Tumor Pathology 2025

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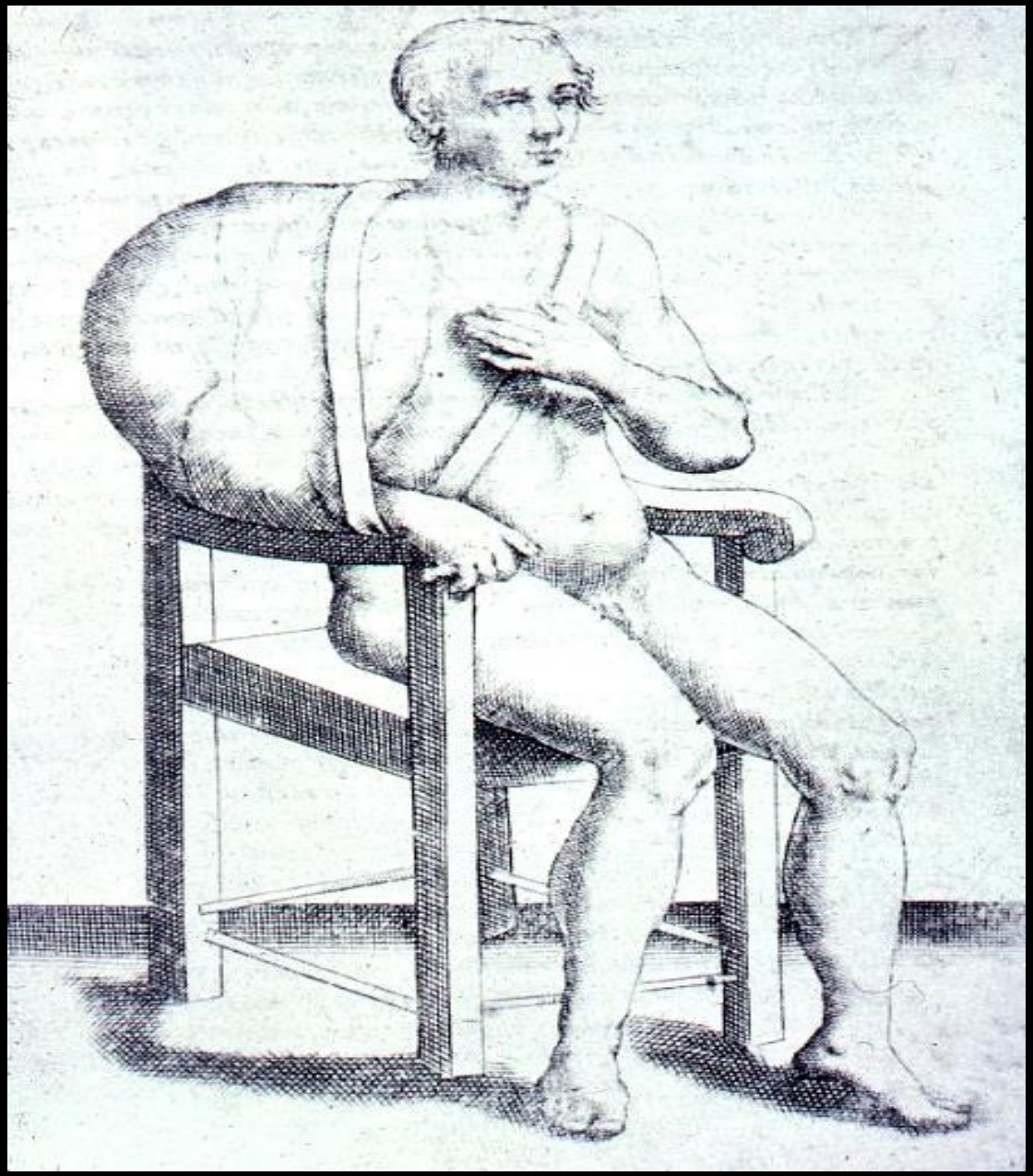
Overview

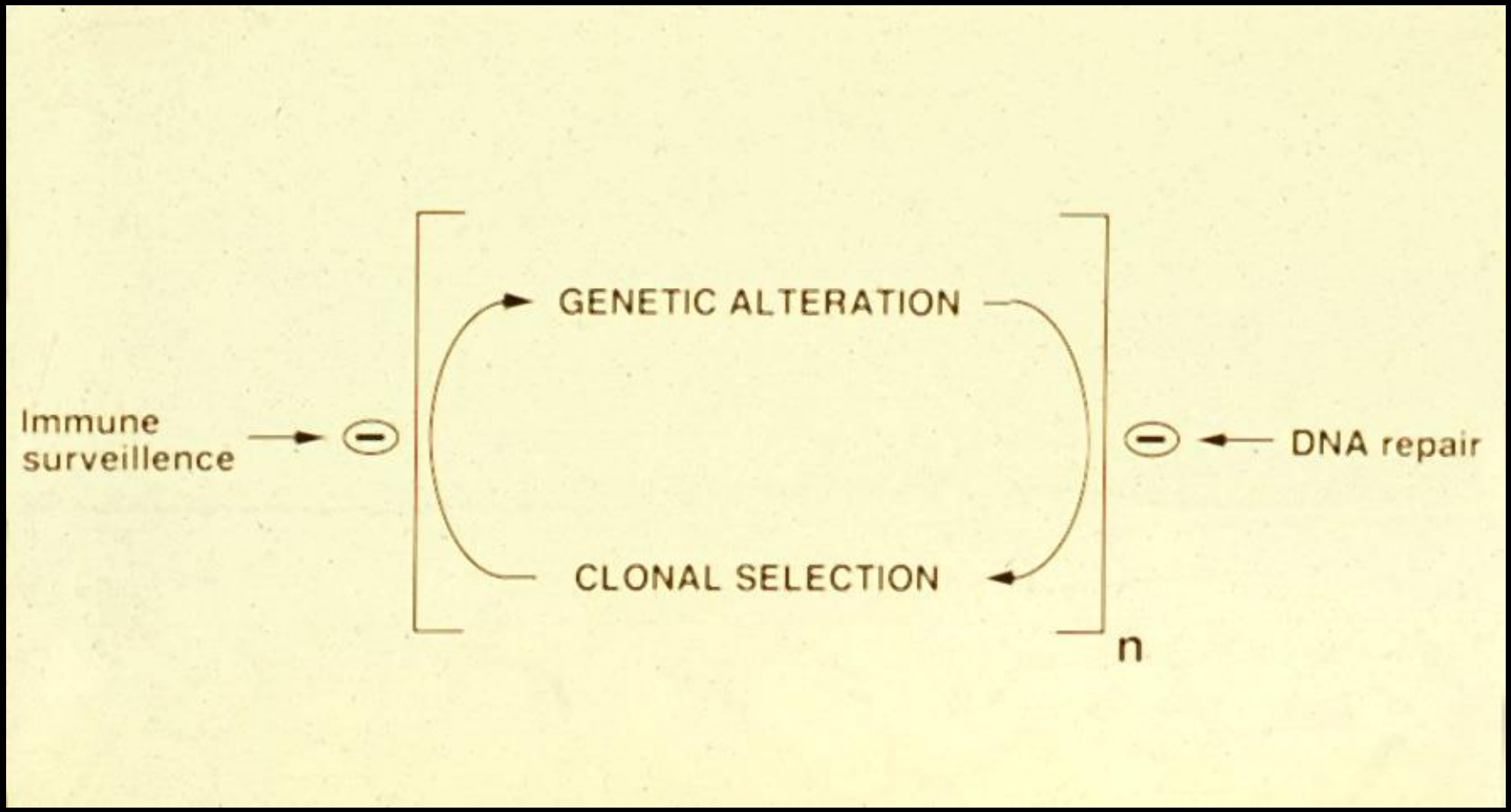
Nature of Cancer, Weinberg, partly Chapter 2

- Nature of proliferative lesions
- Cancer as a genetic/epigenetic lesion
- Effect on cells and tissue organization, in situ and invasive.
- Tumor growth and heterogeneity
- Cancer incidence across gender, organs..
- Pathology evaluation of neoplasms, classification, histogenesis vs differentiation, benign and malignant, grade, stage+
- Cancer evolution



Proliferative causes of a mass…

- Hyperplasia: Polyclonal proliferation, physiological, reversible, not genetic alteration based
- Dysplasia: Disordered growth with proliferation and atypia, non obligatory precursor to cancer
- Neoplasm: Abnormal clonal proliferation, somewhat autonomous, driven by genetic and epigenetic changes
- Other: Hamartoma, choristoma and metaplasia, (mass forming: inflammation, hematoma)


GENETIC ALTERATION
Immune surveillance
DNA repair
CLONAL SELECTION
n

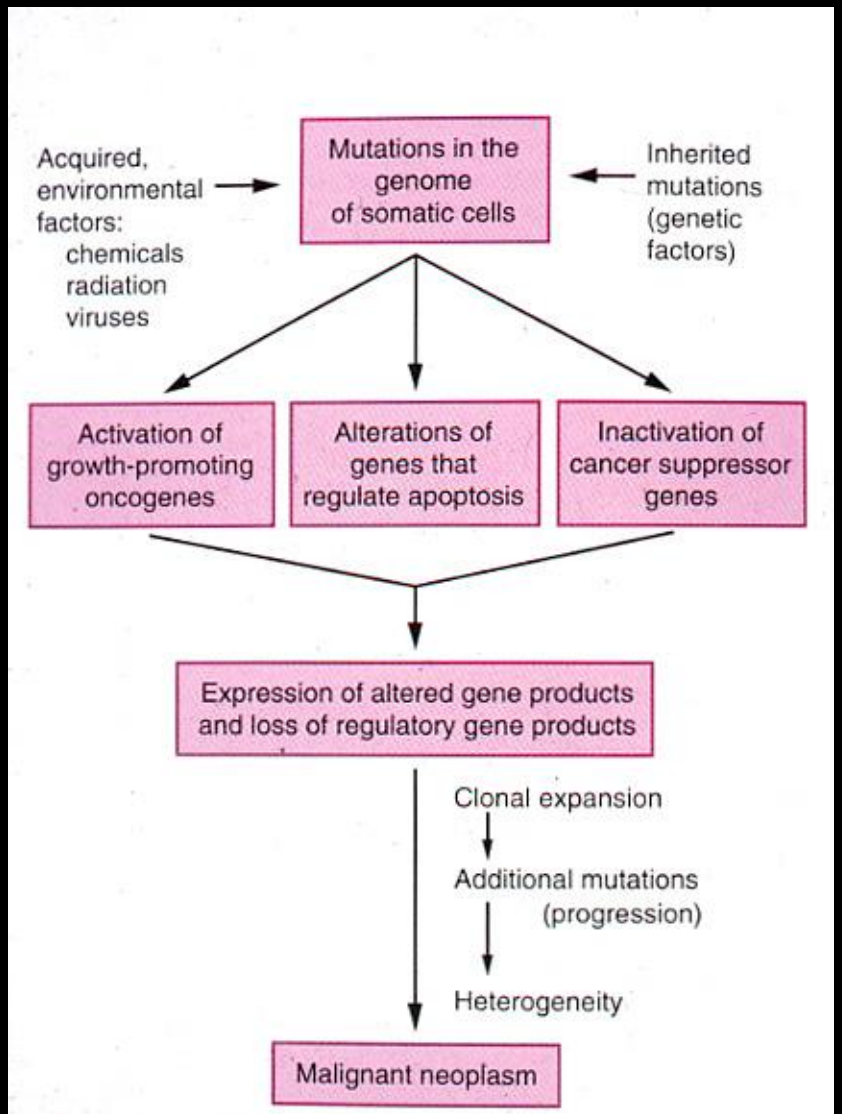
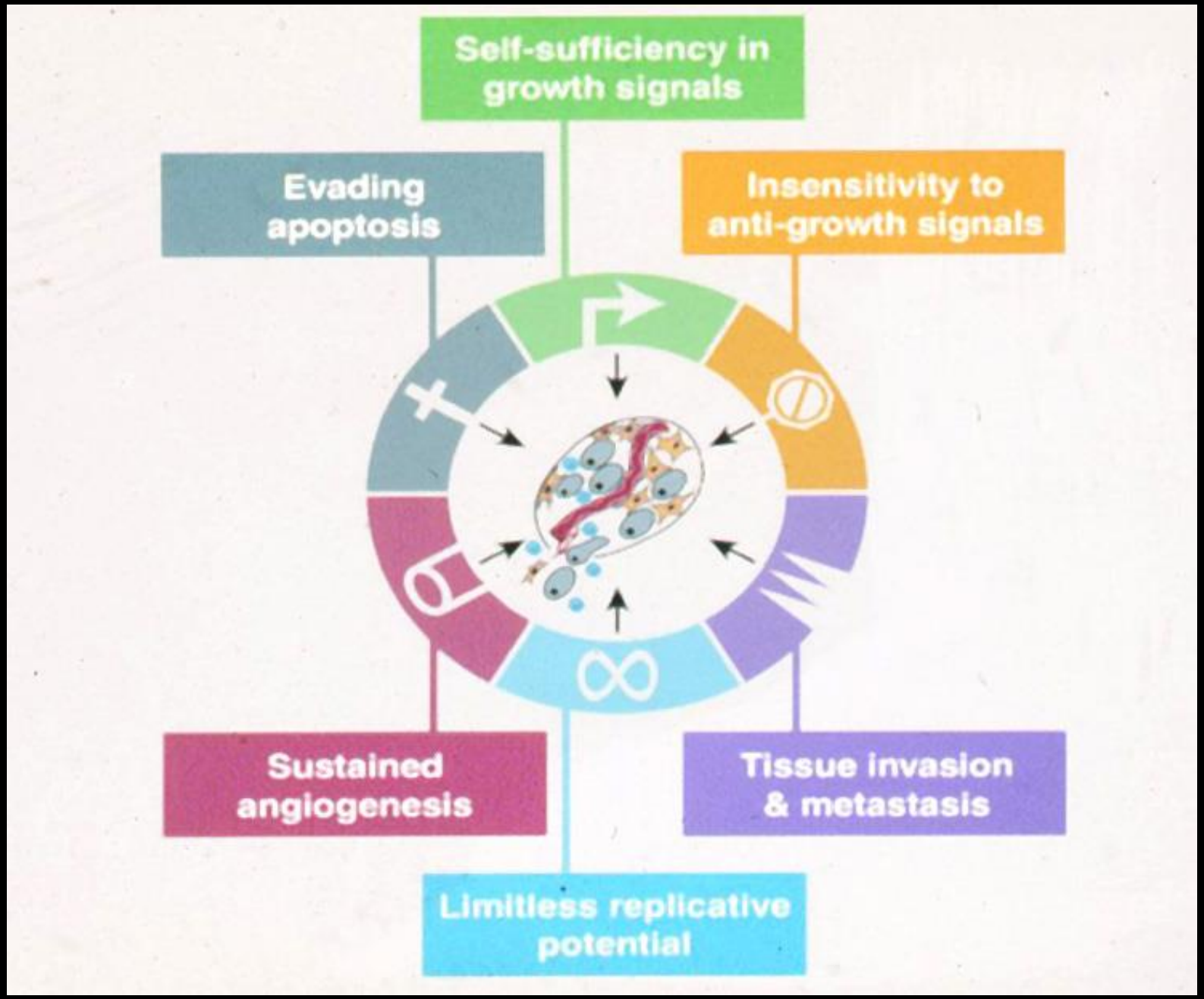
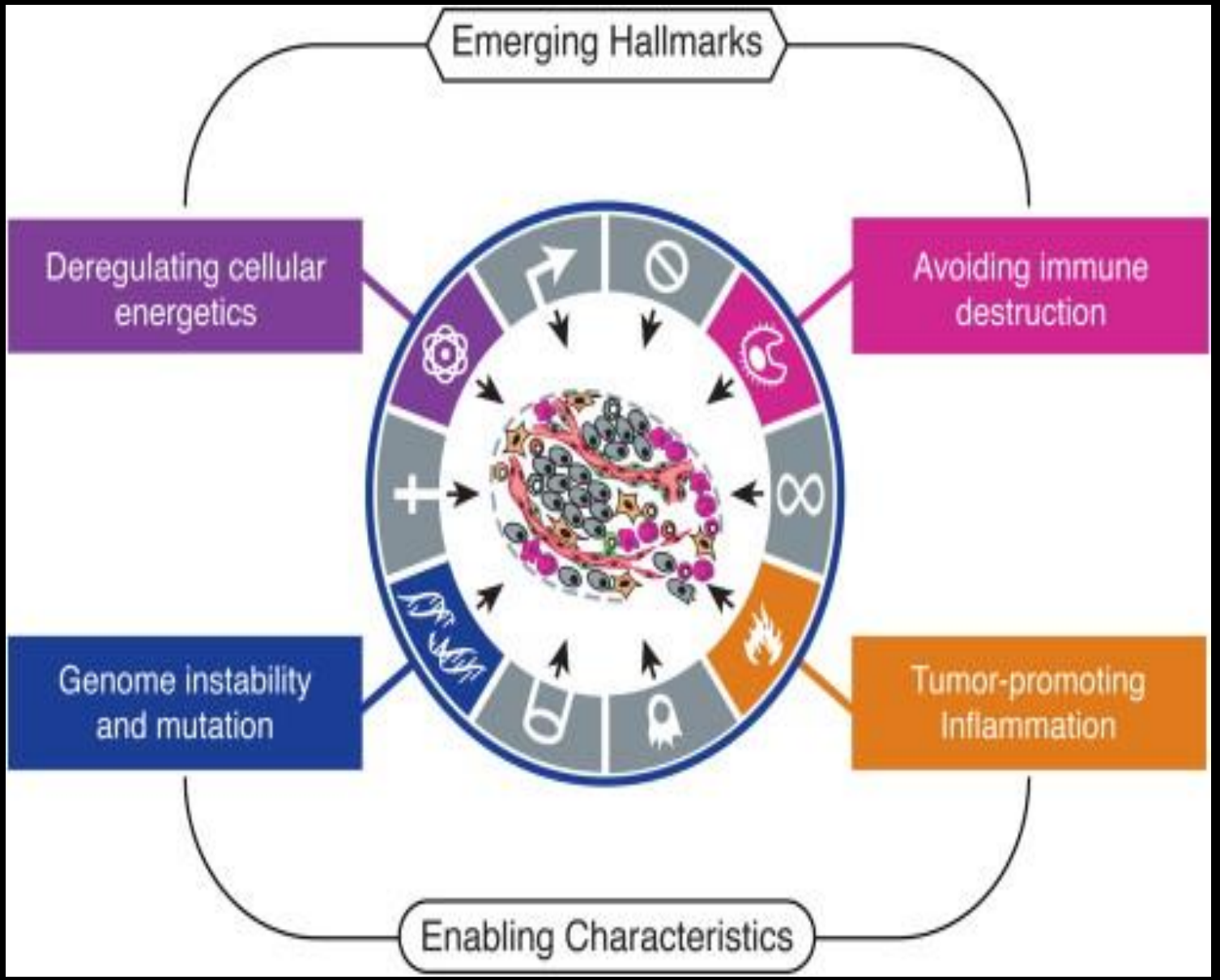
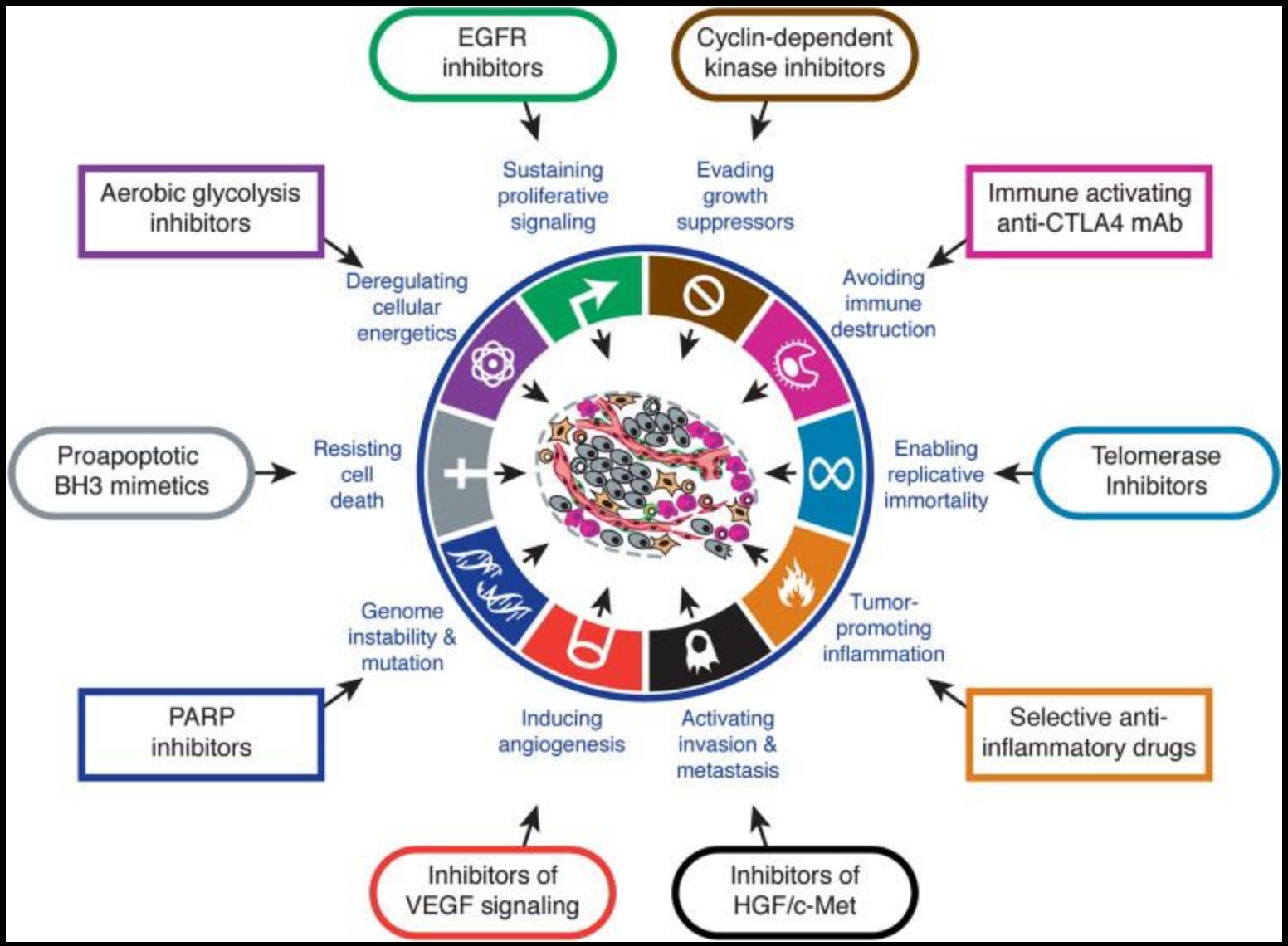
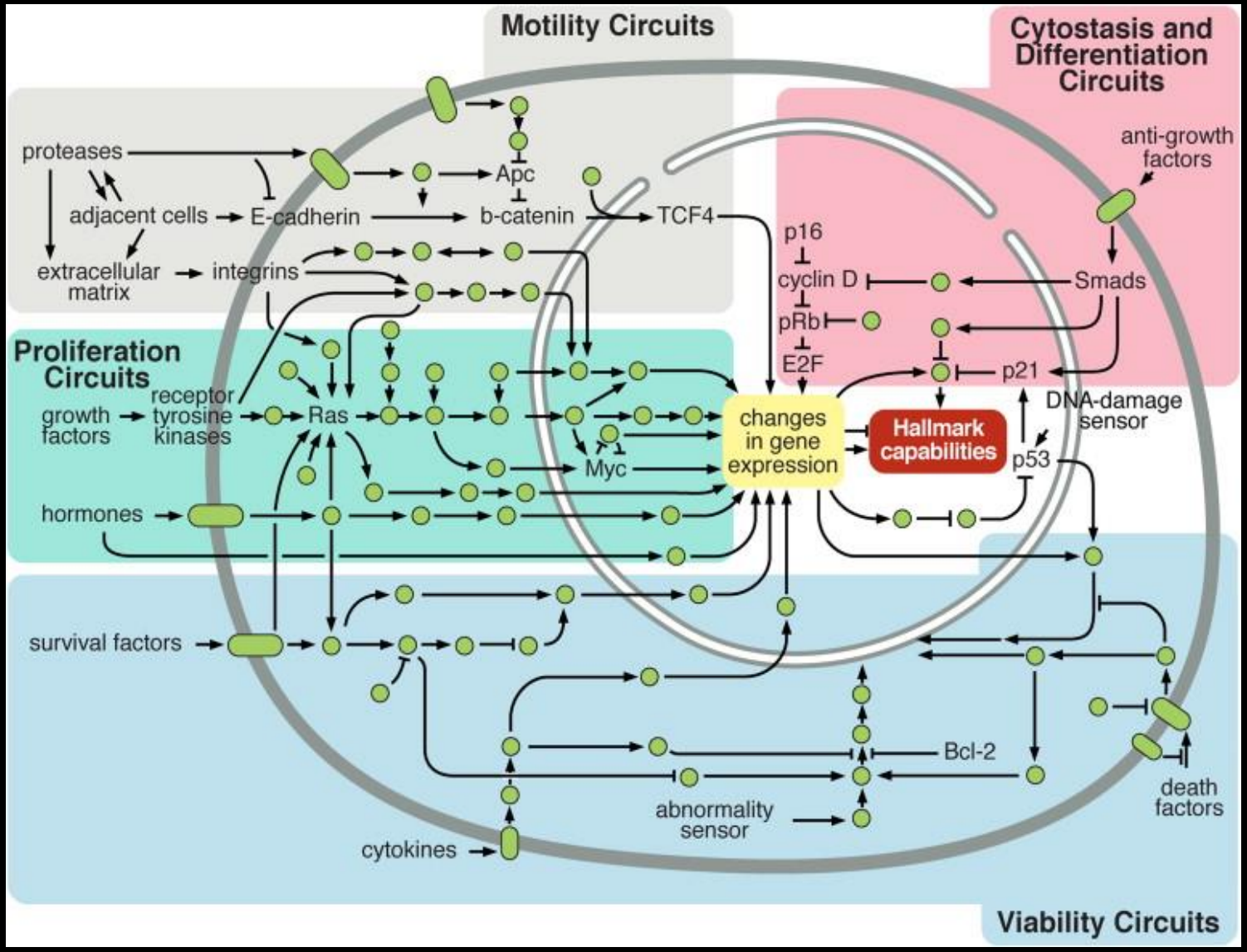


