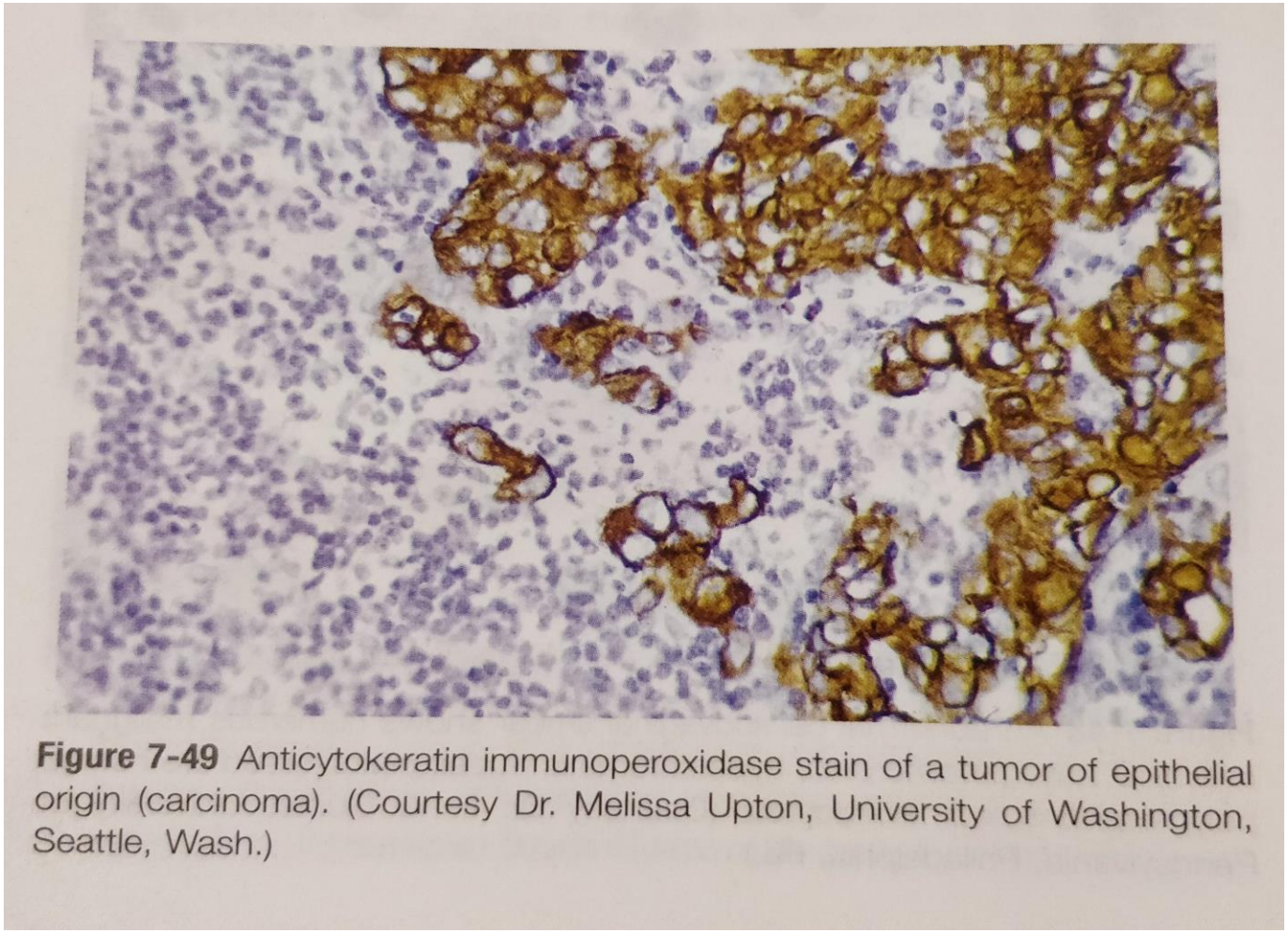
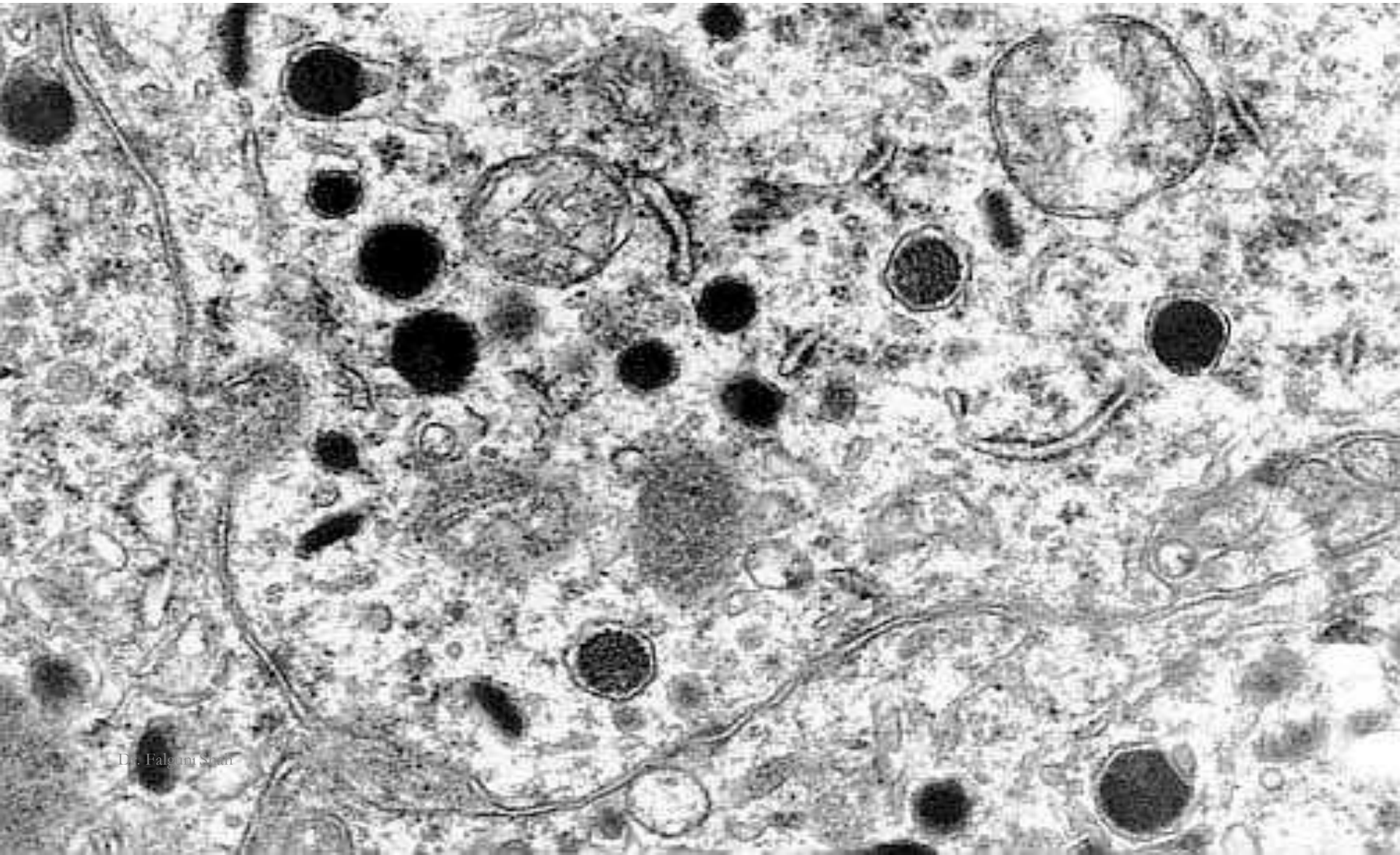