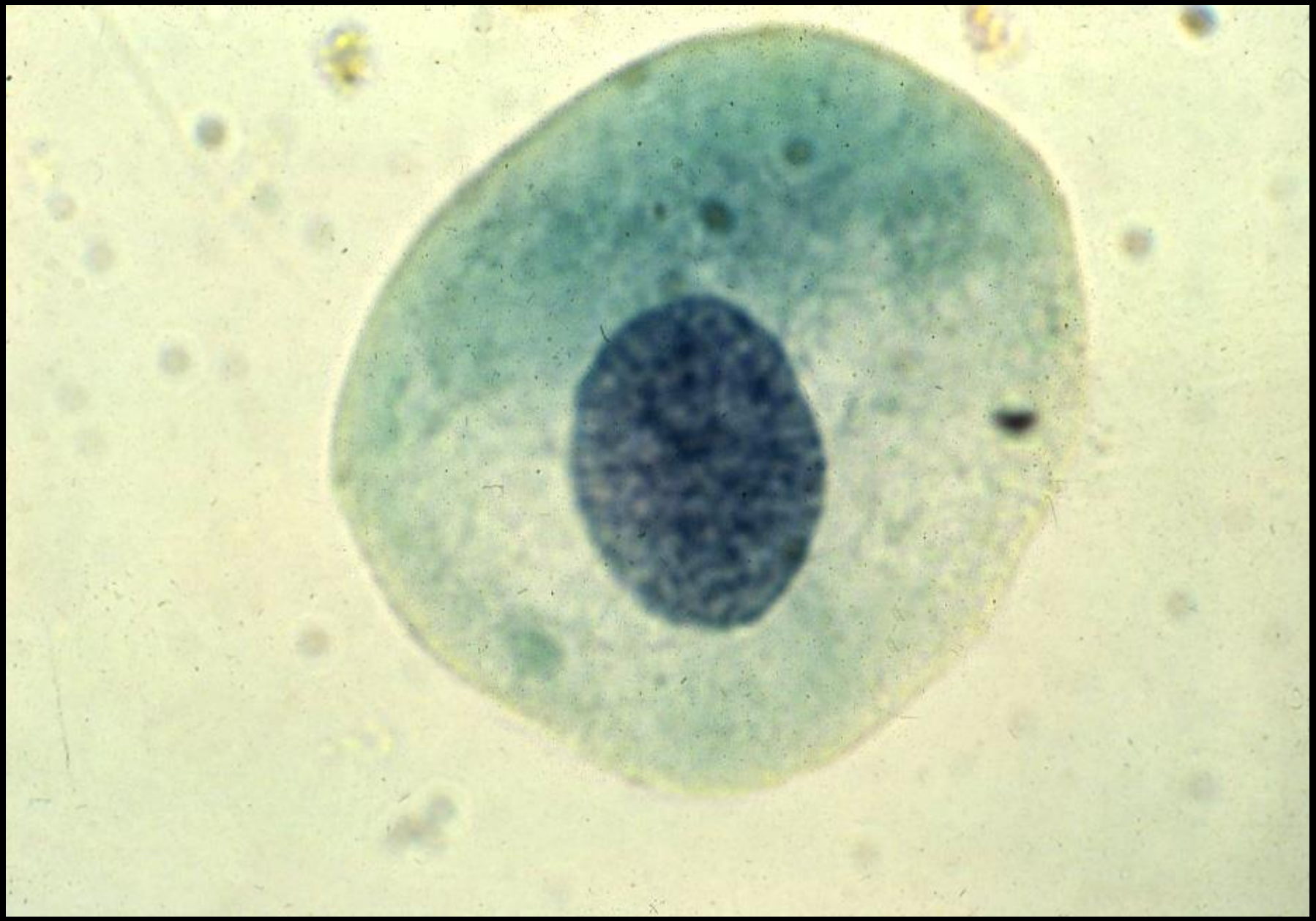
Figure 7–22. Flow chart depicts a simplified scheme of cancer pathogenesis.

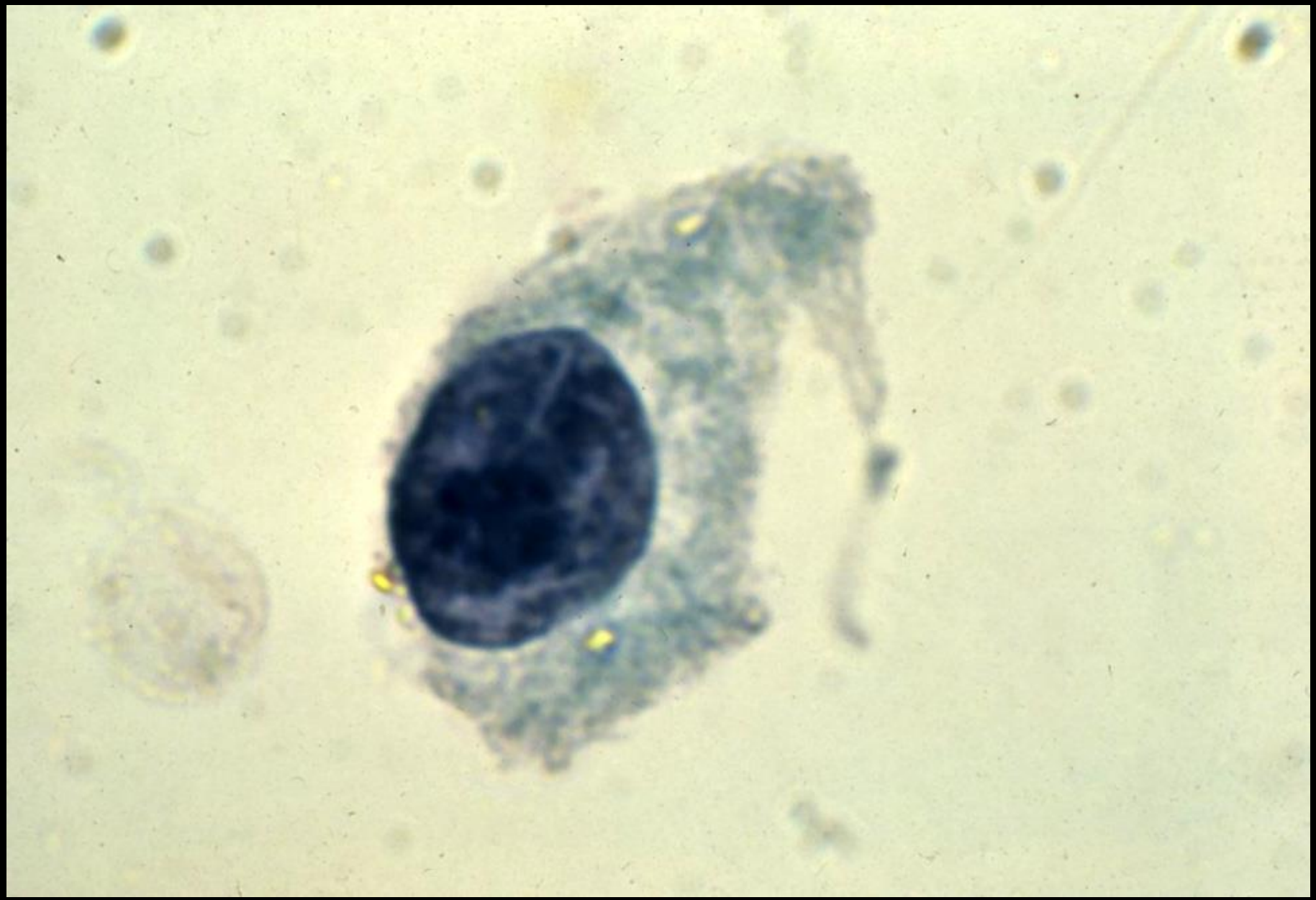

Self-sufficiency in growth signals
Evading apoptosis
Insensitivity to anti-growth signals
Sustained angiogenesis
Tissue invasion & metastasis
Limitless replicative potential

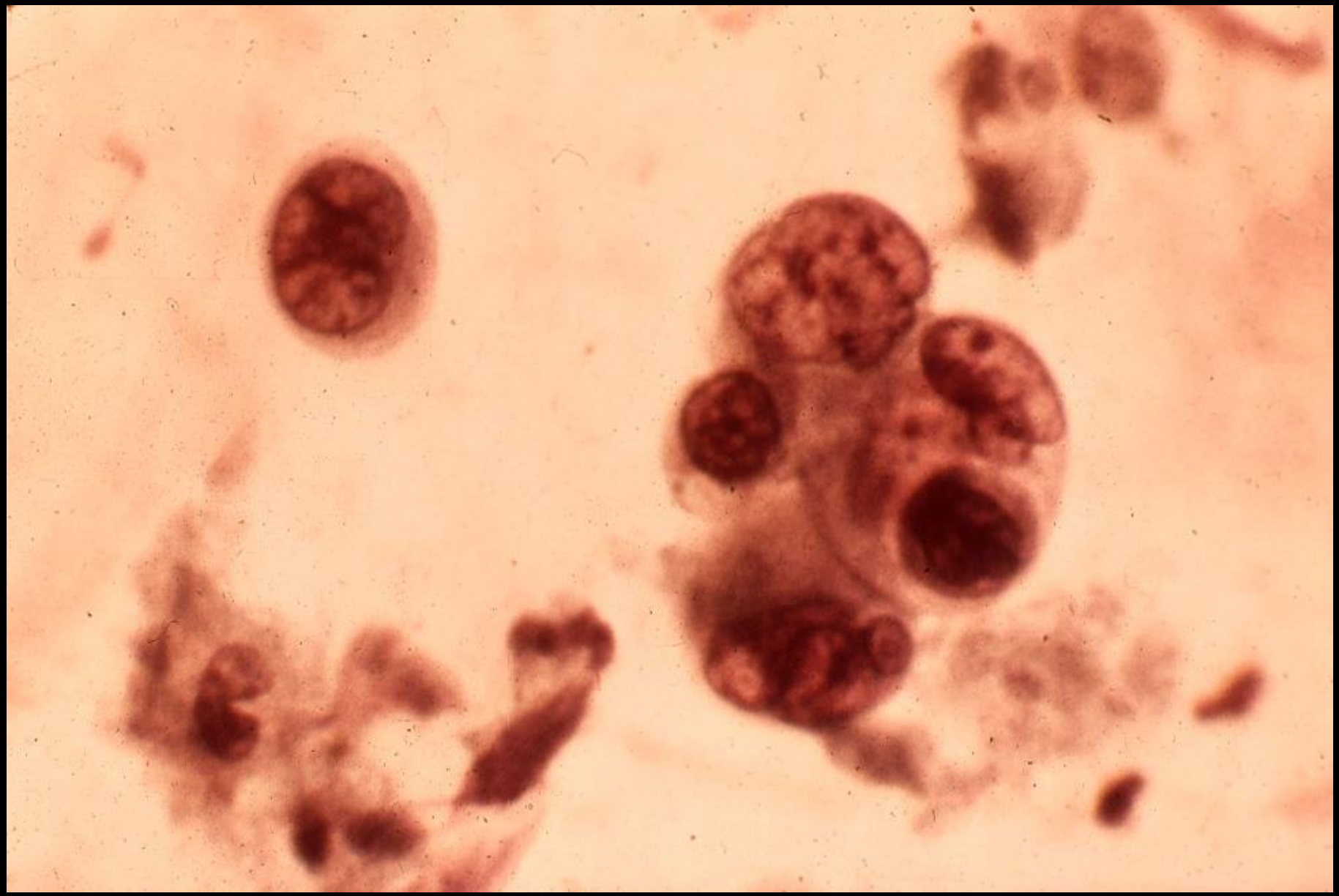

Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

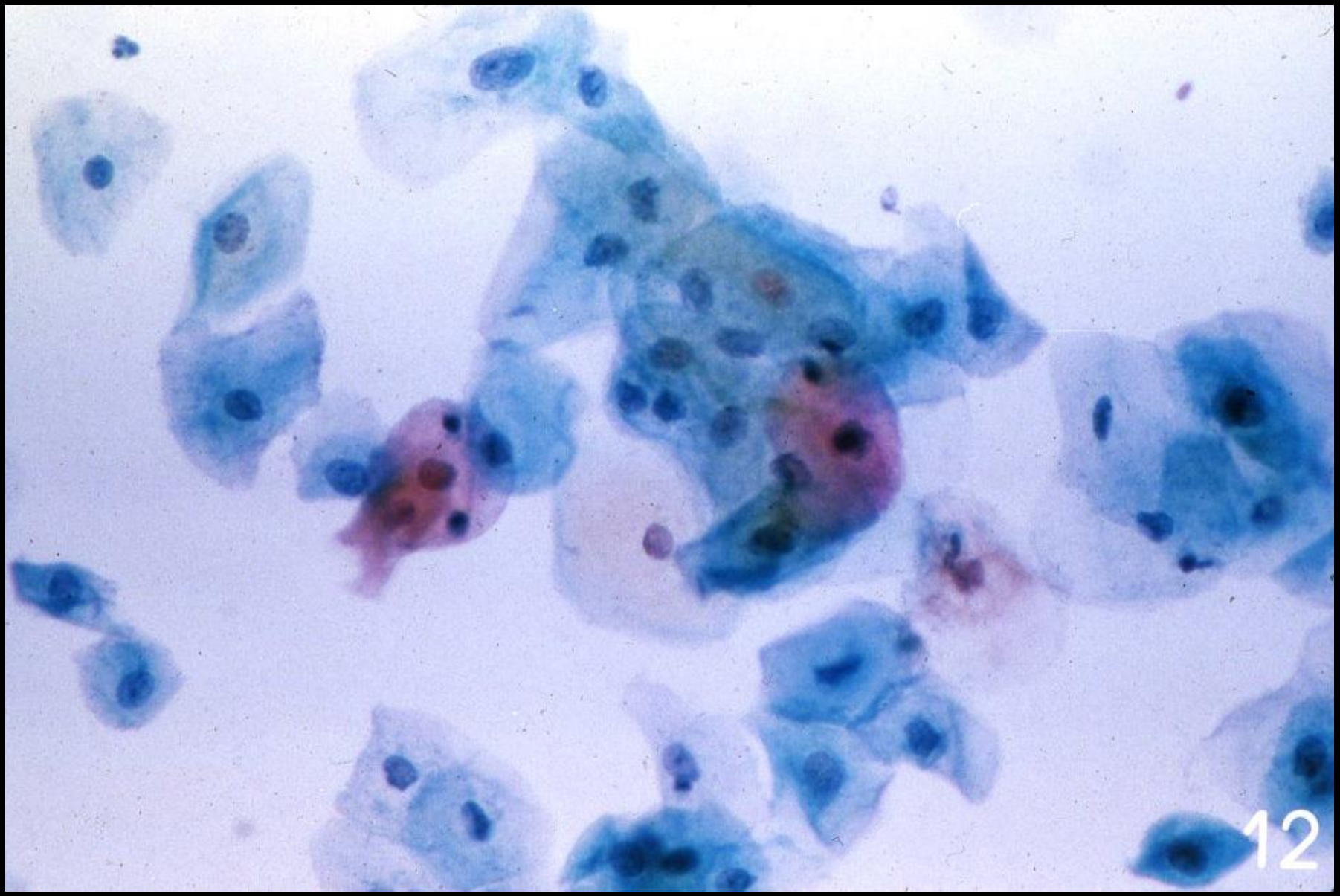

EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met


Motility Circuits
Cytostasis and Differentiation Circuits
Proliferation Circuits
Viability Circuits
proteases
adjacent cells
extracellular matrix
integrins
E-cadherin
Apc
b-catenin
TCF4
anti-growth factors
p16
cyclin D
pRb
E2F
Smads
p21
DNA-damage sensor
p53
growth factors
receptor tyrosine kinases
Ras
Myc
changes in gene expression
Hallmark capabilities
hormones
survival factors
Bcl-2
abnormality sensor
death factors
cytokines