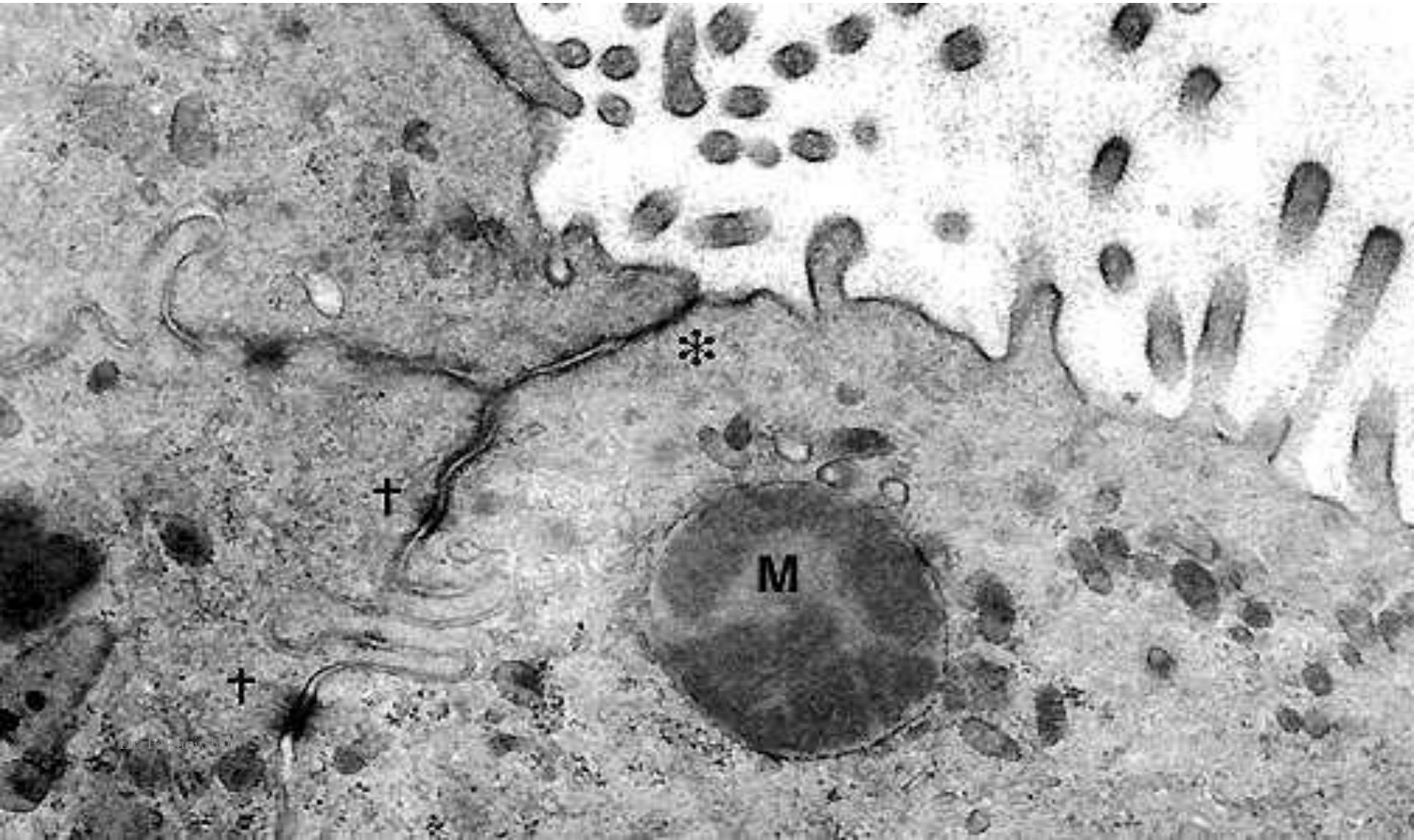
Figure 7-49 Anticytokeratin immunoperoxidase stain of a tumor of epithelial origin (carcinoma). (Courtesy Dr. Melissa Upton, University of Washington, Seattle, Wash.)

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

EM: Neurosecretory granules



EM: microvilli, tight junction in an adenocarcinoma



Flow Cytometry

- Flow cytometry can rapidly and quantitatively measure several individual cell characteristics, such as membrane antigens and DNA content of tumor cells
- Cell surface antigens can be used for classification; ex. leukemias/lymphomas
- Relationship between DNA content and prognosis; ex. aneuploidy-poorer prognosis

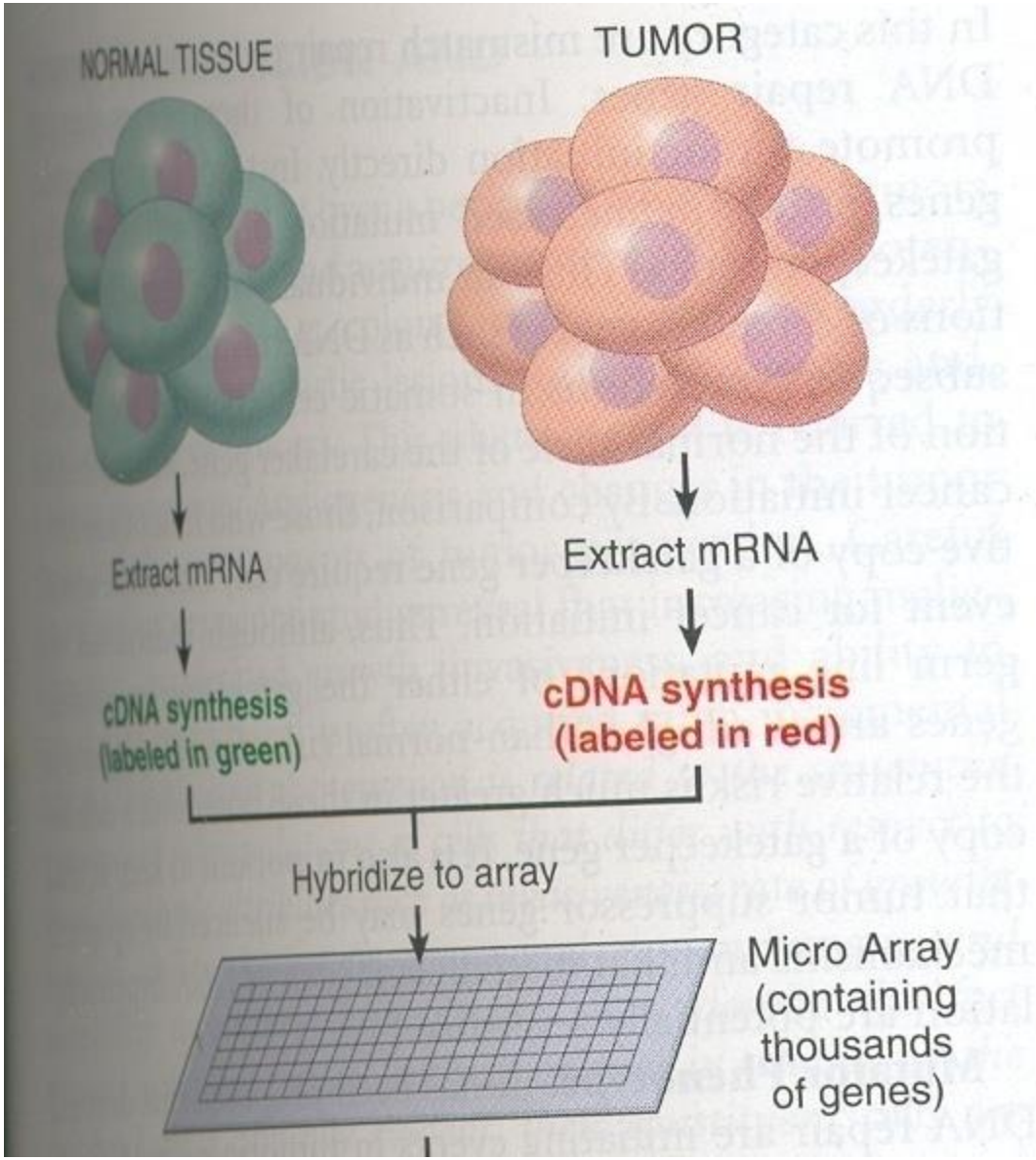
Molecular Diagnosis

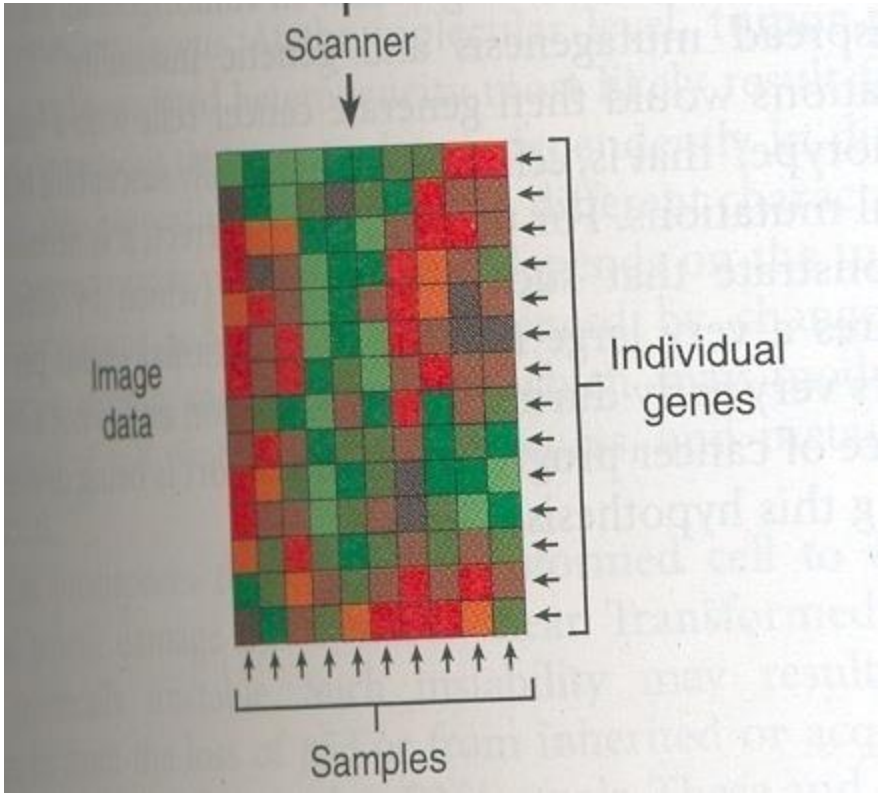
- 1) Diagnosis of malignant tumors; ex. molecular techniques used in differentiating benign (polyclonal) proliferations of T or B cells from malignant (monoclonal) proliferations
- 2) Prognosis of malignant neoplasms; ex. N-myc gene and deletions of 1p bode poorly for patients with neuroblastoma