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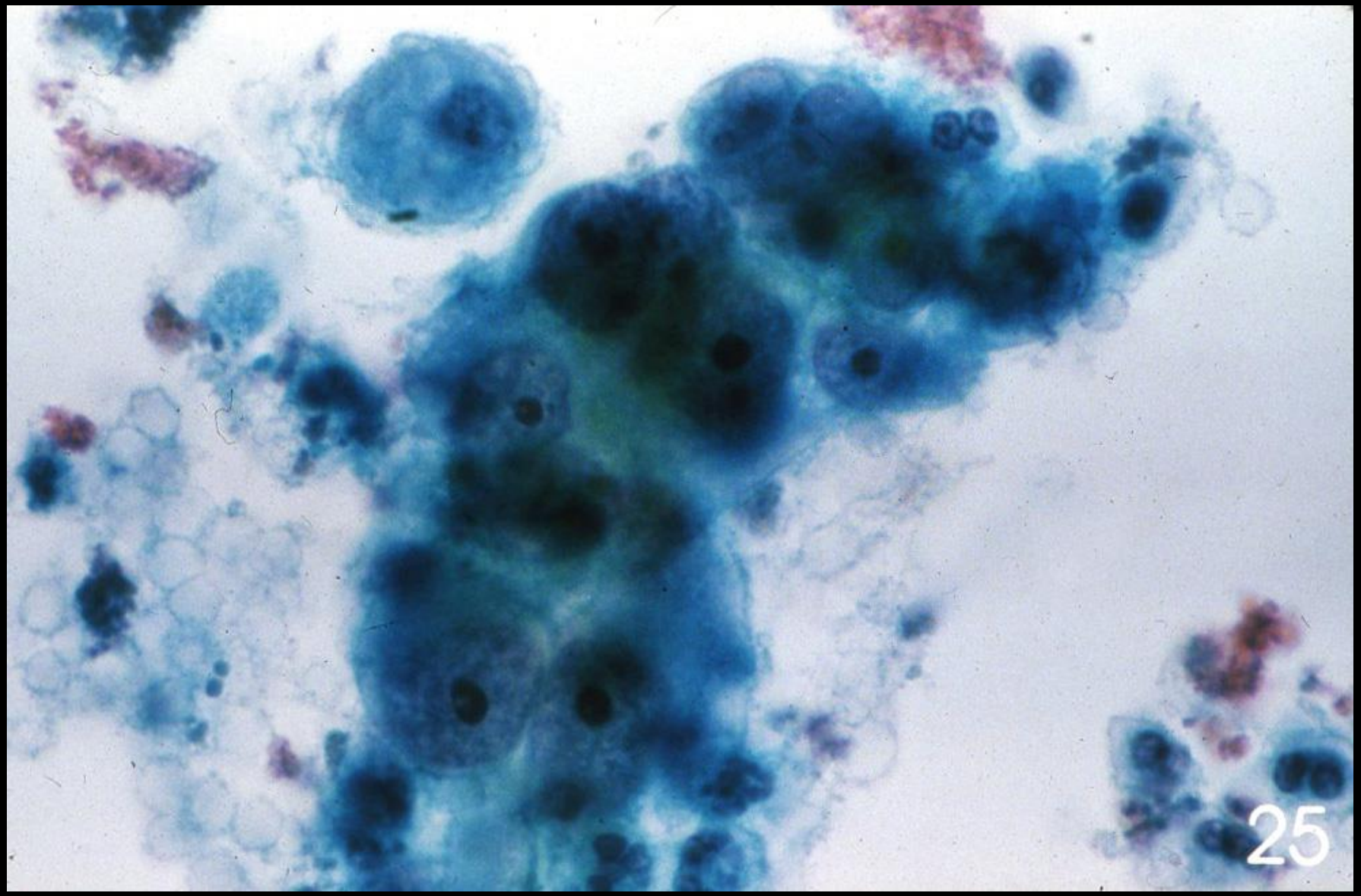
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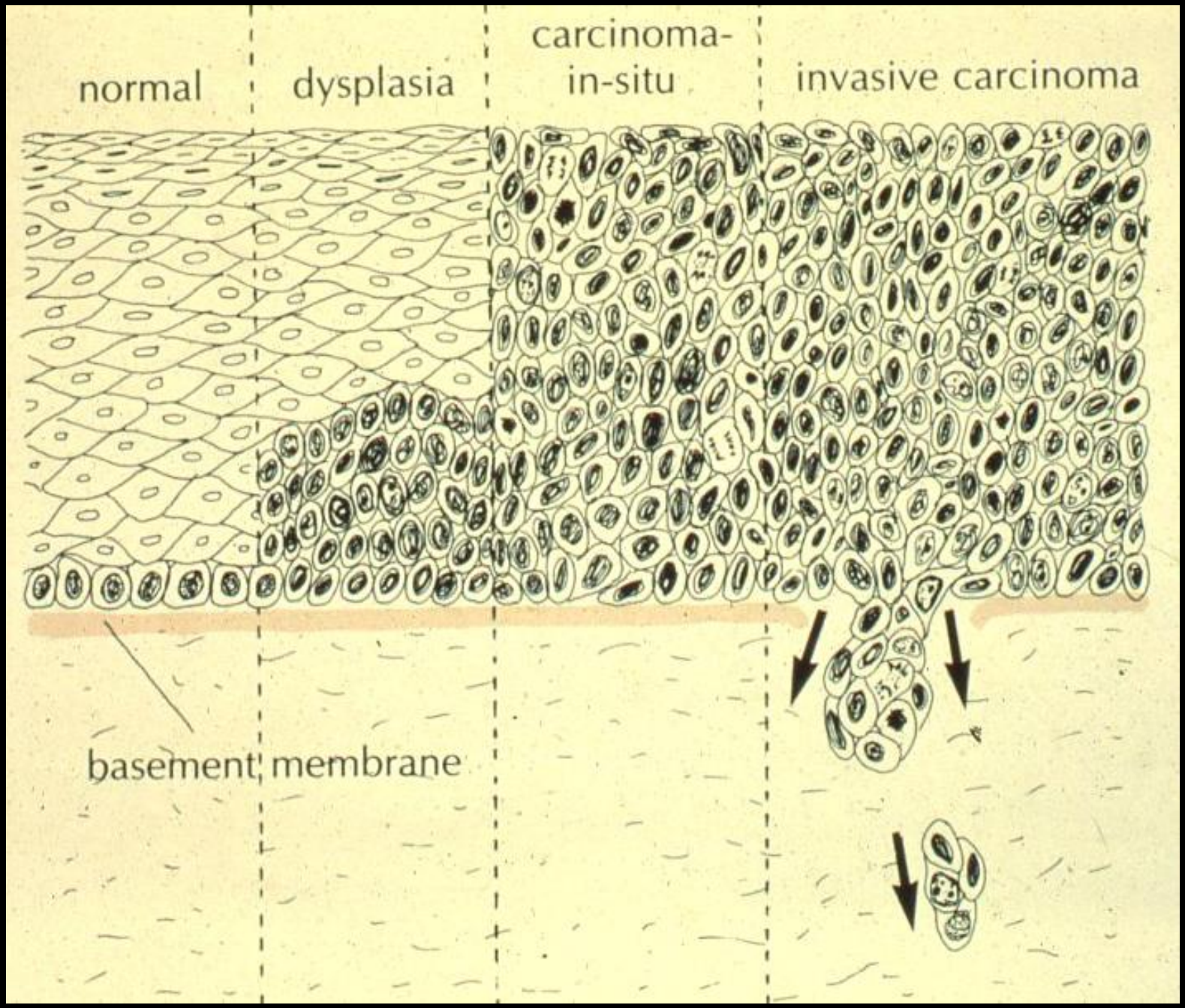
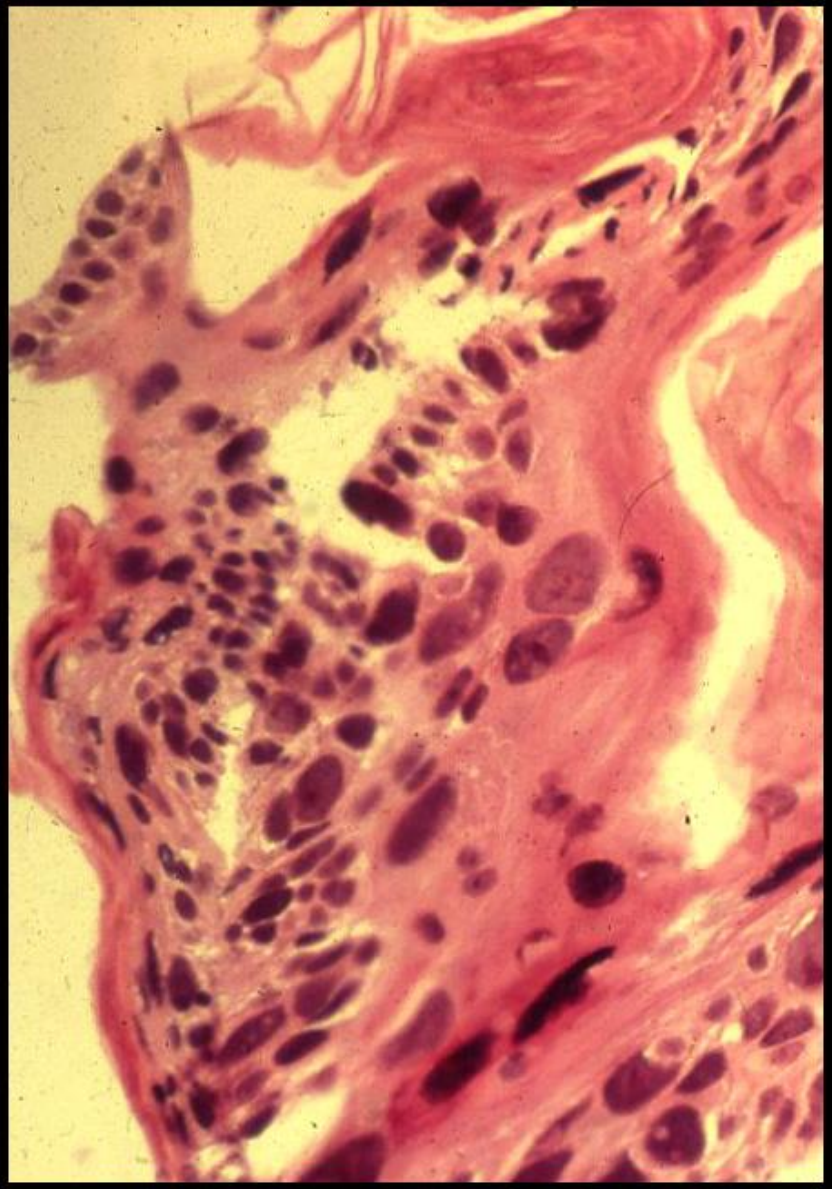
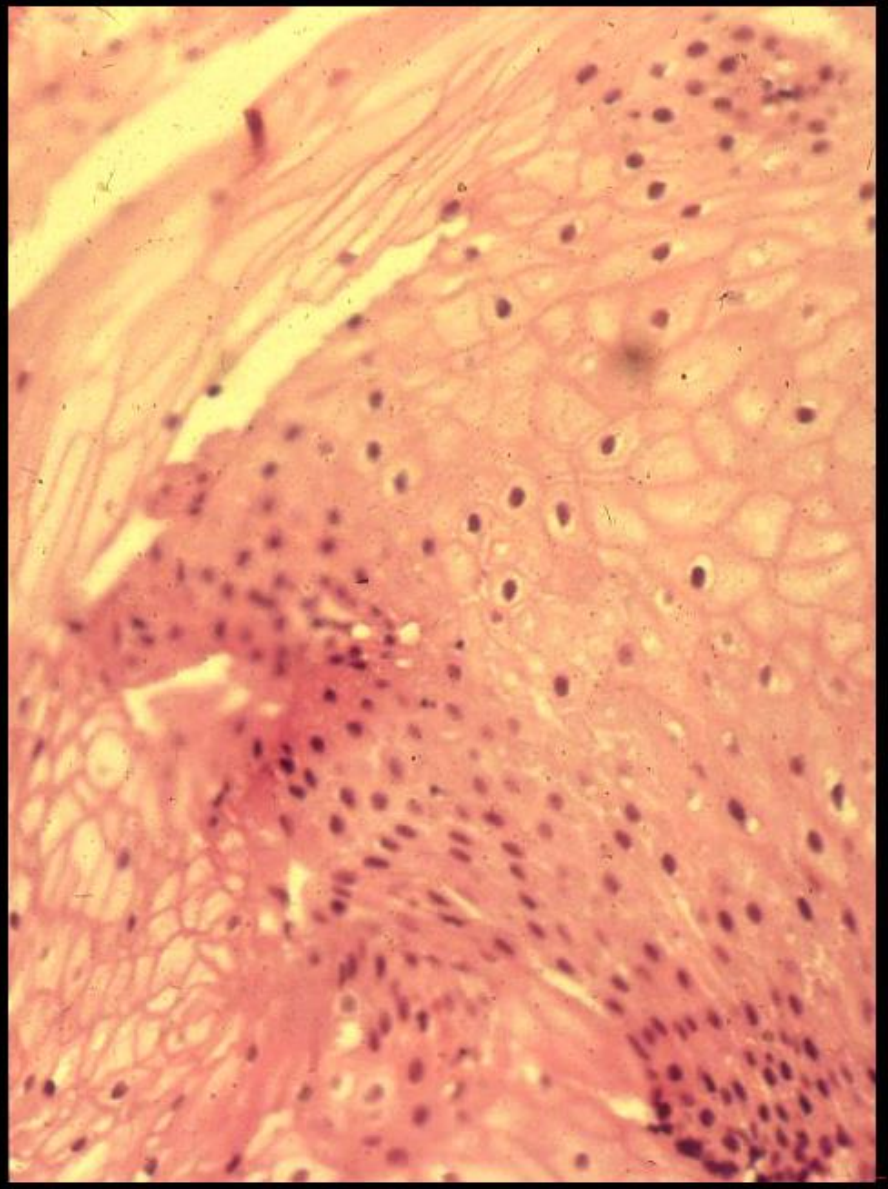
Table 5. Morphologic and Ultrastructural Properties of Highly Malignant Tumor Cells*

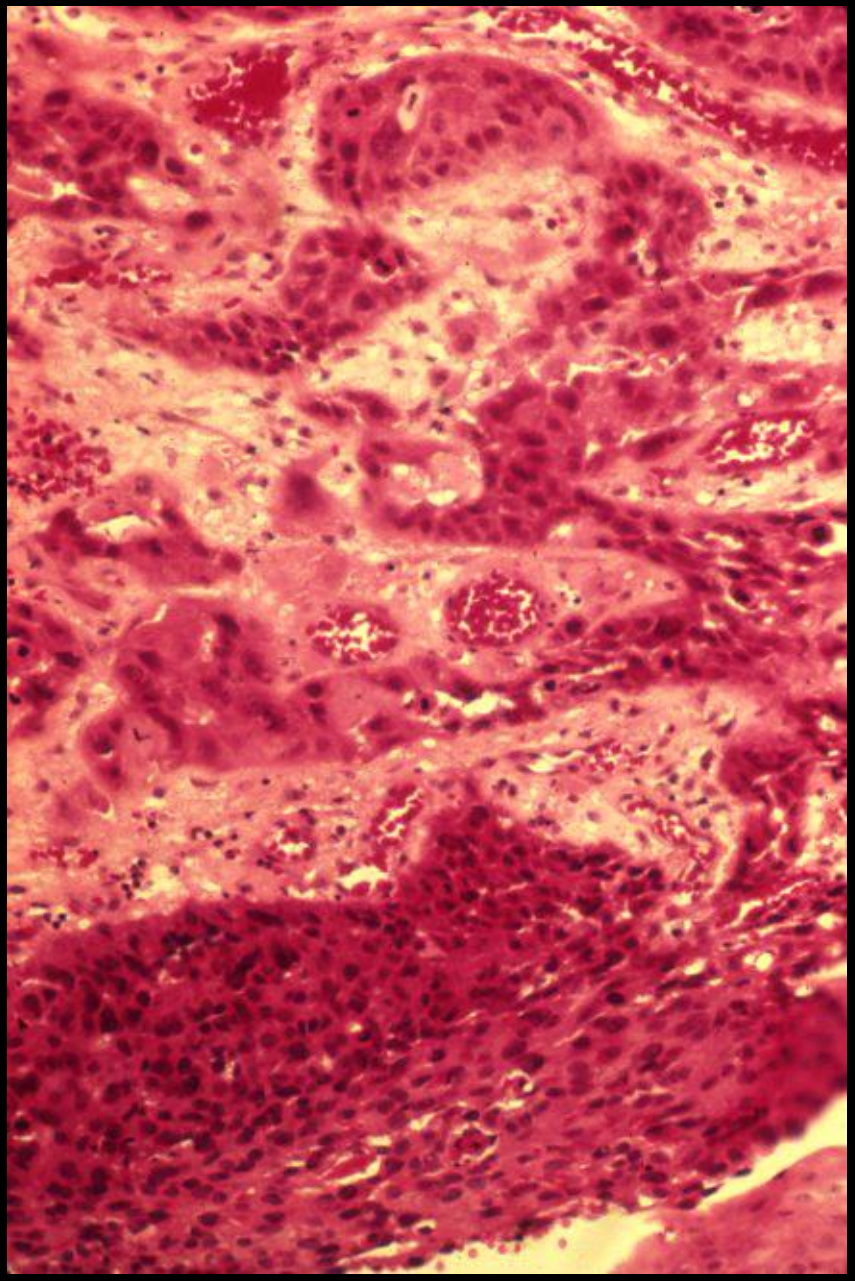
Nucleus	Cytoplasm
1. High nuclear - cytoplasmic ratio 2. Prominent and aberrant nucleoli 3. Clumped chromatin 4. Chromosomal abberrations: heteroploidy abnormal chromosomes increased DNA content 5. Abnormal mitoses	1. Cytoplasmic basophilia, due to increase in number of free ribosomes 2. Decrease in endoplasmic reticulum 3. Fewer and smaller mitochondria

*Note that not all tumor cells display these properties and no individual property is specific to tumor cells.


normal
dysplasia
carcinoma-
in-situ
invasive carcinoma
basement membrane







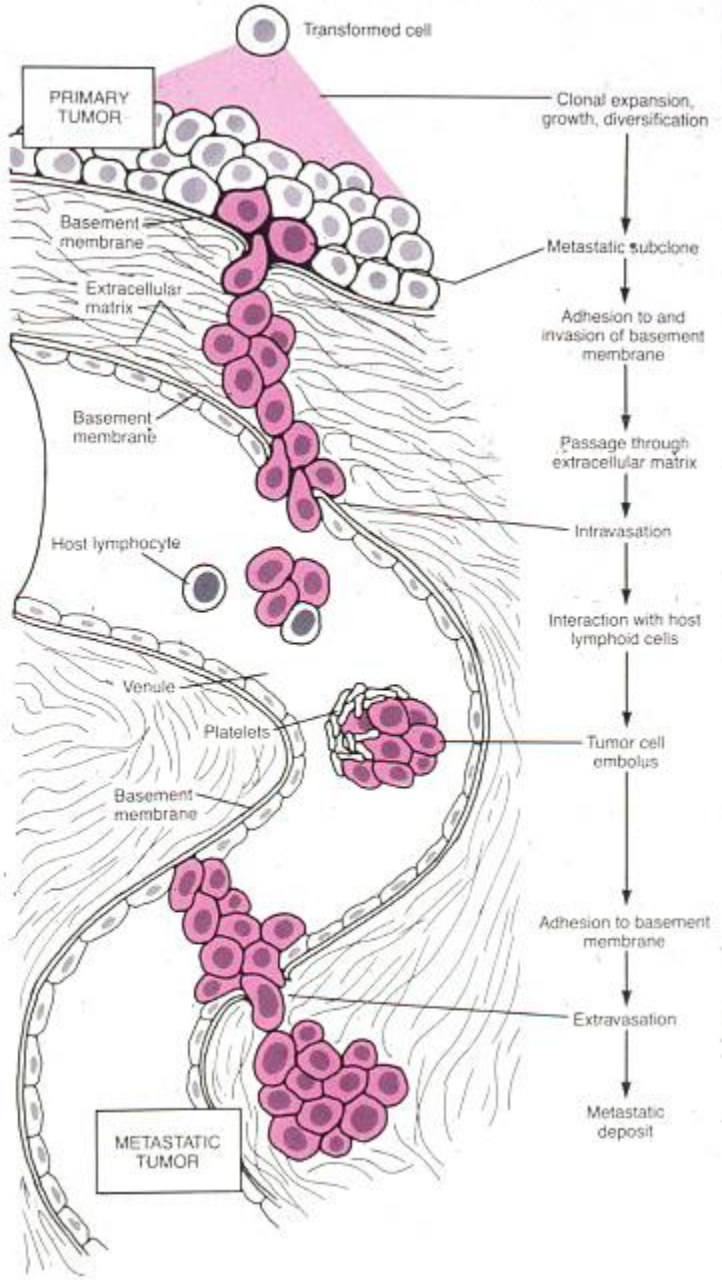
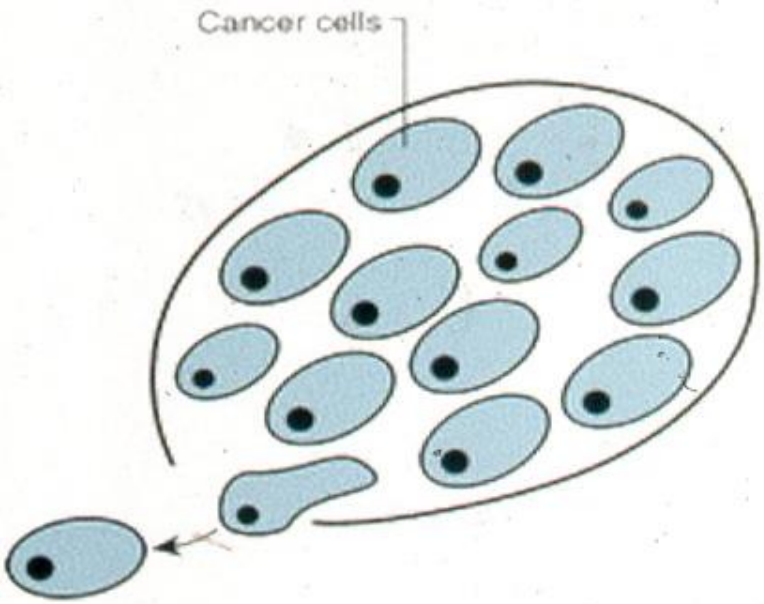
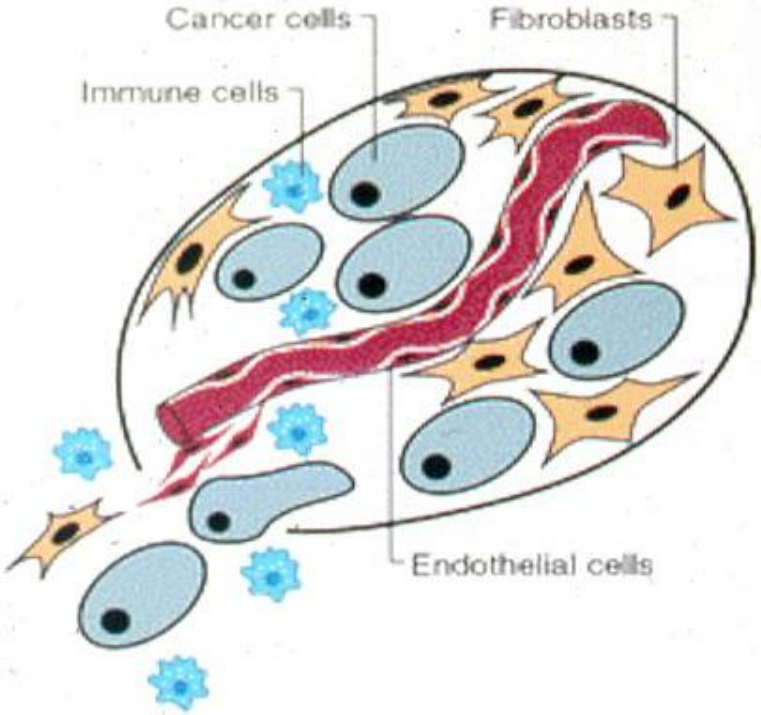


Figure 7–33. The metastatic cascade. Schematic illustration of the sequential steps involved in the hematogenous spread of a tumor.

The Reductionist View



A Heterotypic Cell Biology



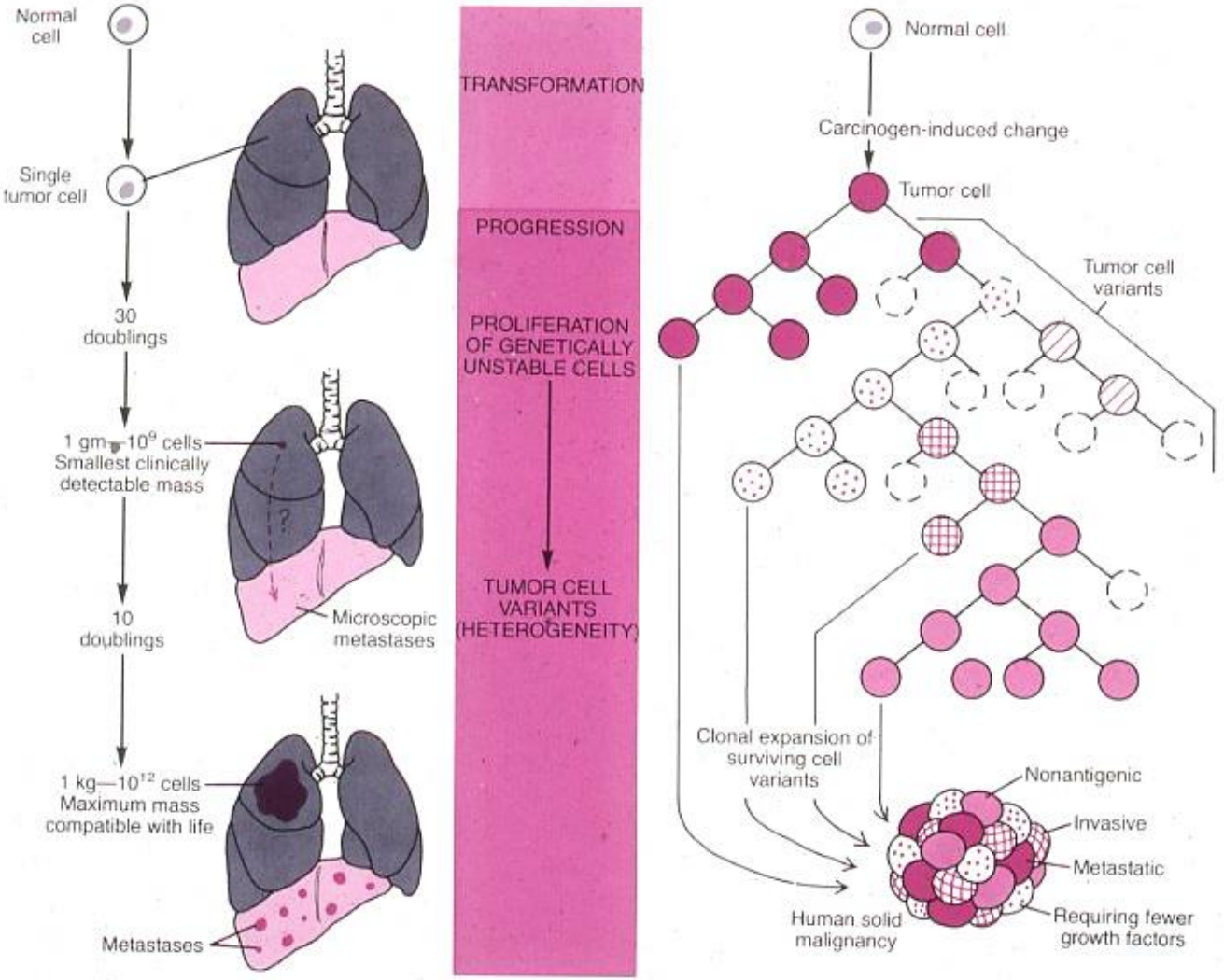


Figure 7–31. Biology of tumor growth. The left panel depicts minimal estimates of tumor cell doublings that precede the formation of a clinically detectable tumor mass. It is evident that by the time a solid tumor is detected, it has already completed a major portion of its life cycle as measured by cell doublings. The right panel illustrates clonal evolution of tumors and generation of tumor cell heterogeneity. New subclones arise from the descendants of the original transformed cell, and with progressive growth the tumor mass becomes enriched for those variants that are more adept at evading host defenses and are likely to be more aggressive. (Adapted from Tannock, I.F.: Biology of tumor growth. Hosp. Pract. *18*:81, 1983.)

Cancer incidence and death rate in US

Estimated New Cases

Male			Female		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**		**All sites**	**891,480**	

Estimated Deaths

Male			Female		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	**321,670**		**All sites**	**285,210**	

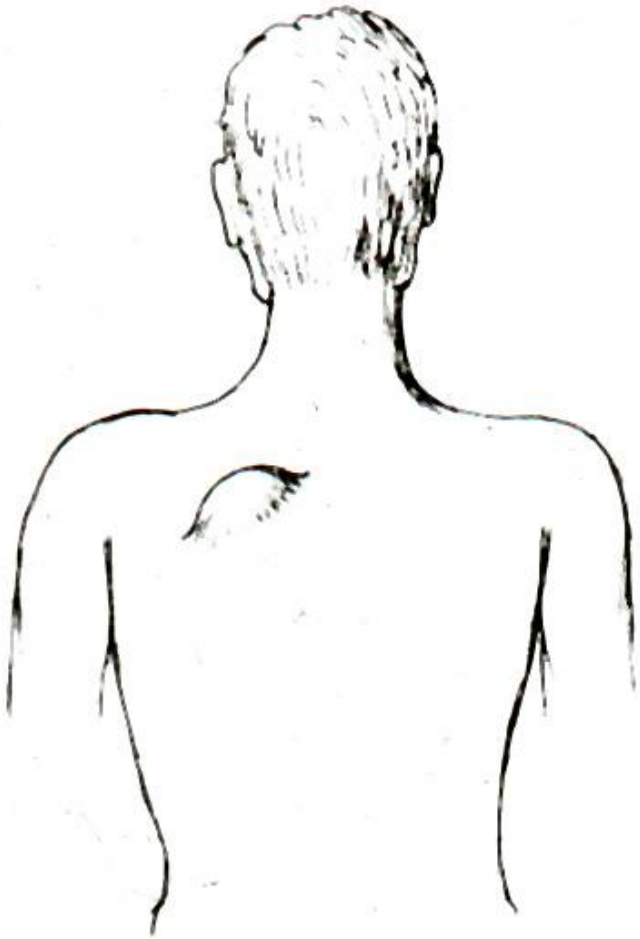
Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

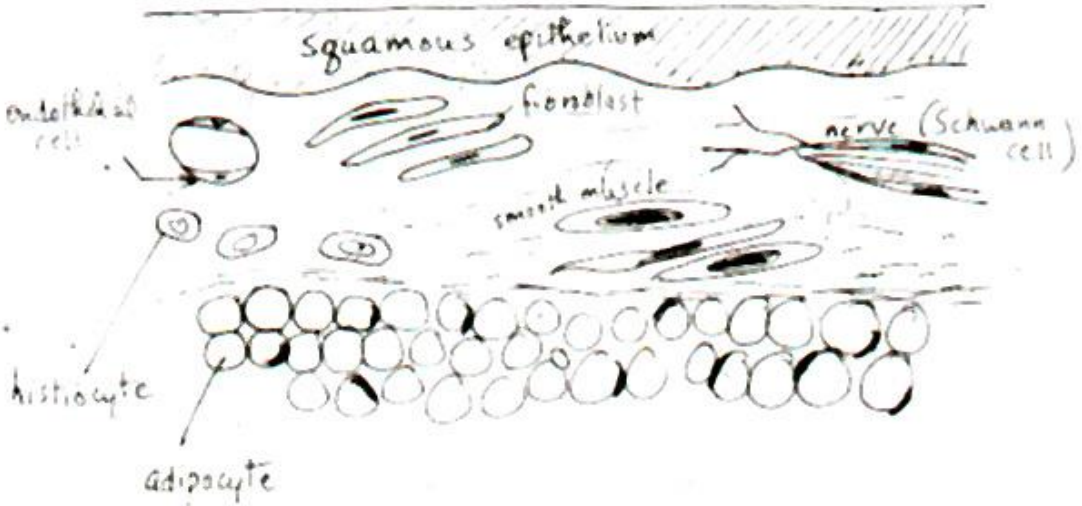
Pathologic evaluation of tumors: The case of integrated representation

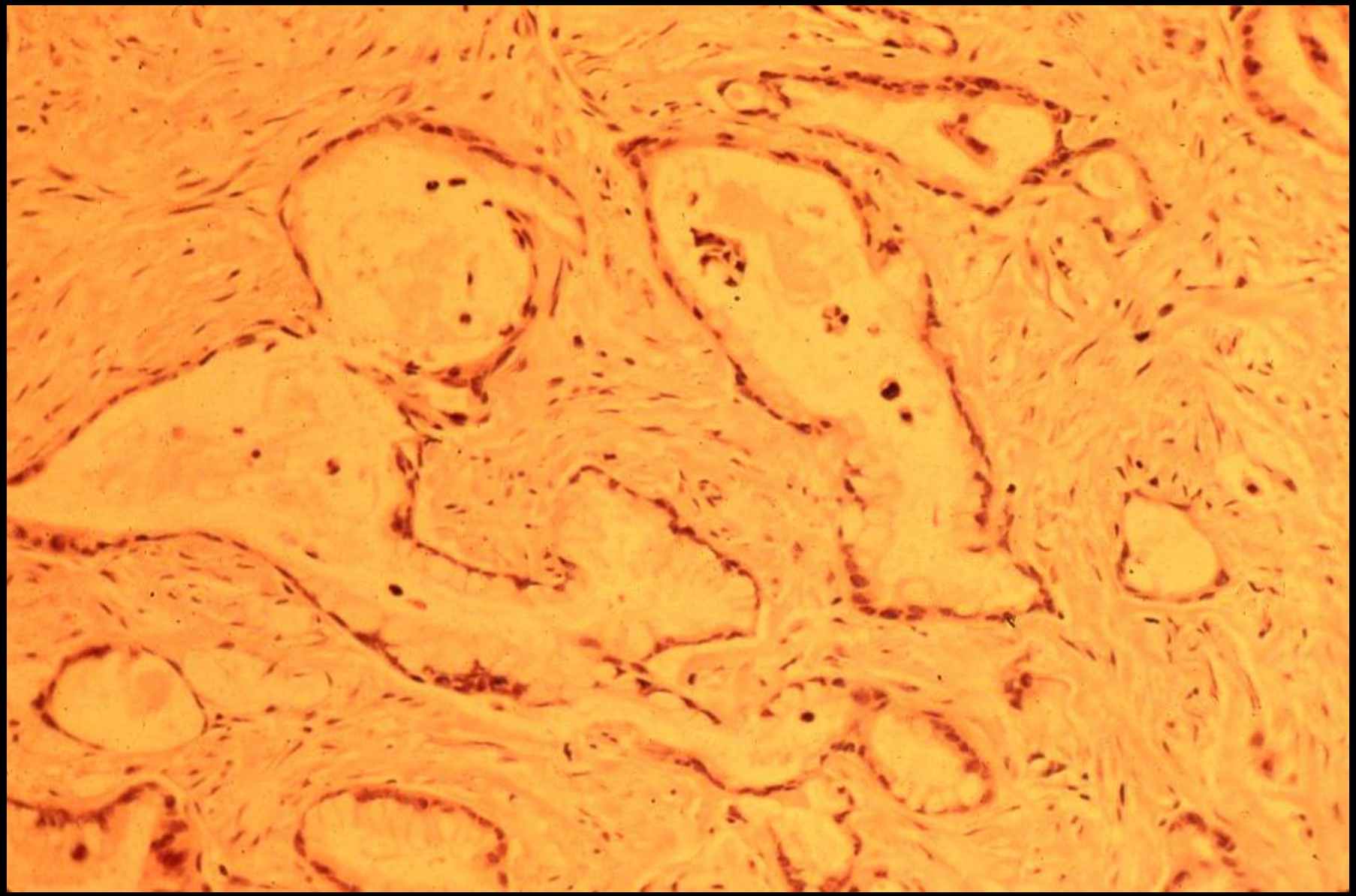
- Light microscopy, Electron microscopy
- Immunohistochemistry:identifying diagnostic prognostic and predictive proteins.
- Flow cytometry: characterizing cell surface antigens/cell population.
- Molecular genetic characterization: Multiomic approach: copy number changes, translocations, expression, mutational analysis, micro RNA, methylation, proteomics…

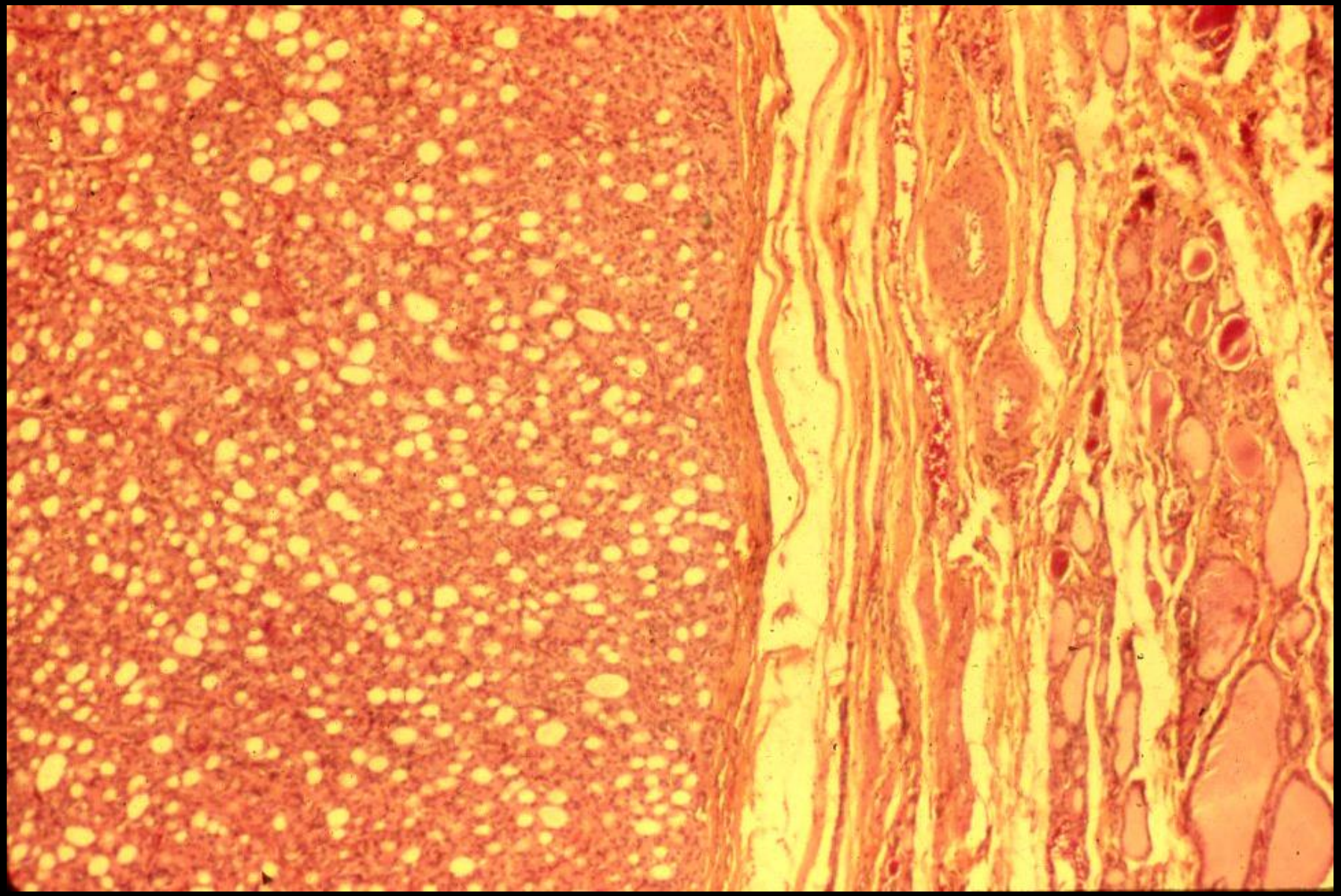
Classification of Neoplasia

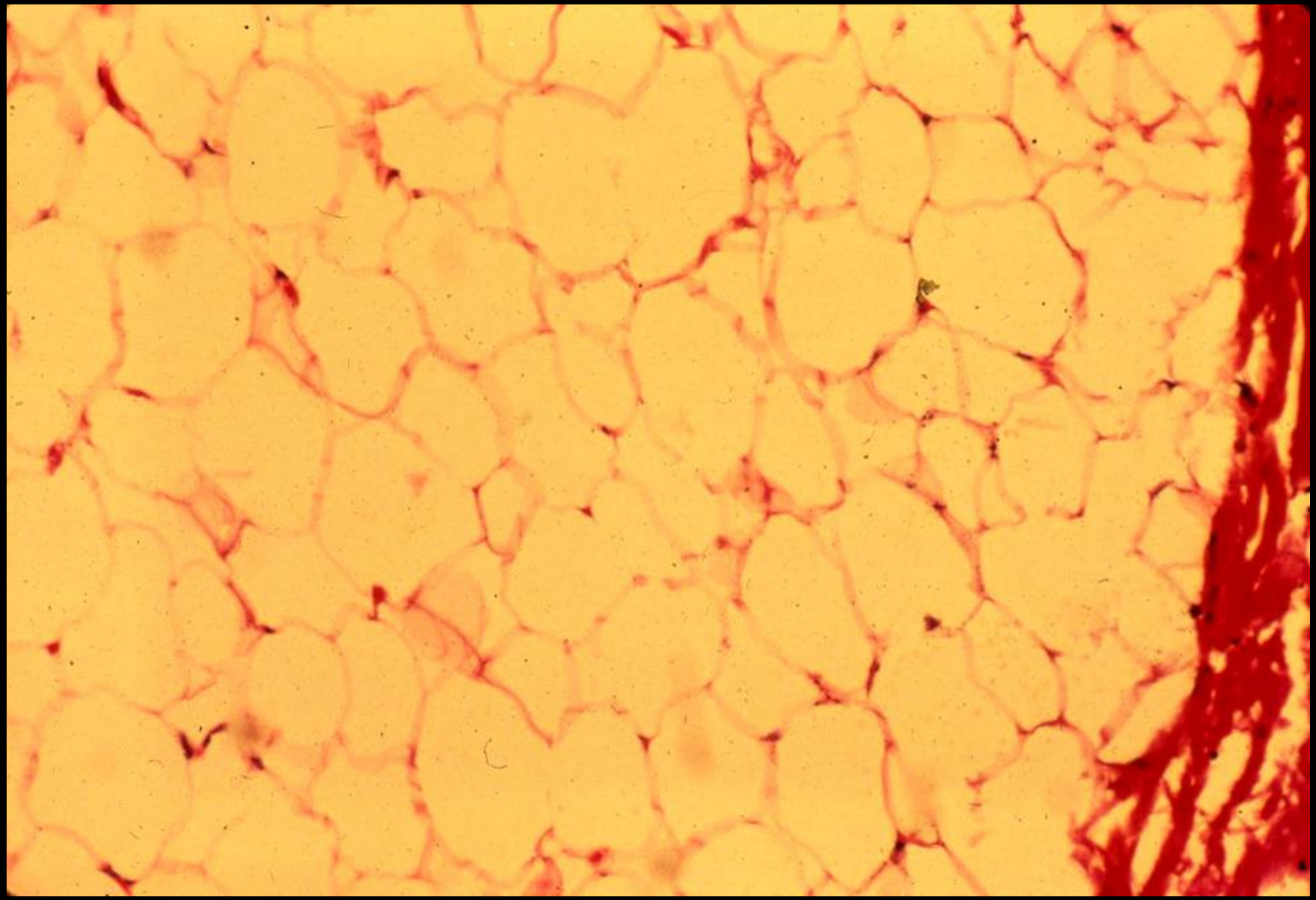
- Histogenesis/differentiation-Organ of origin and tissue and cell type
- Grade: degree of differentiation i.e. resemblance to normal/mature tissue (Well, Mod, Poorly Diff, 1,2,3)
- Molecular features: diagnostic, prognostic, predictive
- Biological behavior: benign to malignant continuum
- Stage: extent of disease/spread (size, lymph node status, distant disease)

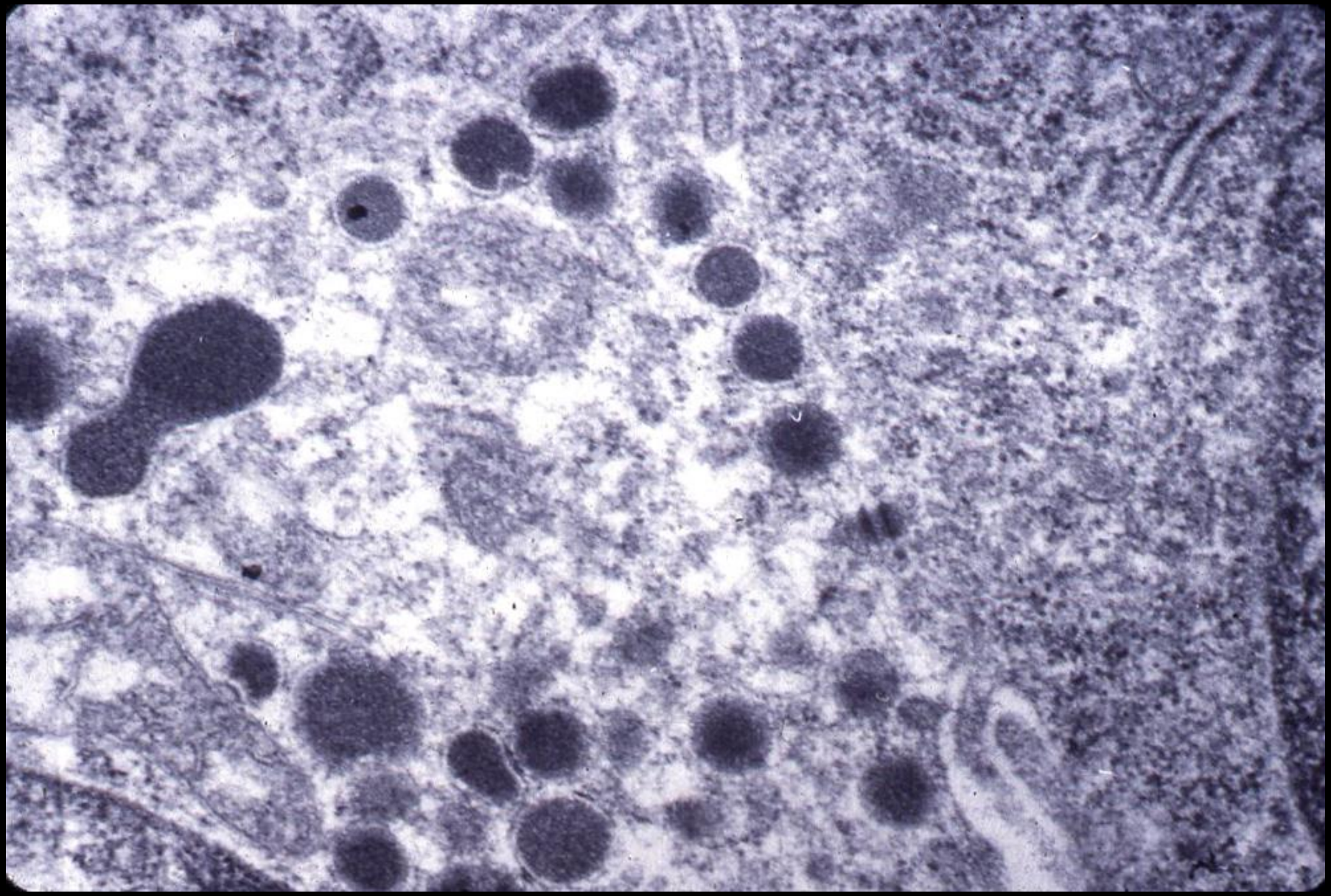


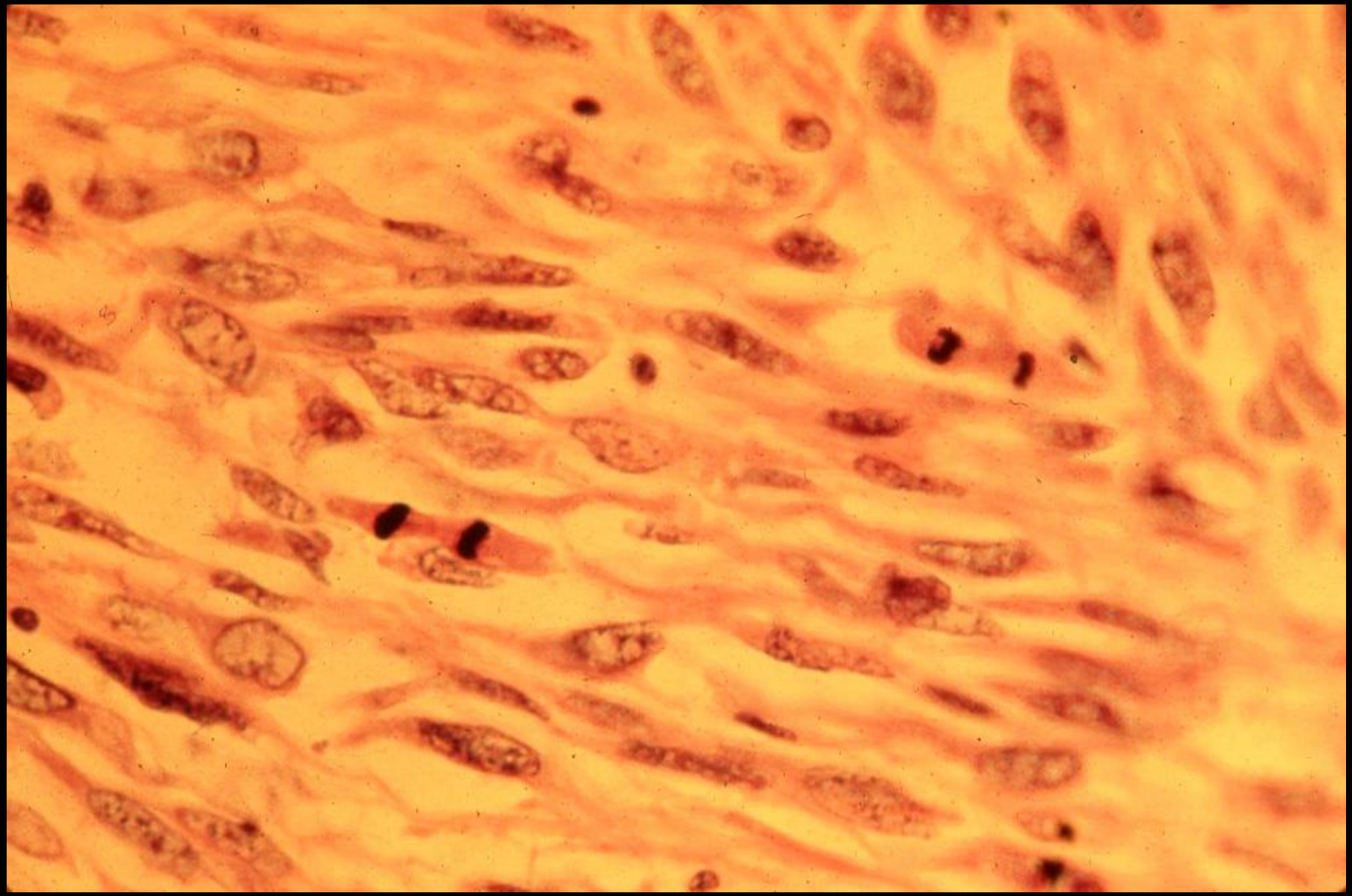

squamous epithelium
fibroblast
nerve (Schwann cell)
smooth muscle
histiocyte
adipocyte