- 3) Detection of minimal residual disease; ex. PCR-based amplification gives a measure of residual leukemia cells in treated pts. with chronic myeloid leukemia
- 4) Diagnosis of hereditary predisposition to cancer; ex. germ line mutation in cancer-suppressor genes is associated with an extremely high risk of developing specific cancers

Microarrays-Gene chip technology

- In this method, DNA fragments either c-DNA or oligonucleotides are spotted on a glass-slide or on some solid support. As the techniques used for the spotting are similar to those employed to produce semiconductor chips for electronic products, the arrays are known as GENE CHIPS.


NORMAL TISSUE
TUMOR
Extract mRNA
Extract mRNA
cDNA synthesis
(labeled in green)
cDNA synthesis
(labeled in red)
Hybridize to array
Micro Array
(containing
thousands
of genes)


Scanner
Image data
Individual genes
Samples

Molecular Profiles of tumor- The future of cancer diagnosis

- Epigenome- sequence of an entire genome
- -quantify all RNA expressed in cell population
- -snapshot of all cell metabolites
- National Cancer Institute called THE CANCER GENOME ATLAS (TCGA)
- Provide a snapshot of all genetic alterations that exist in a particular tumor, identification of new mutations & used to manage patient

Biochemical assays

- Tumor markers: sometimes diagnostic or prognostic
- Can be helpful in monitoring effectiveness of therapy or in detecting relapses/recurrences

Tumor Markers

- Tumor markers are biochemical indicators of the presence of a tumor
- Tumor markers include: cell surface antigens, cytoplasmic proteins, enzymes and hormones
- Example: Carcinoembryonic antigen (CEA) is found in carcinomas of colon, pancreas, lung, stomach and breast

- CEA assays lack both specificity and the sensitivity required for the detection of early cancers,but good to know relapse or as follow up procedure..
- Alpha-fetoprotein (AFP) is associated with liver cell cancer and nonseminomatous germ cell tumors of the testis
- AFP can be seen in non-neoplastic conditions such as cirrhosis and hepatitis

Hormones

MARKERS	CANCERS
Human chorionic gonadotropin	Trophoblastic tumors; Non-seminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid

Hormones

MARKERS

- Catecholamine and metabolites
- Ectopic hormones

CANCERS

- Pheochromocytoma and related tumors
- Tumors of the Paraneoplastic Syndrome group

Oncofetal Antigens

MARKERS	CANCERS
Alpha-fetoprotein	Liver cell cancer; Non-Seminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of colon, pancreas, lung, stomach & breast

Isoenzymes

MARKERS	CANCERS
Prostatic acid phosphatase	Prostate cancer
Neuron-specific antigen	Small cell cancer of lung, Neuroblastoma

Specific Proteins

MARKERS

- Immunoglobulins
- Prostate-specific antigen

CANCERS

- Multiple myeloma and other Gammopathies
- Prostate cancer

Mucins & Other Glycoproteins

MARKERS	CANCERS
CA-125	Ovarian cancer
CA-19-9	Colon, pancreatic cancer
CA-15-3	Breast cancer

Summary

- The prognosis of a patient with any type of neoplasm depends on a number of factors including: the rate of growth of the tumor, the size of the tumor, the tumor site, the cell type and degree of differentiation, the presence of metastasis, responsiveness to therapy, and the general health of the patient.