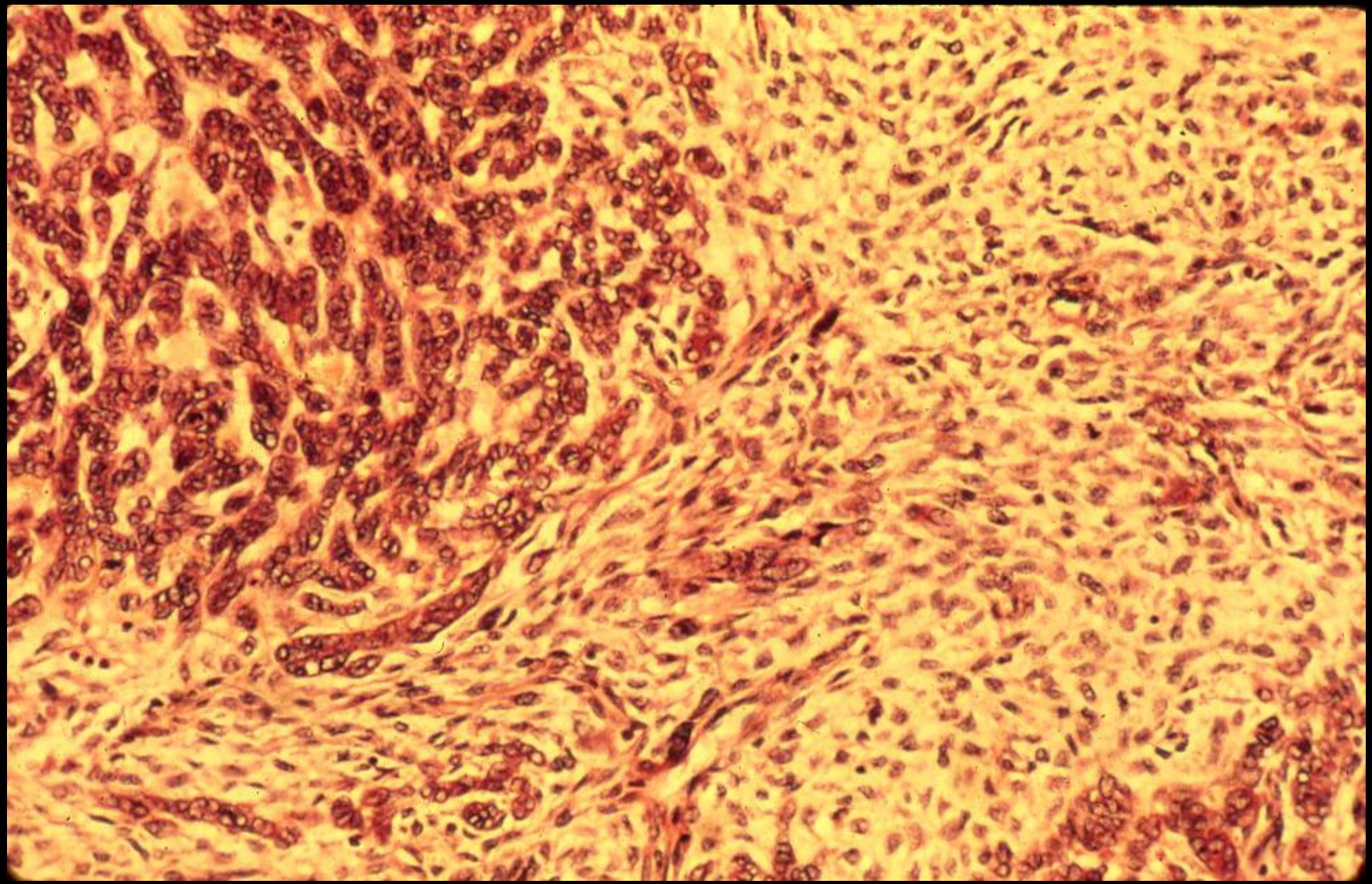












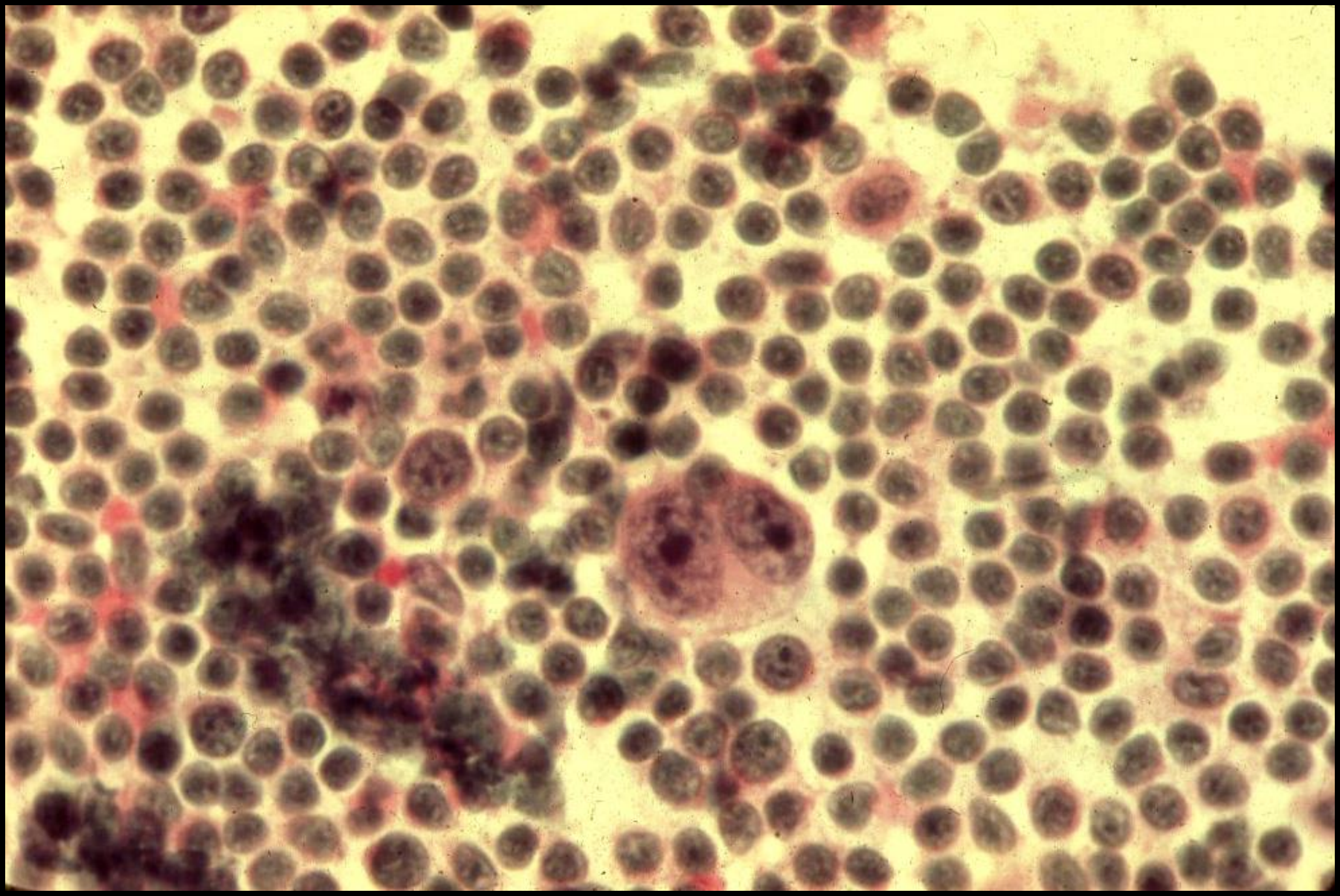


Table 7–10. INTERMEDIATE FILAMENTS AND THEIR DISTRIBUTION

Keratins	Carcinomas
	Mesothelioma
Desmin	Muscle tumors: smooth, striated
Vimentin	Mesenchymal tumors, some carcinomas
Glial filaments	Gliomatous tumors
Neurofilaments	Neuronal tumors

Immunohistochemical characterization of unknown primary

- Carcinoma: pan CK, HMWCK, LMWCK, CK7, CK20, Ck5, p63, p40, TTF1-lung/thyroid, CDX-2-GI, PAX-8-Mullerian, renal, thyroid, prostate NKX3.1 and PSA, AR

Breast: TRPS-1, Mammaglobin, GCDFP-15, GATA3, ER PR

Sarcoma: Desmin, S100, SOX-10, Skeletal muscle (MyoD1, myogenin), endothelium(CD34, CD31, ERG)

Lymphoma: CD45, CD3, CD20, Ig gene rearrangement

Melanoma: SOX10, S100, HMB45, Melan A, Tyrosinase, Prame, MiTF

Table 7–11. SELECTED TUMOR MARKERS

MARKERS	ASSOCIATED CANCERS
Hormones	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See Paraneoplastic Syndromes in Table 7–9
Oncofetal Antigens	
Alpha-fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and breast
Isoenzymes	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small cell cancer of lung, neuroblastoma
Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer


Diagnosis
Immunohistochemical & Molecular Markers
* = preferred
Adrenal cortical carcinoma
Inhibin
Synap
Melan-A
Calretinin
Vimentin
Chromogr
CK7
CK20
Breast - ductal carcinoma
CK7
ER
PR
GATA3
Mammaglobin (50-70%)
GCDFP-15 (50-70%)
E-cadherin
HMWCK
CK20
PAX2
ER/PR/HER2 on all newly diagnosed cases
Breast - lobular carcinoma
CK7
ER
PR
GCDFP-15
GATA3
Mammaglobin (50-70%)
E-cadherin
CK20
Breast - myoepithelial markers
p63
Calponin
SMMHC
Cervix - squamous cell ca
p63
p16
Cervix - adenocarcinoma
CK7*
p16 (>90%)*
CEA
ER
P63*
CK20
CDX2
TTF-1
Cholangiocarcinoma
CK7
CK19
N-cadherin
HMWCK
CK20
CDX2
Colon - adenocarcinoma
CK20
CDX2
CEA
CK7
MSI-colon IHC on all newly diagnosed cases of pT3 or pT4 w/o prior chemo/rt
Endometrioid carcinoma
CK7*
ER*
Vimentin*
CA125
CK20
CDX2
CEA*
*p16 can be positive by non-HPV mechanisms in poorly differentiated endometrial carcinomas (especially squamous morules)
Esophagus - adenocarcinoma
CK7
CDX2
Hepatocellular carcinoma
Glypican
Hepatocyte
AFP
CEA
CD10
CK7
CK20
PAX2
Dysplastic nodules also glypican positive, hepatic adenomas and normal hepatocytes are negative
Lung - adenocarcinoma
CK7
TTF1
CEA
CD15
Napsin
HMWCK
CK5/6
Calretinin
WT-1
HBME
D2-40
CDX-2
Lung - squamous cell carcinoma
p63
HMWCK
Napsin (20%)
TTF-1
Lung - small cell carcinoma
CK/CKT
Synaptophysin
Chromogranin
TTF-1
NSE
CD56
CK20
Napsin
Nasopharyngeal carcinoma
EBER (ISH)
CK/CKT
p63
Ovary - mucinous carcinoma
CK7
CK20
CDX2 (90%)
ER supports if positive
Ovary - serous carcinoma
WT1*
CK7*
ER*
p53
CA125
PAX 2 (67%)
CK20
CDX2
Paget's disease
CK7*
CAM5.2
EMA
CEA
Her2
S100*
Pancreas - ductal carcinoma
CK7
HMWCK
CK20
N-cadherin (30%)
CDX2 (often + in duodenal/ampullary lesions)
Prostate carcinoma
PSA
PSAP
p504 racemase
Androgen Receptor
Erg (40%)
CK7
HMWCK
CK20
p63
PAX2
GATA3
PIN4 cocktail includes p63 (nuclear, myoepithelial cells, brown), CK5/14 (nuclear, myoepithelial cells, brown), and racemase (cytoplasmic, most adenocarcinoma, red)
Renal - clear cell carcinoma
RCC
CD10 (membranous)
Vimentin
PAX2
CK7
CD117
CK20
Renal - papillary carcinoma
RCC
CD10 (membranous)
CK7
PAX2
Vimentin
p504s
AMACR
napsin
CK7
CK20
CD117
Renal - chromophobe carcinoma
Hale's Colloidal Iron
CD117
CK7
PAX2
RCC
CD10
Vimentin
Salivary - Ductal
Androgen Receptor
GCDFP-15
Her2
SOX10
SOX10 positive salivary gland tumors: acinic, adenoid cystic, epithelial myoepithelial, myoepithelial carcinomas, pleomorphic adenomas
SOX10 negative salivary gland tumors: salivary duct, mucoepidermoid, oncocytic carcinoma, oncocytomas, Warthin's
Stomach:
Intestinal type
CK7
CDX2
CK20
Diffuse/signet ring type
CK7
CK20
E-cadherin
CDX2
HER2 IHC on newly diagnosed cases
Thyroid - papillary & follic. carc.
TTF1
Thyroglobulin
CK7
HMWCK
Vimentin
HBME-1
Napsin
Thyroid - medullary carcinoma
TTF1
Calcitonin
CK7
Thymic carcinoma
CD117
CK5/6
CD5
P63
Urachal carcinoma
CK20
CDX2
CK7
Urothelial carcinoma
p63
CK7
CK5/6
HMWCK (34betaE12)
GATA3
CK20
PAX2

Table 7–2. COMPARISONS BETWEEN BENIGN AND MALIGNANT TUMORS

CHARACTERISTICS	BENIGN	MALIGNANT
Differentiation/anaplasia	Well-differentiated; structure may be typical of tissue of origin	Some lack of differentiation with anaplasia; structure is often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures are rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive and expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating the surrounding normal tissues; sometimes may be seemingly cohesive and expansile
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

Nomenclature of Tumors

	Cell Type of Origin	*Benign*	*Malignant*
Epithelial	Squamous cell	Papilloma	Epidermal (squamous cell) carcinoma
	Glandular cell	Adenoma	Adenocarcinoma
Mesenchymal	Fibroblast	Fibroma	Fibrosarcoma
	Fat cell	Lipoma	Liposarcoma
	Endothelial cell	Angioma	Angiosarcoma
	Cartilage cell	Chondroma	Chondrosarcoma
	Bone cell	Osteoma	Osteosarcoma

Table 7–1. NOMENCLATURE OF TUMORS

TISSUE OF ORIGIN	BENIGN	MALIGNANT
I. Composed of One Parenchymal Cell Type		
A. Mesenchymal tumors		
1. Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
2. Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Synovium		Synovial sarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
3. Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Malignant lymphomas
4. Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
B. Epithelial tumors		
1. Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
2. Basal cells of skin or adnexa		Basal cell carcinoma
3. Epithelial lining		
Glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinoma
	Cystadenoma	Cystadenocarcinoma
4. Respiratory passages		Bronchogenic carcinoma
		Bronchial "adenoma" (carcinoid)
5. Neuroectoderm	Nevus	Malignant melanoma
6. Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
7. Liver cells	Liver cell adenoma	Hepatocellular carcinoma
8. Urinary tract epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
9. Placental epithelium (trophoblast)	Hydatidiform mole	Choriocarcinoma
10. Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
II. More Than One Neoplastic Cell Type—Mixed Tumors		
1. Salivary glands	Pleomorphic adenoma (mixed tumor of salivary origin)	Malignant mixed tumor of salivary gland origin
2. Breast	Fibroadenoma	Malignant cystosarcoma phyllodes
3. Renal anlage		Wilms' tumor
III. More Than One Neoplastic Cell Type Derived From More Than One Germ Layer—Teratogenous		
1. Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Nomenclature of Malignant Tumors

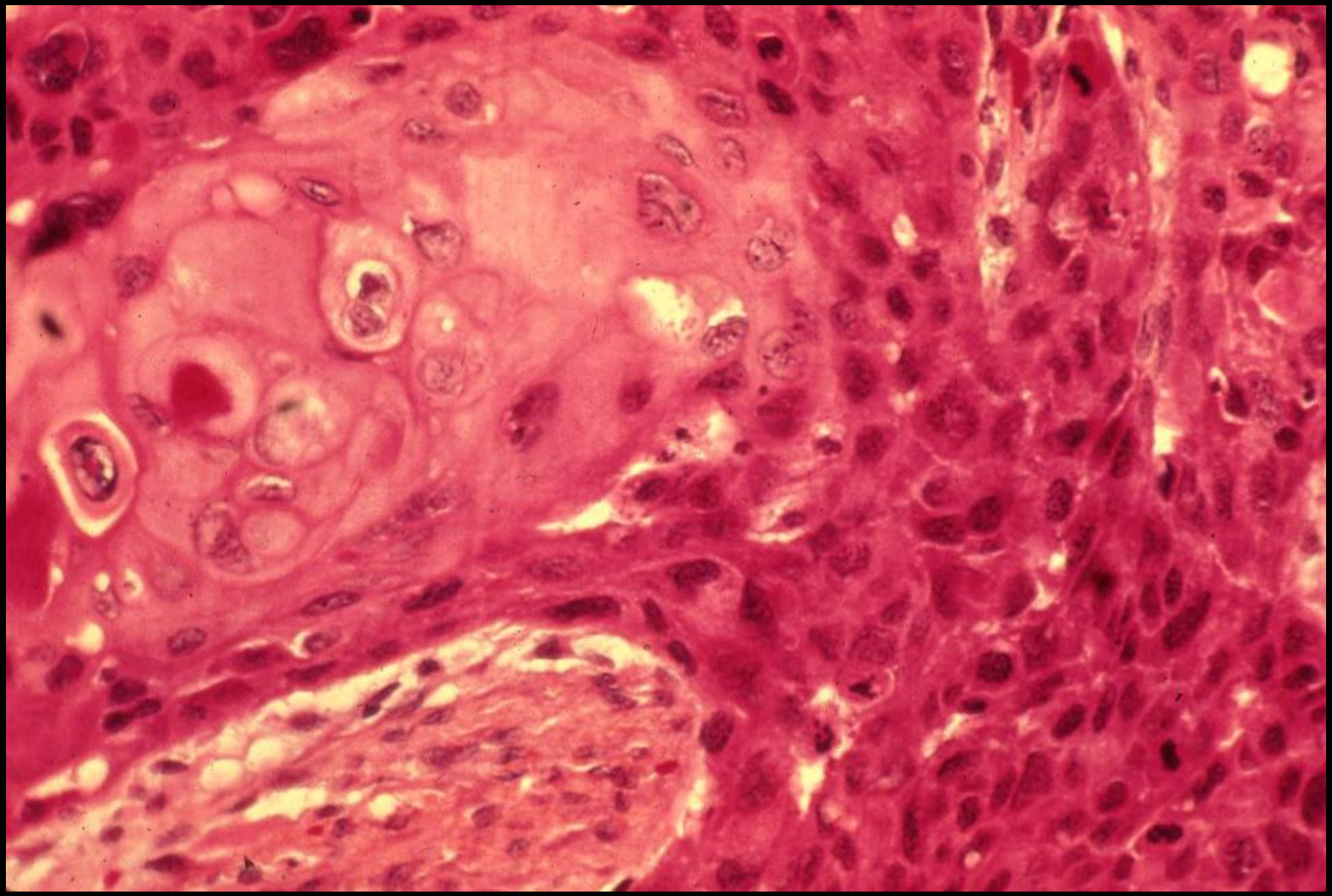
Carcinomas	Tumors arising in epithelium
Sarcomas	Tumors arising in mesenchymal tissues
Leukemias, lymphomas	Tumors arising in mesenchymal stem cells of bone marrow and lymphoid tissues
Carcinosarcomas	Tumors containing both malignant epithelial and mesenchymal elements
Teratocarcinomas	Malignant tumors containing tissue from the three primitive germ layers

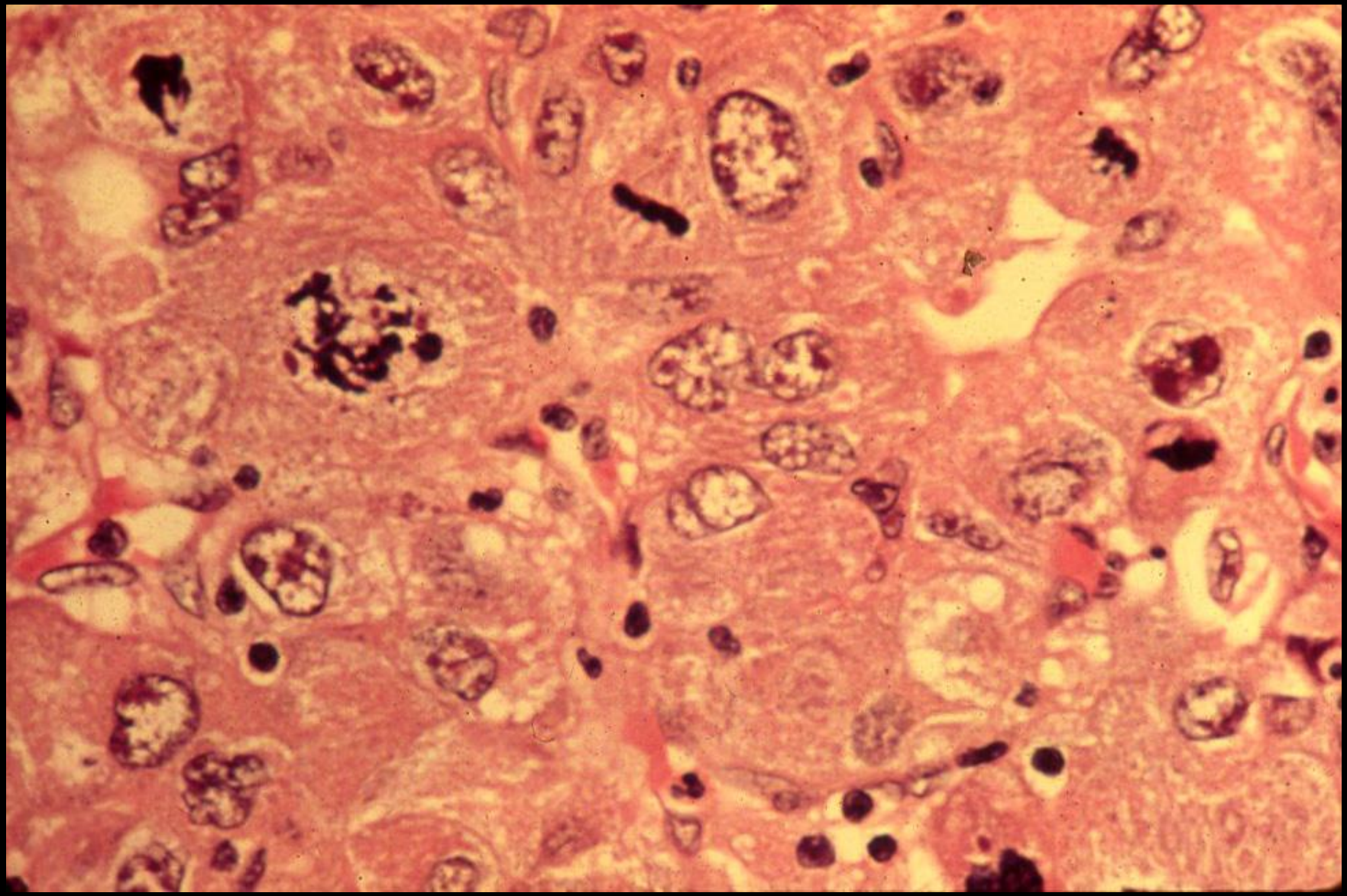
Eponyms of Common Tumors

Brenner	Epithelial ovarian tumor
Burkitt's	Lymphoma
Ewing's	Sarcoma of bone
Grawitz's	Carcinoma of the kidney
Kaposi's	Hemangiosarcoma
Krukenberg's	Carcinoma of ovary (usually metastatic from stomach)
Pancoast's	Carcinoma of pulmonary sulcus
Rathke's	Craniopharyngioma of pituitary
Warthin's	Tumor of salivary gland
Wilms'	Adenomyosarcoma of kidney

Histologic Grading of Malignant Tumors: General Principles

Grade I (Well differentiated)	Tumor tissue closely resembles tissue of origin (e.g., gland formation in adenocarcinoma, keratinization and epithelial pearls in squamous cell carcinoma) Few mitoses Little variation in size and shape of tumor cells
Grade II (Moderately differentiated)	Tumor tissue resembles tissue of origin less well Increased mitoses Increased variation in size and shape of tumor cells
Grades III, IV (Poorly differentiated)	Tumor tissue does not closely resemble tissue of origin Many mitoses Large variation in size and shape of tumor cells





Staging: extent of malignancy relates to prognosis

- TNM staging: T- tumor size, N- extent of lymph node involvement, M- presence or absence of metastasis

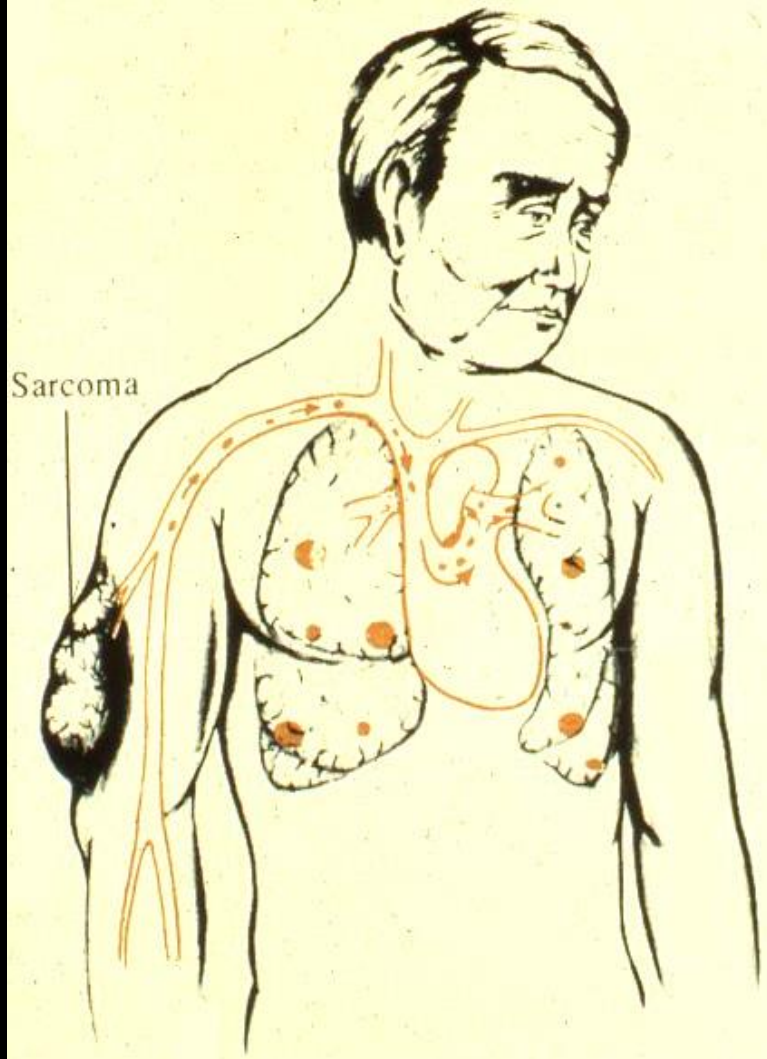
(nonanatomical prognostic factors)

Site and sometimes tumor type specific

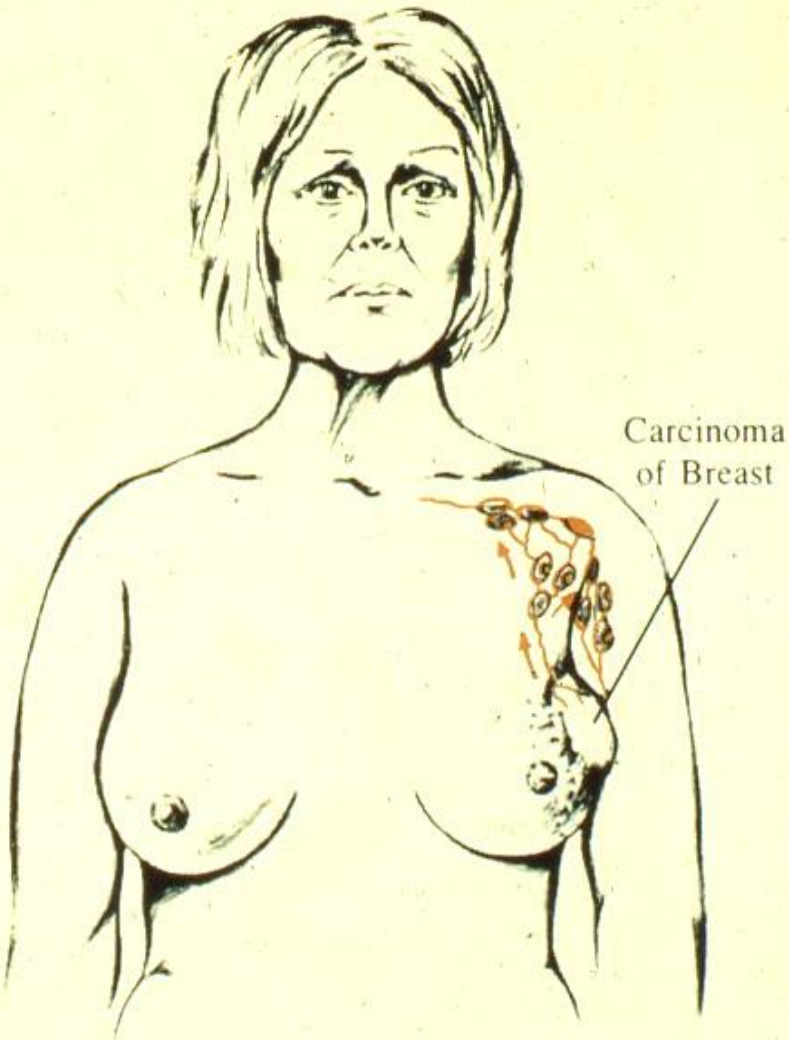
Stage: I,II,III,IV

Cervical cancer staging

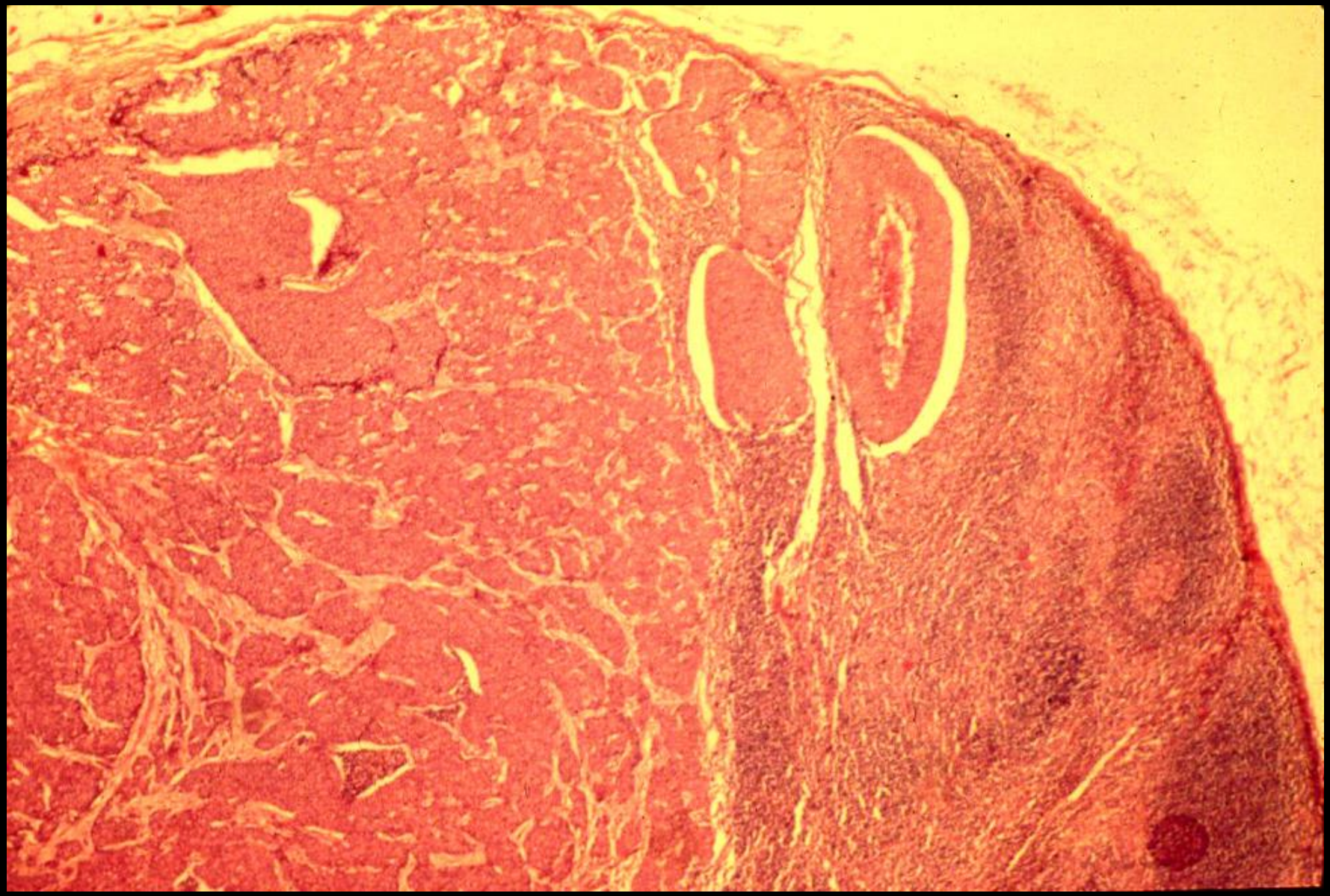
- Stage I: confined to uterus(93%/5yr)
- Stage II: invades beyond uterus but not pelvic wall or lower third of vagina (63%/5yr)
- Stage III: extends to pelvic wall or lower third of vagina (35%/5yr)
- Stage IV: invades bladder or rectal mucosa or beyond true pelvis(16%/5yr)

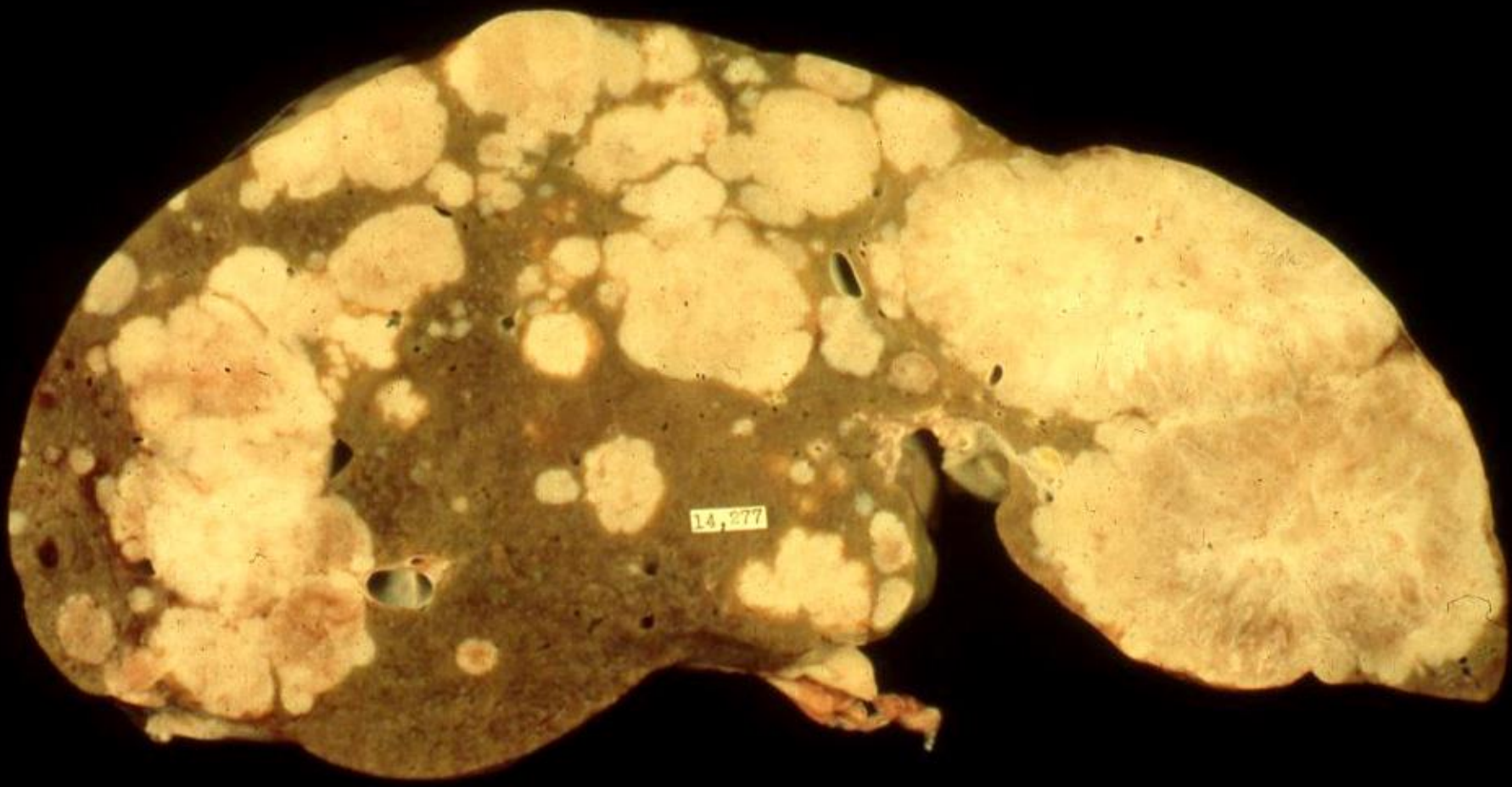


Sarcomas characteristically metastasize via veins to lungs.



Carcinomas characteristically metastasize via lymphatics to regional lymph nodes.

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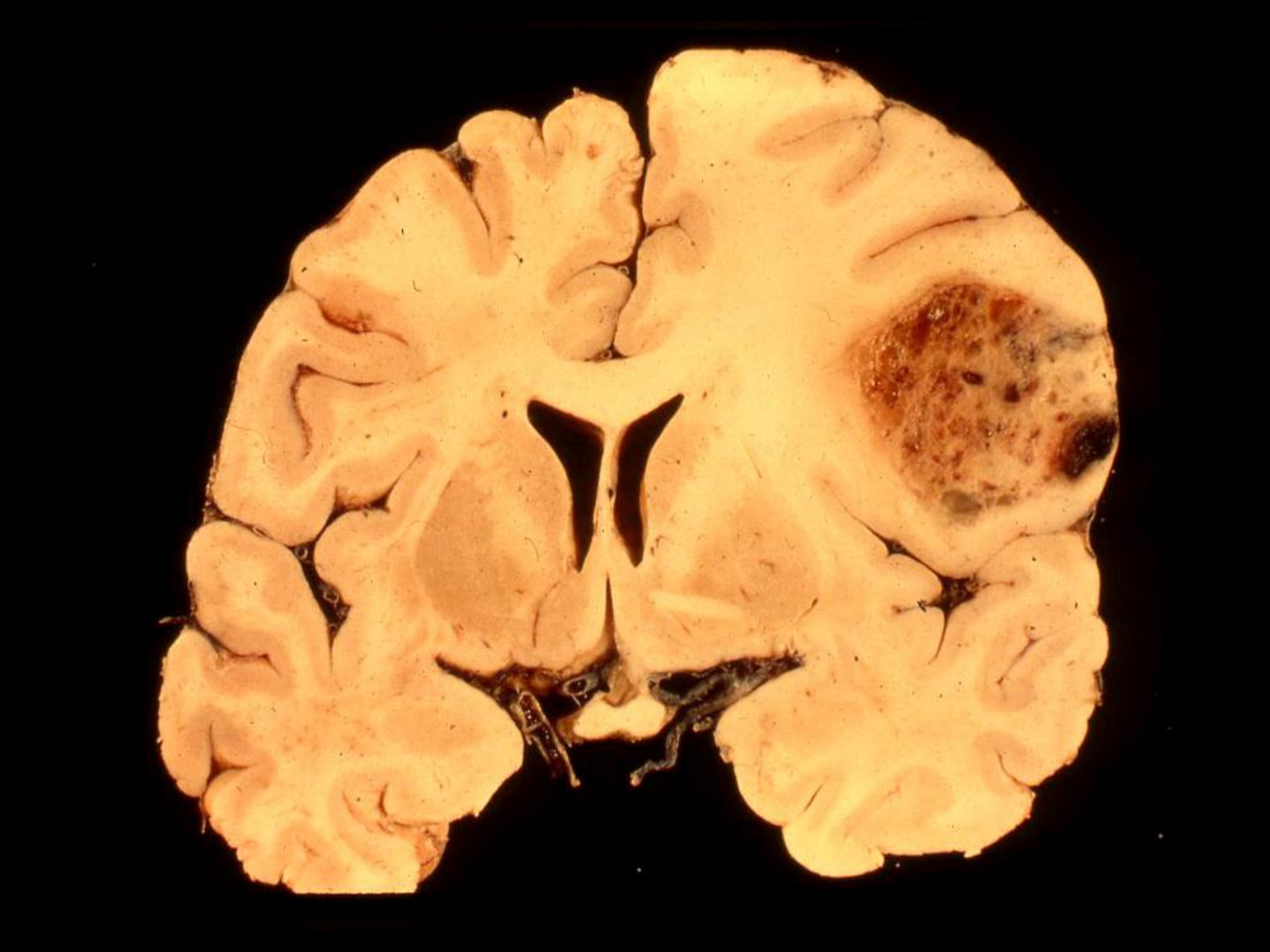


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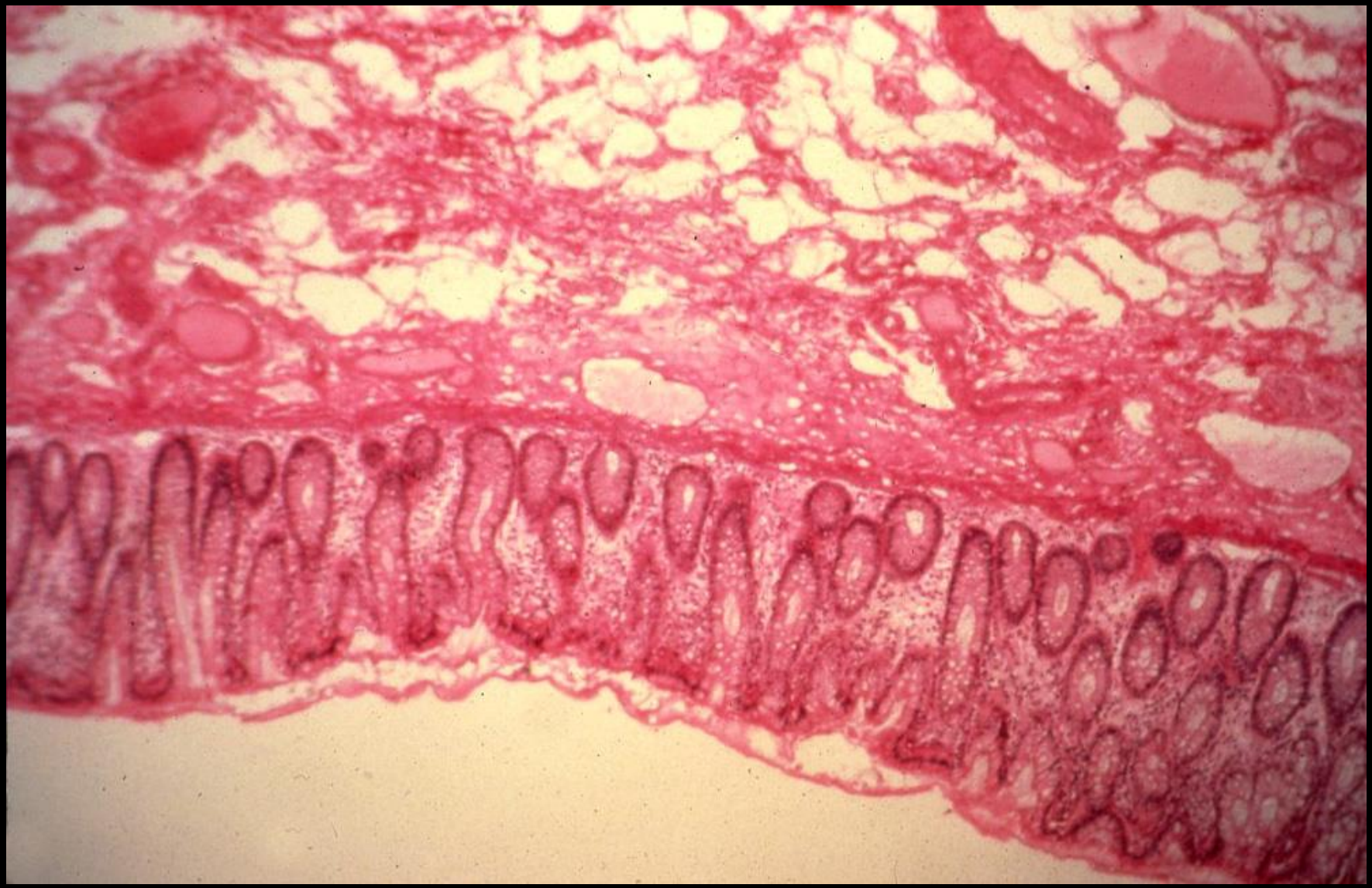
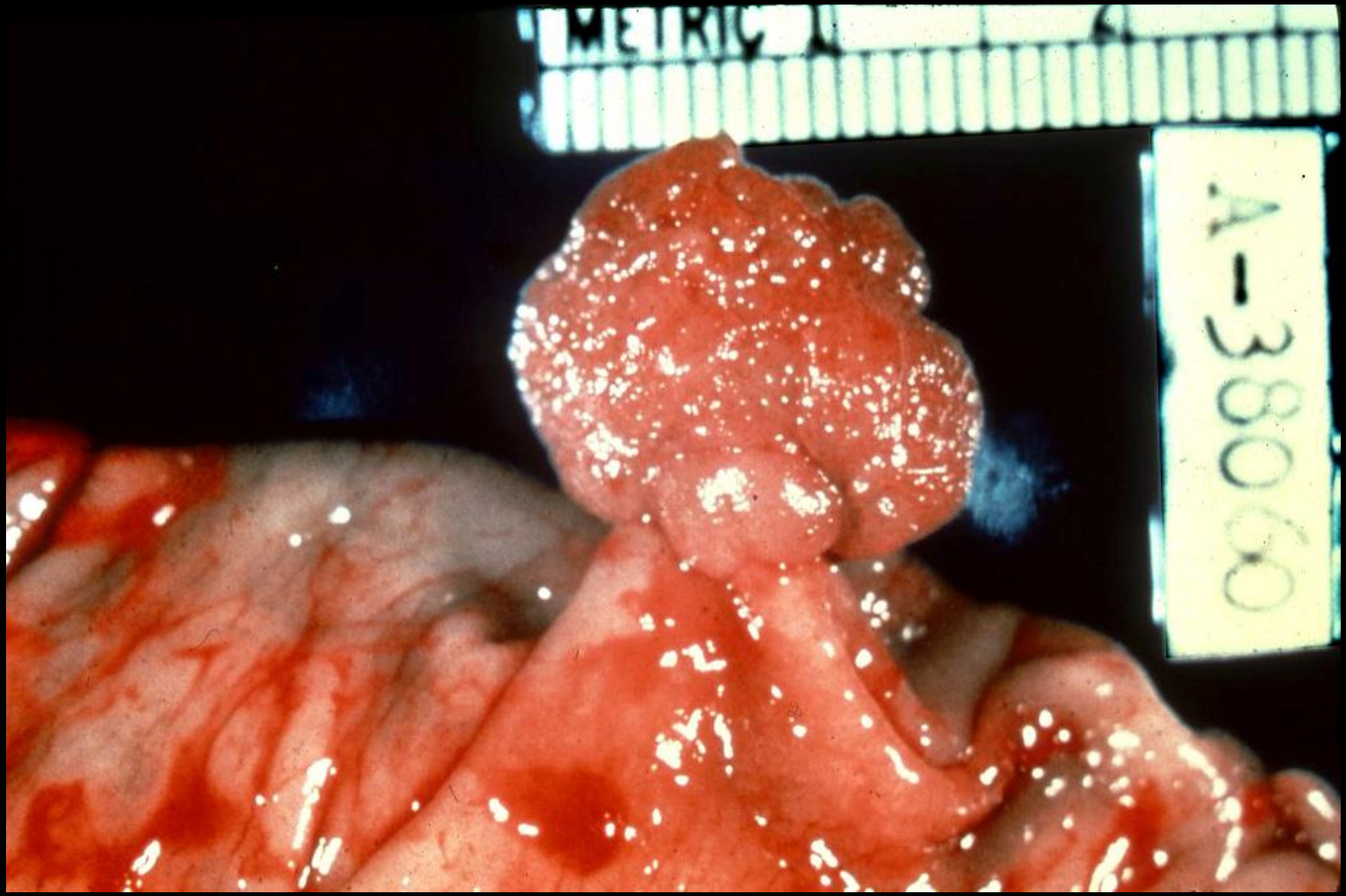
Metastatic Tumor Involvement in Autopsy Cases

Site of Metastatic Involvement	*In 1000 Consecutive Autopsies (%)*	*In 167 Cases of Primary Breast Cancer (%)*	*In 160 Cases of Primary Lung Cancer (%)*	*In 118 Cases of Primary Colon Cancer (%)*
Abdominal nodes	50	44	29	59
Liver	49	61	40	65
Lungs	47	77	47	37
Mediastinal nodes	42	67	83	14
Pleura	28	65	28	14
Bone	27	73	33	9
Adrenal	27	54	36	14
Gastrointestinal tract	27	15	11	27
Diaphragm	20	25	16	11
Brain (cerebrum)	18	9	43	—

(Adapted from Gwynne, J.F.: Death certification in Dunedin hospitals. N.Z. Med. J., *86*:77, 1977.)

Colon Cancer Evolution
Adenoma to Carcinoma

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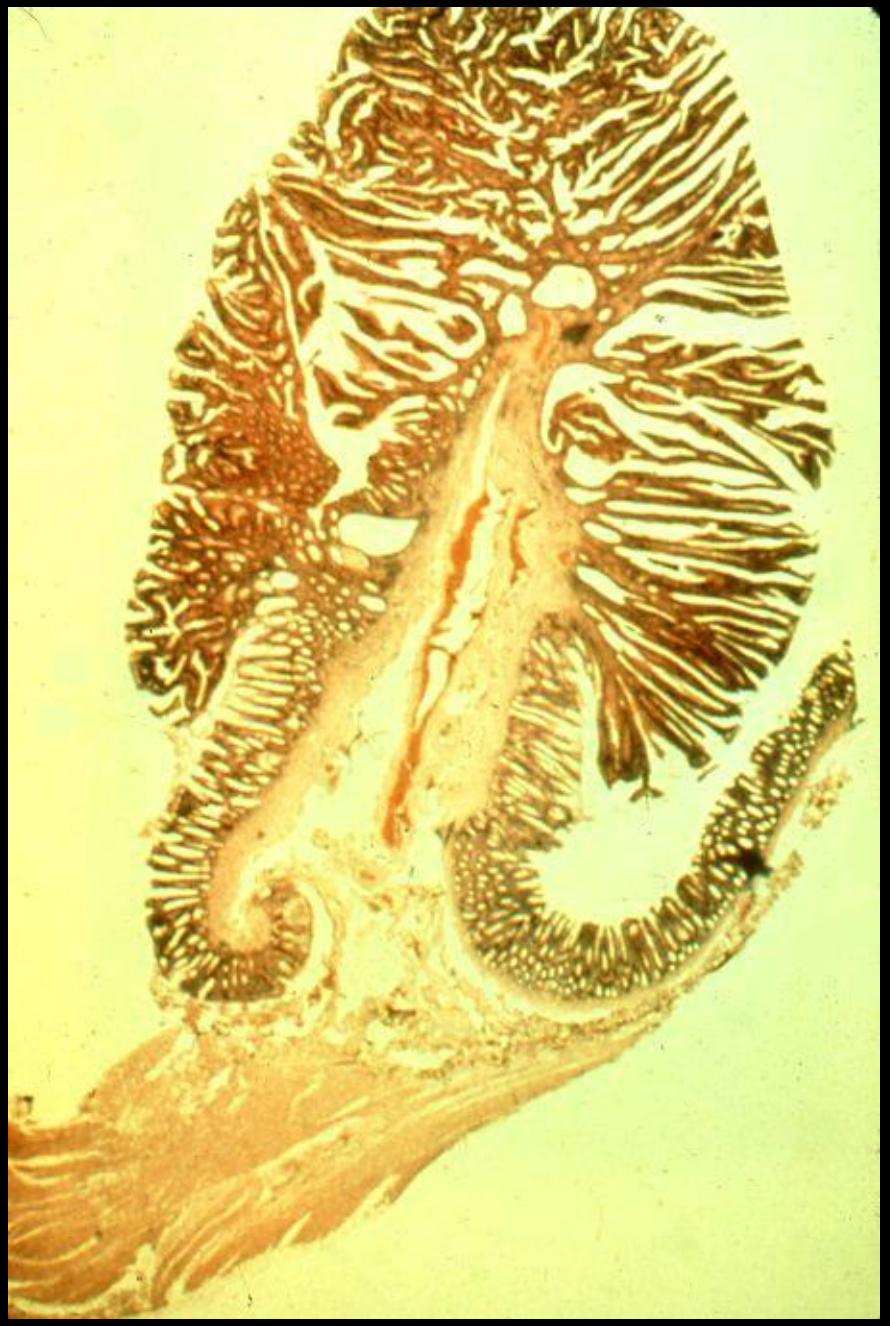

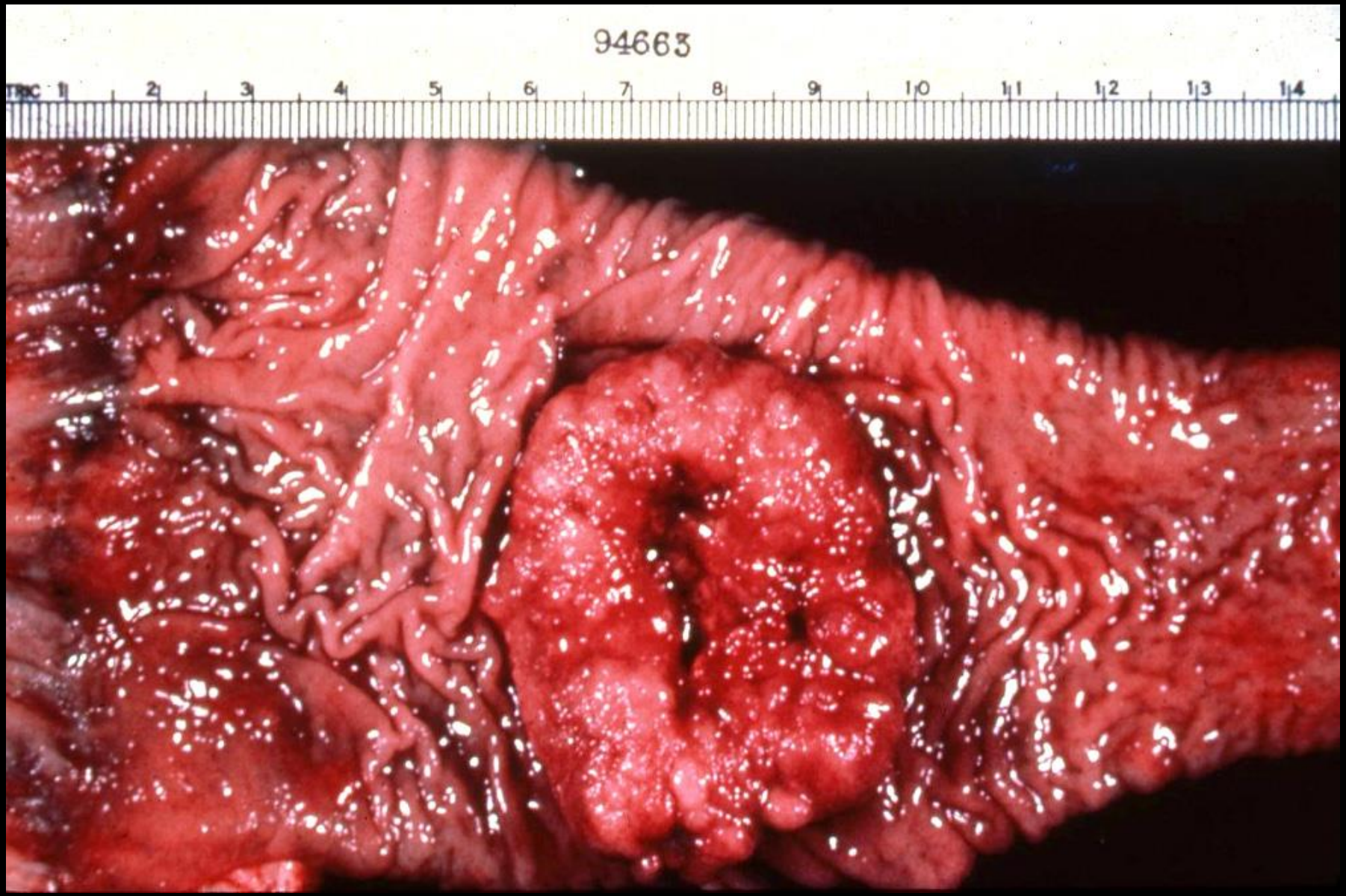
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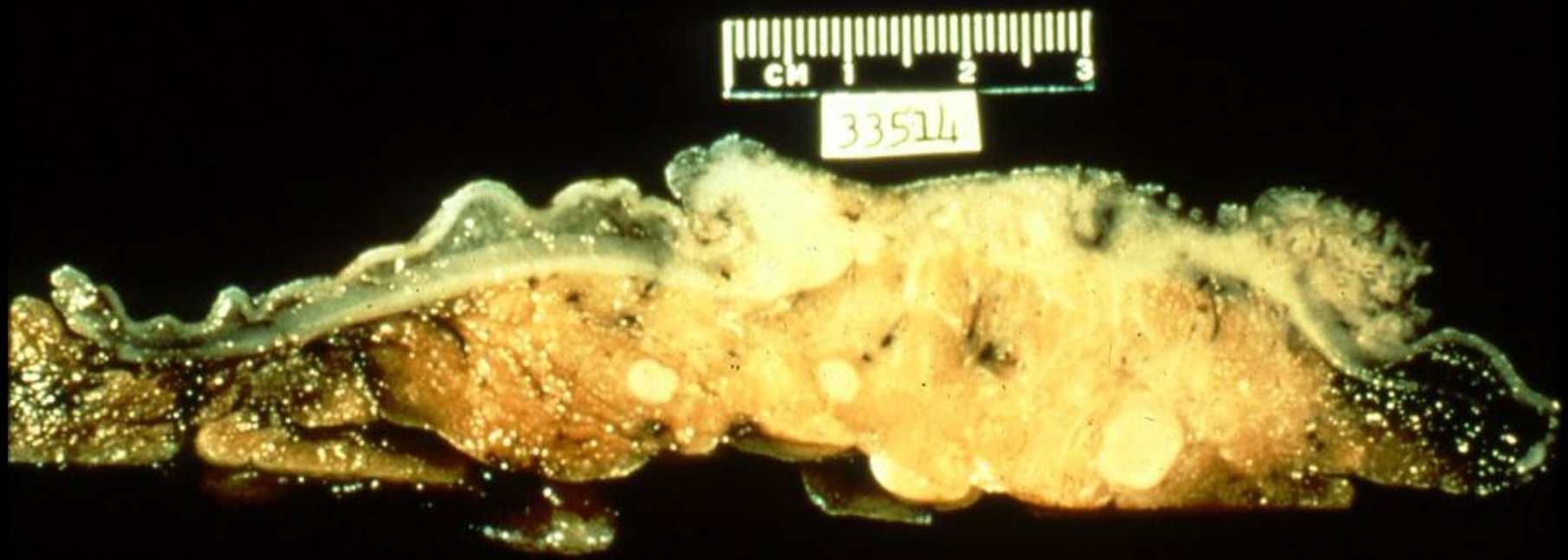
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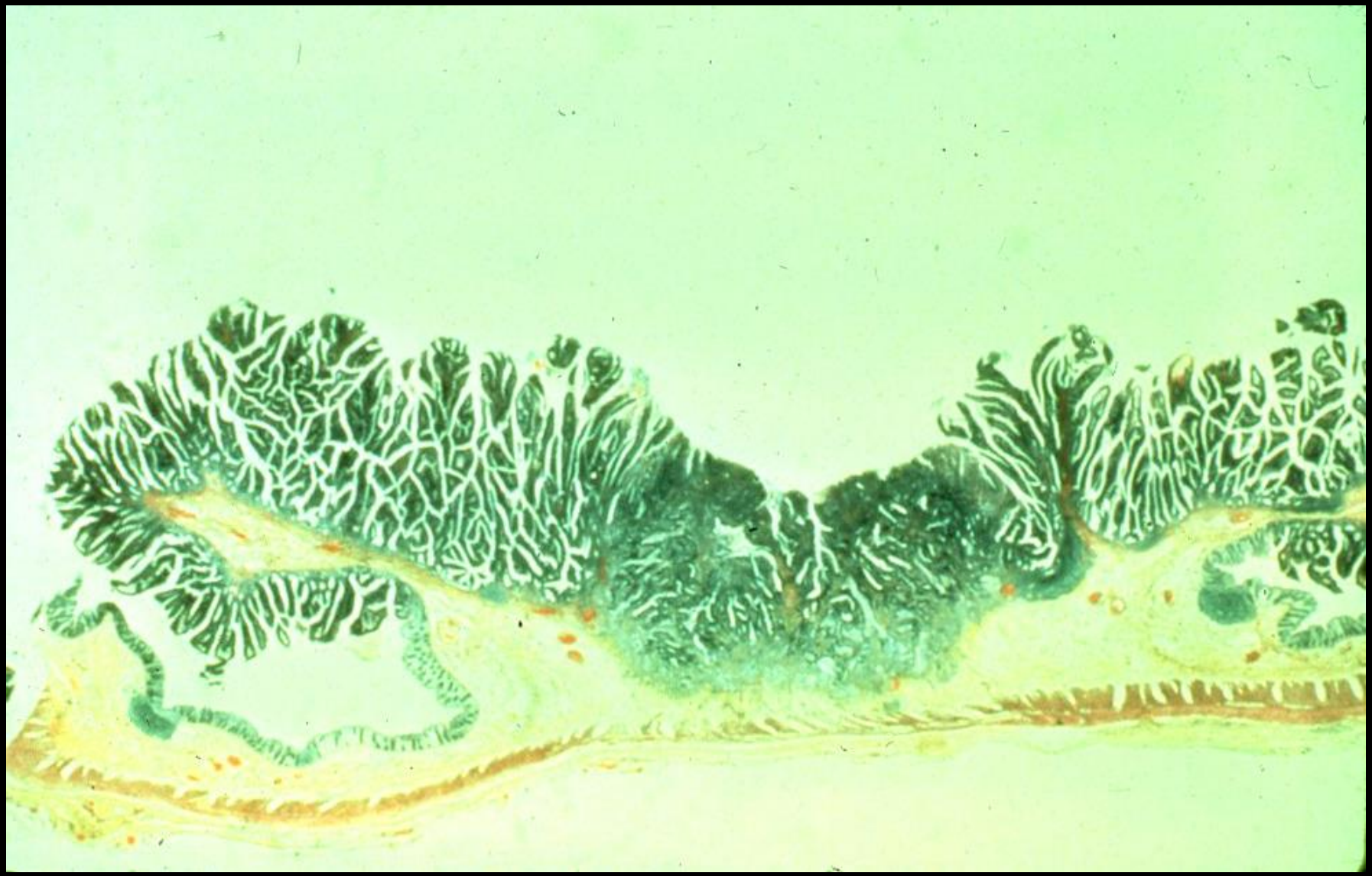
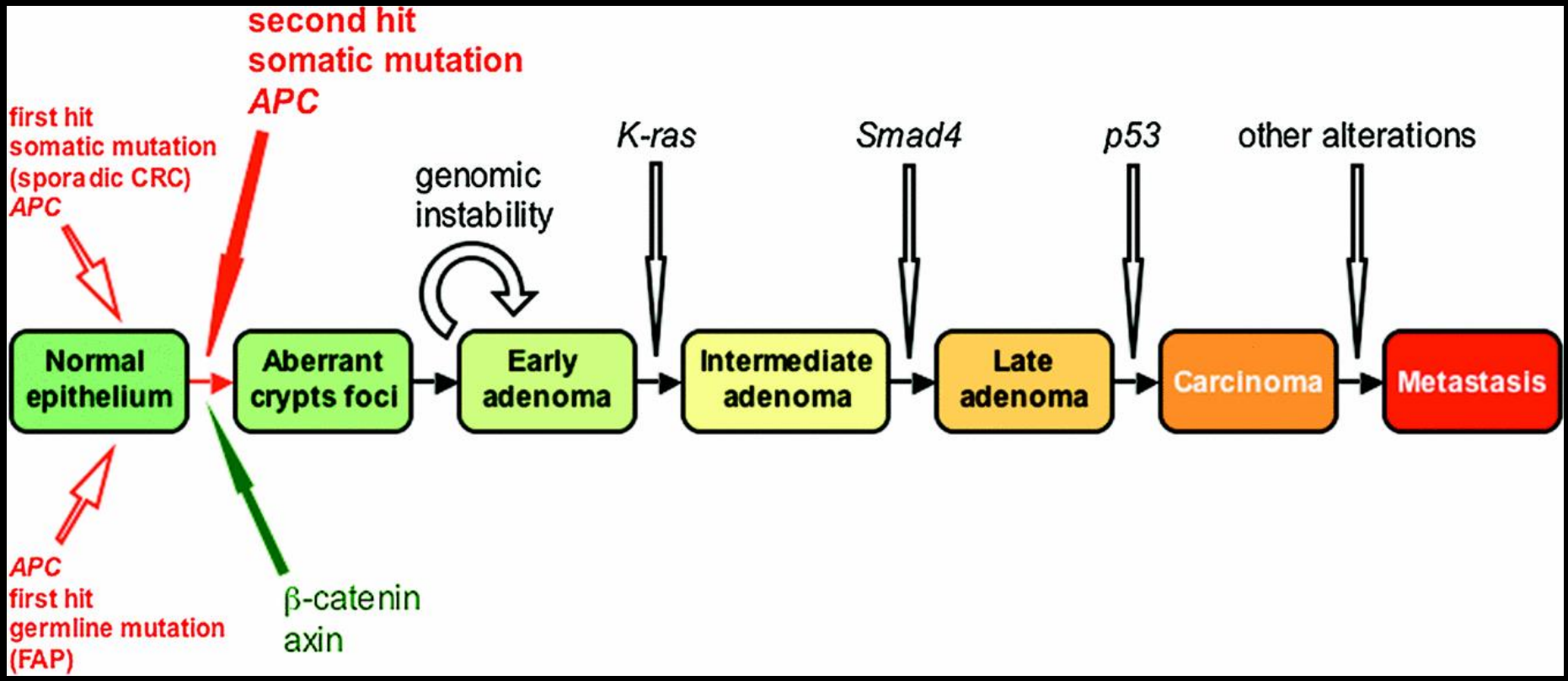
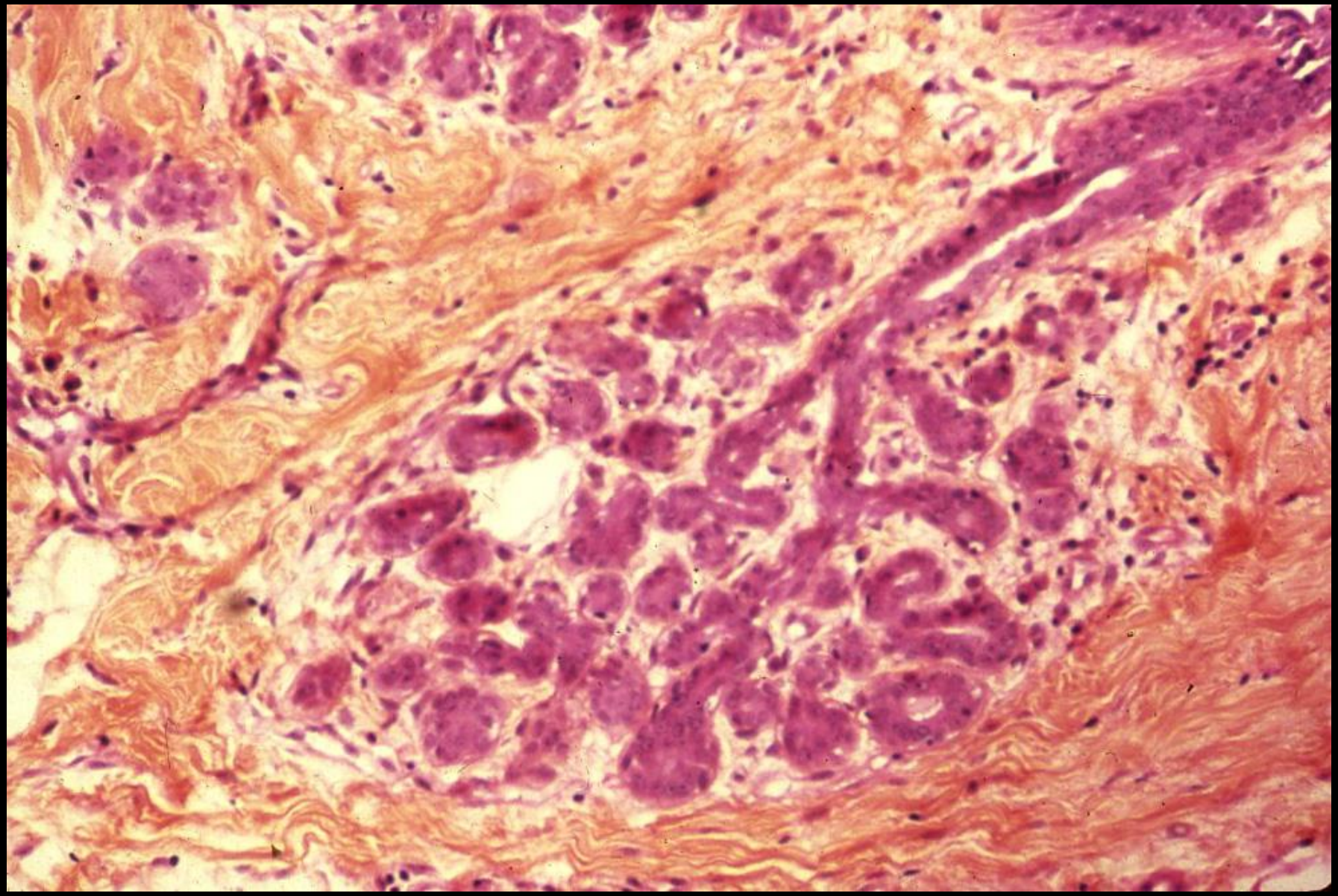
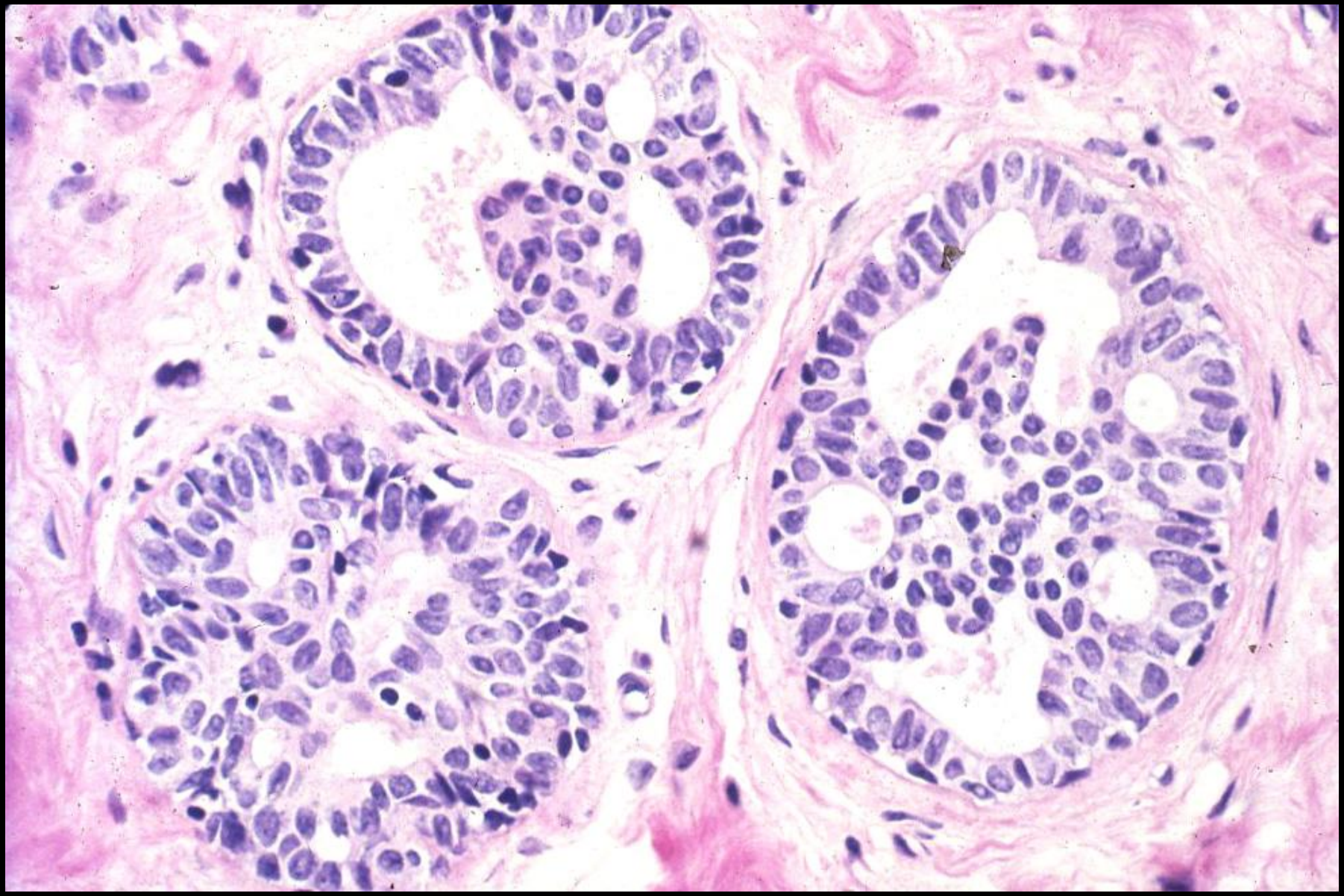


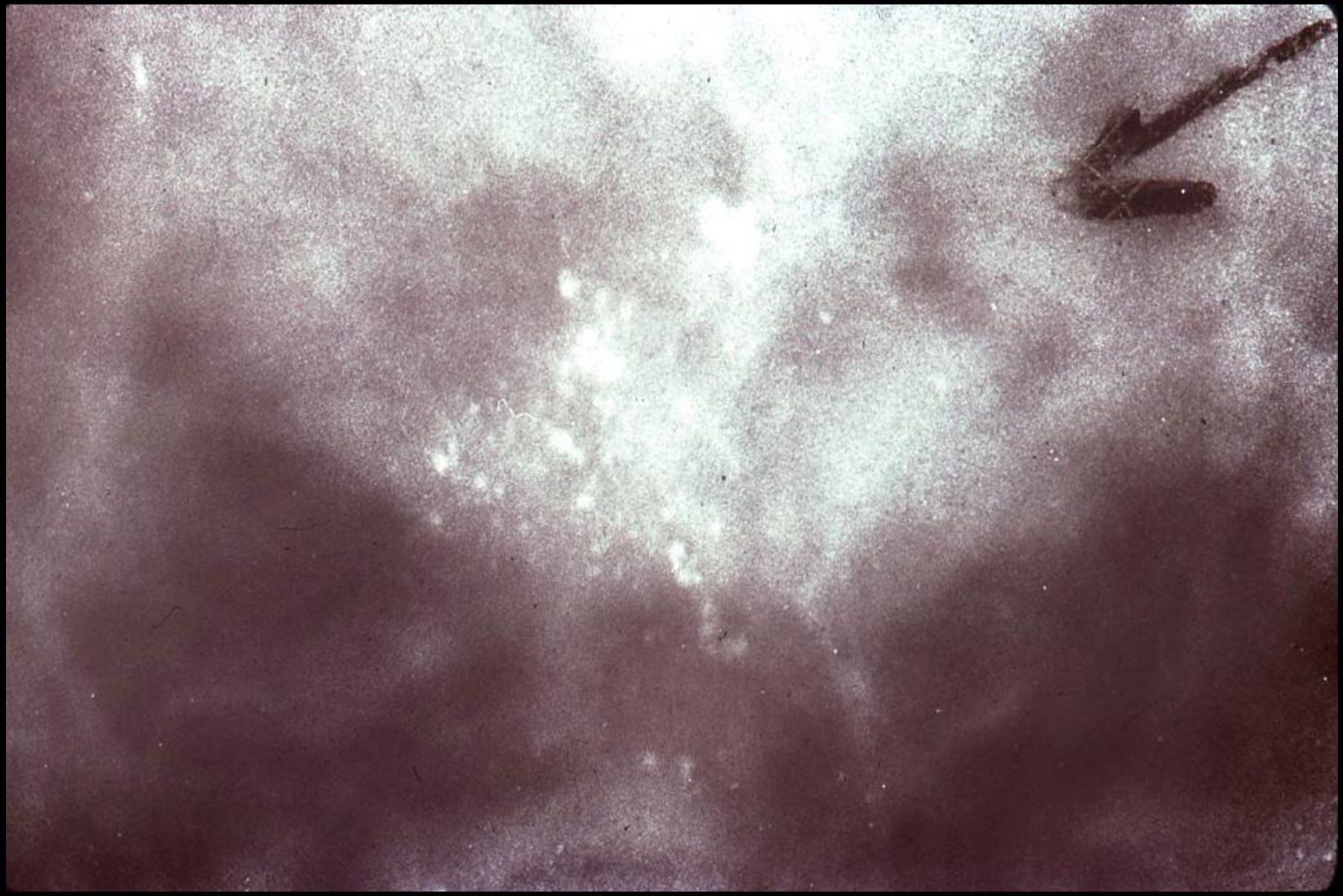
Molecular events in colon cancer

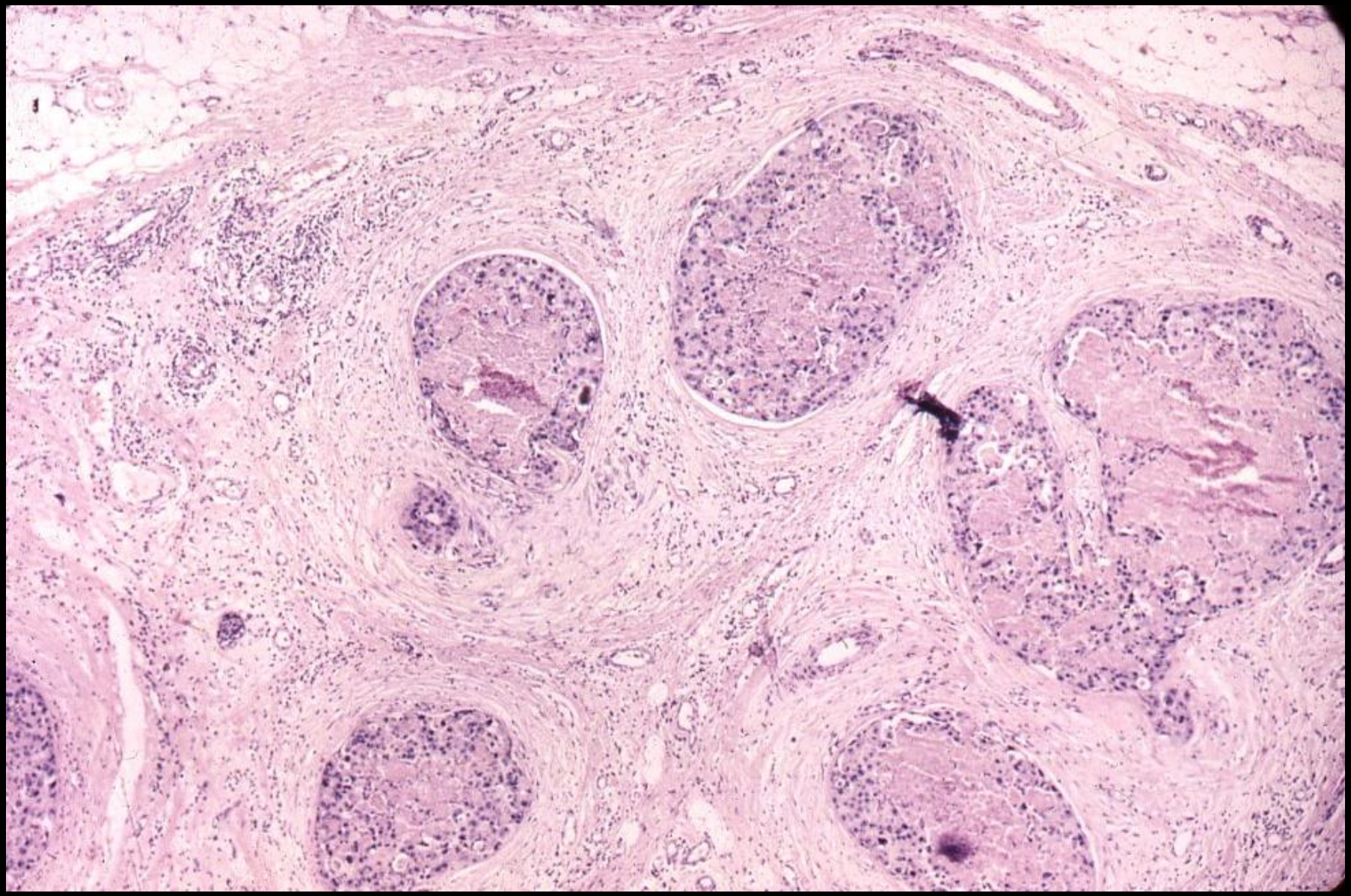


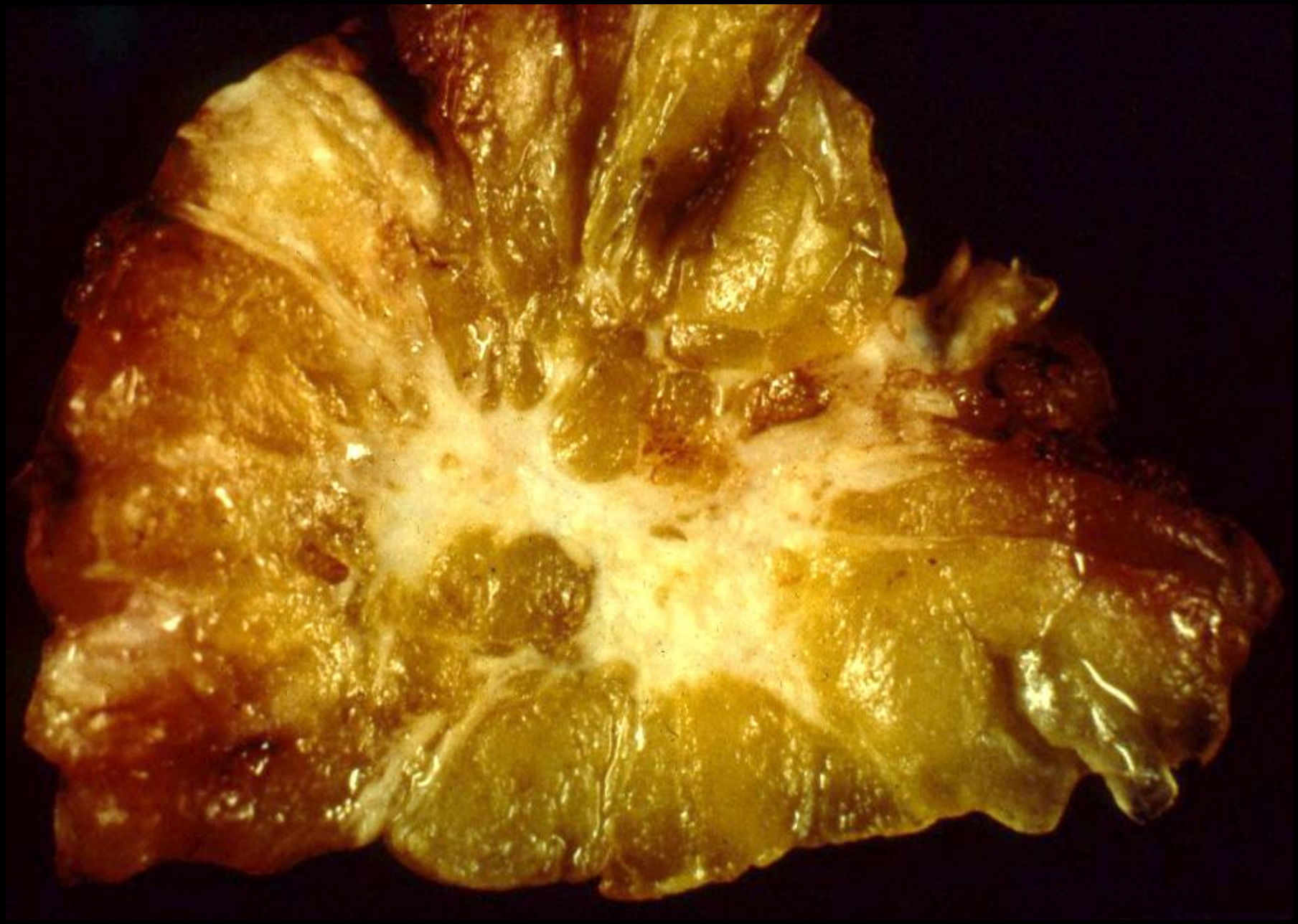
Breast
TDLU, ADH, DCIS, invasive carcinoma

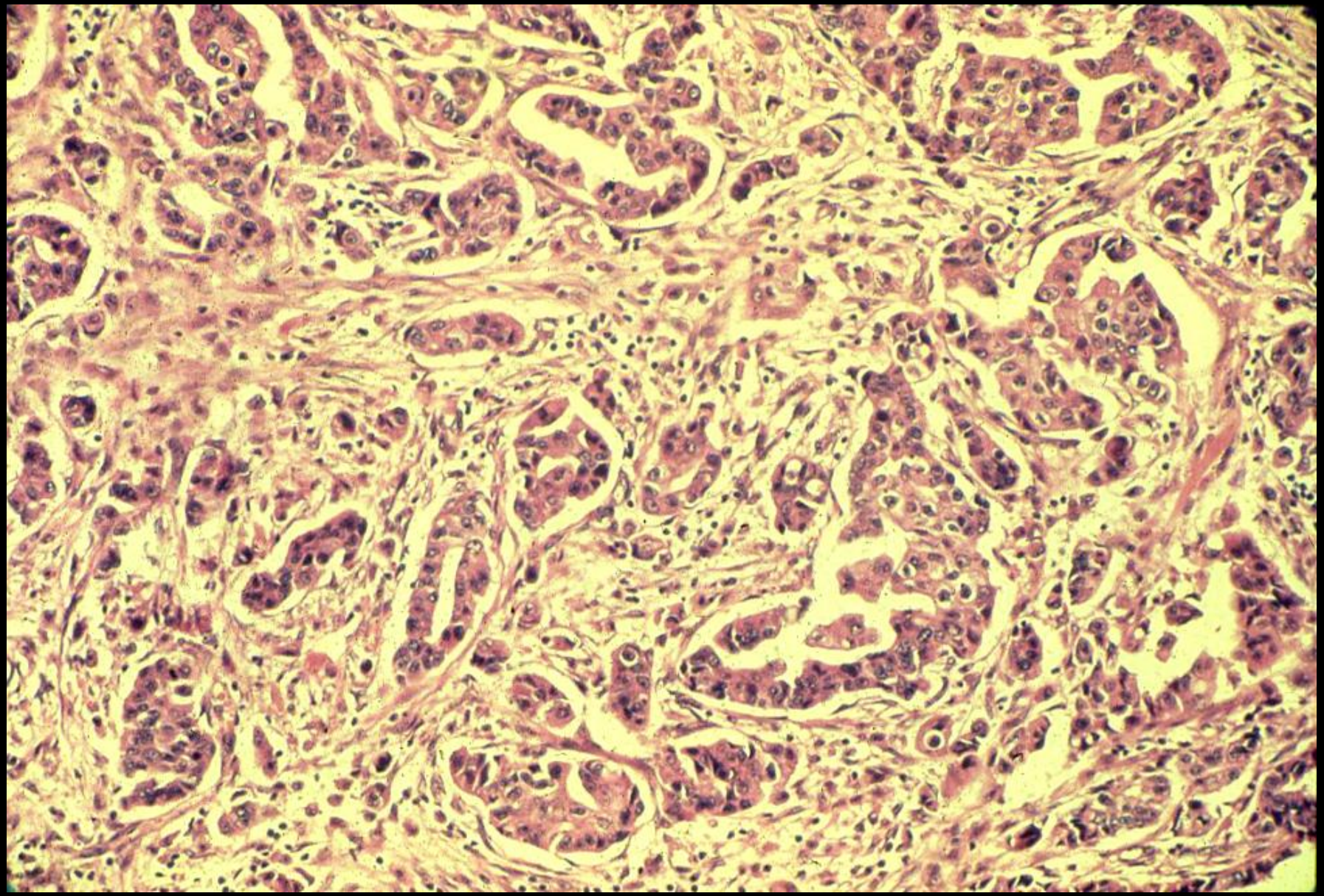


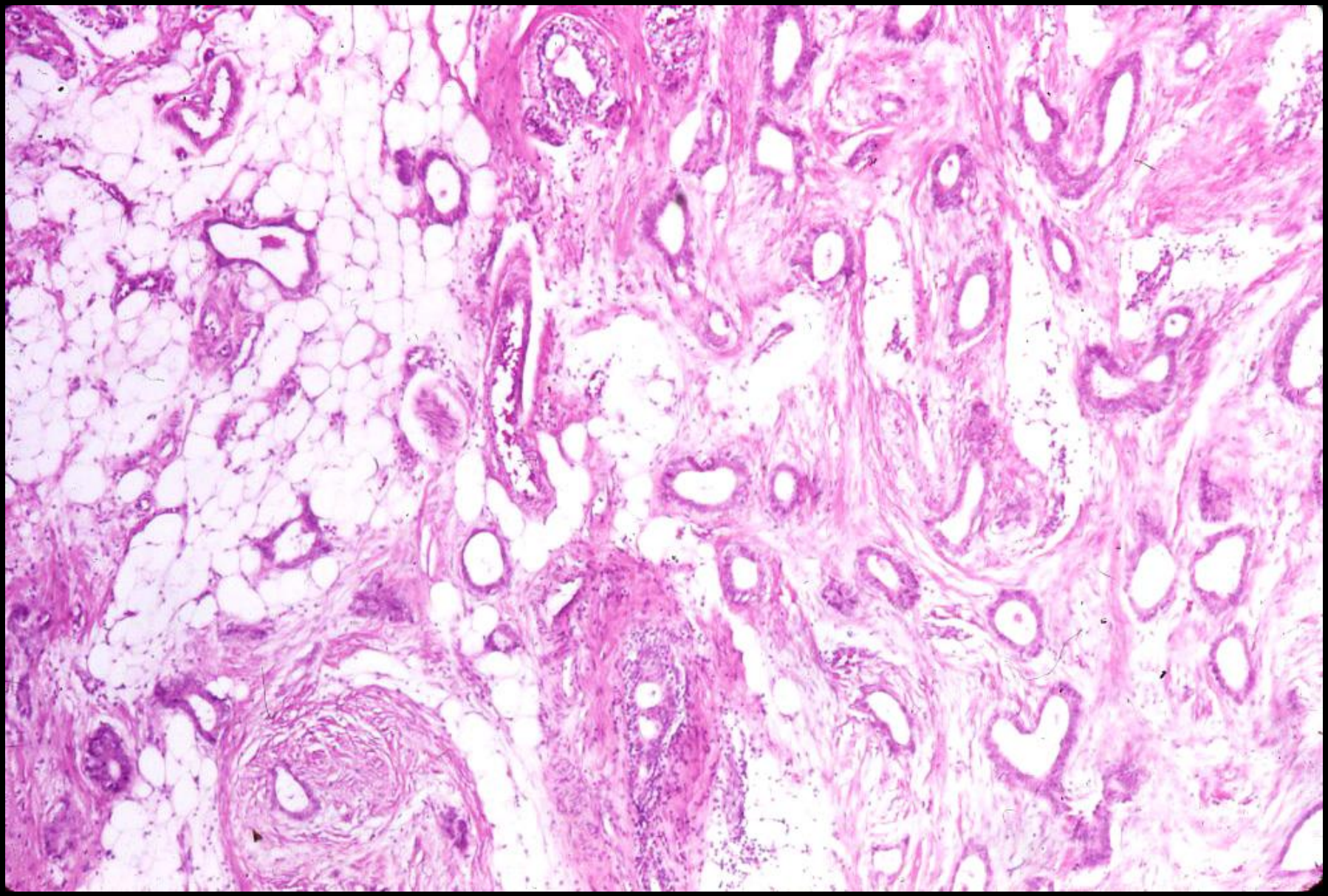


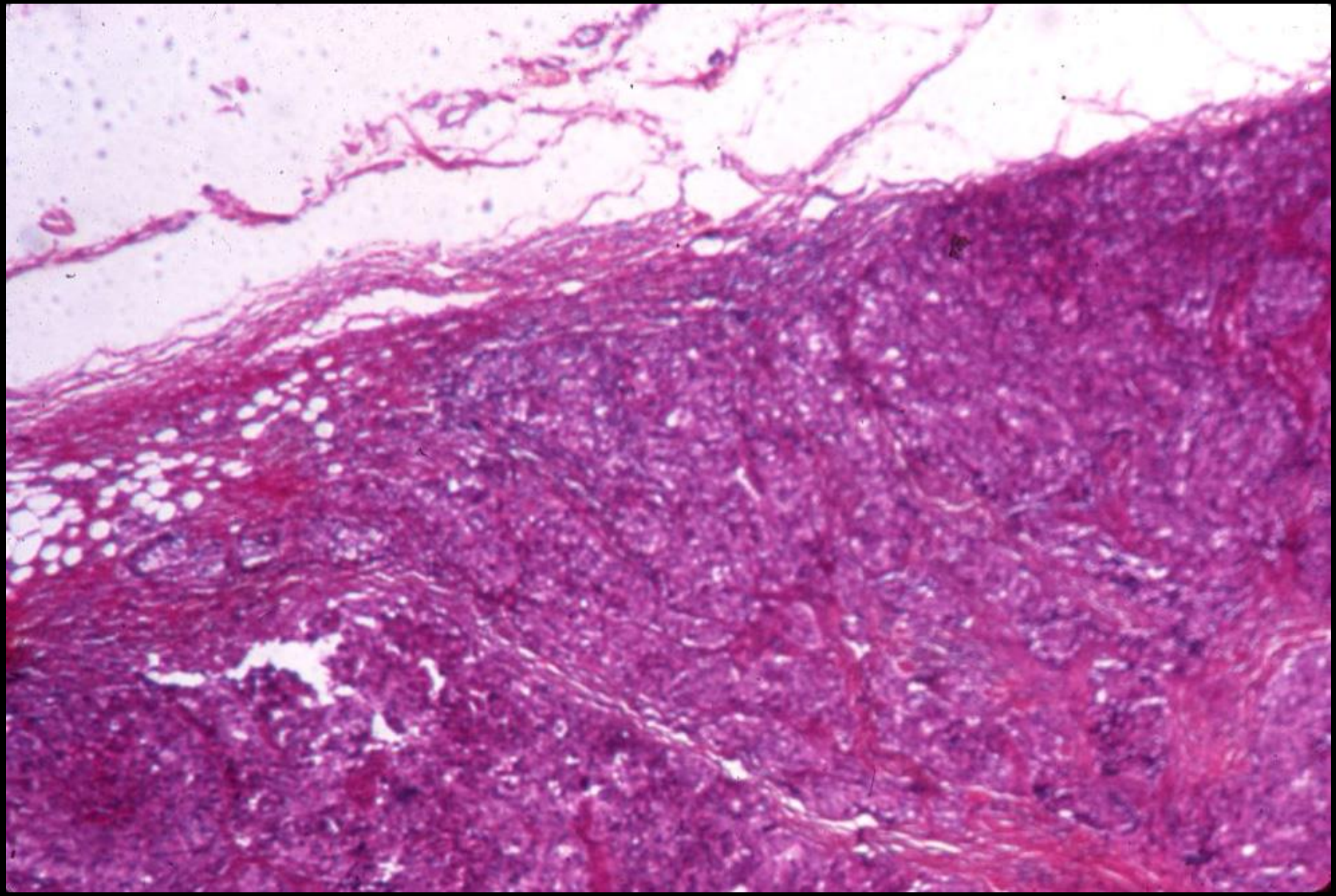


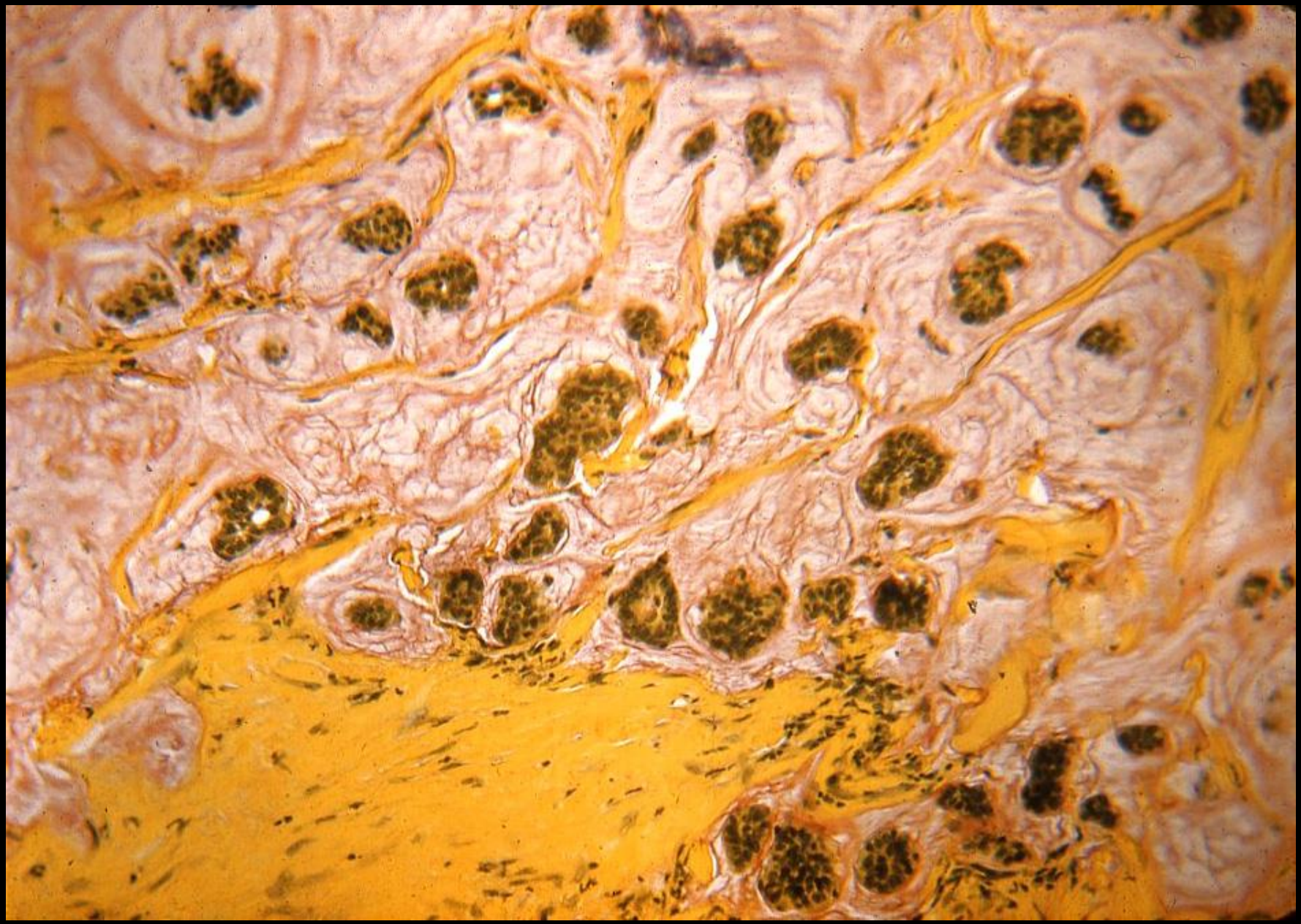


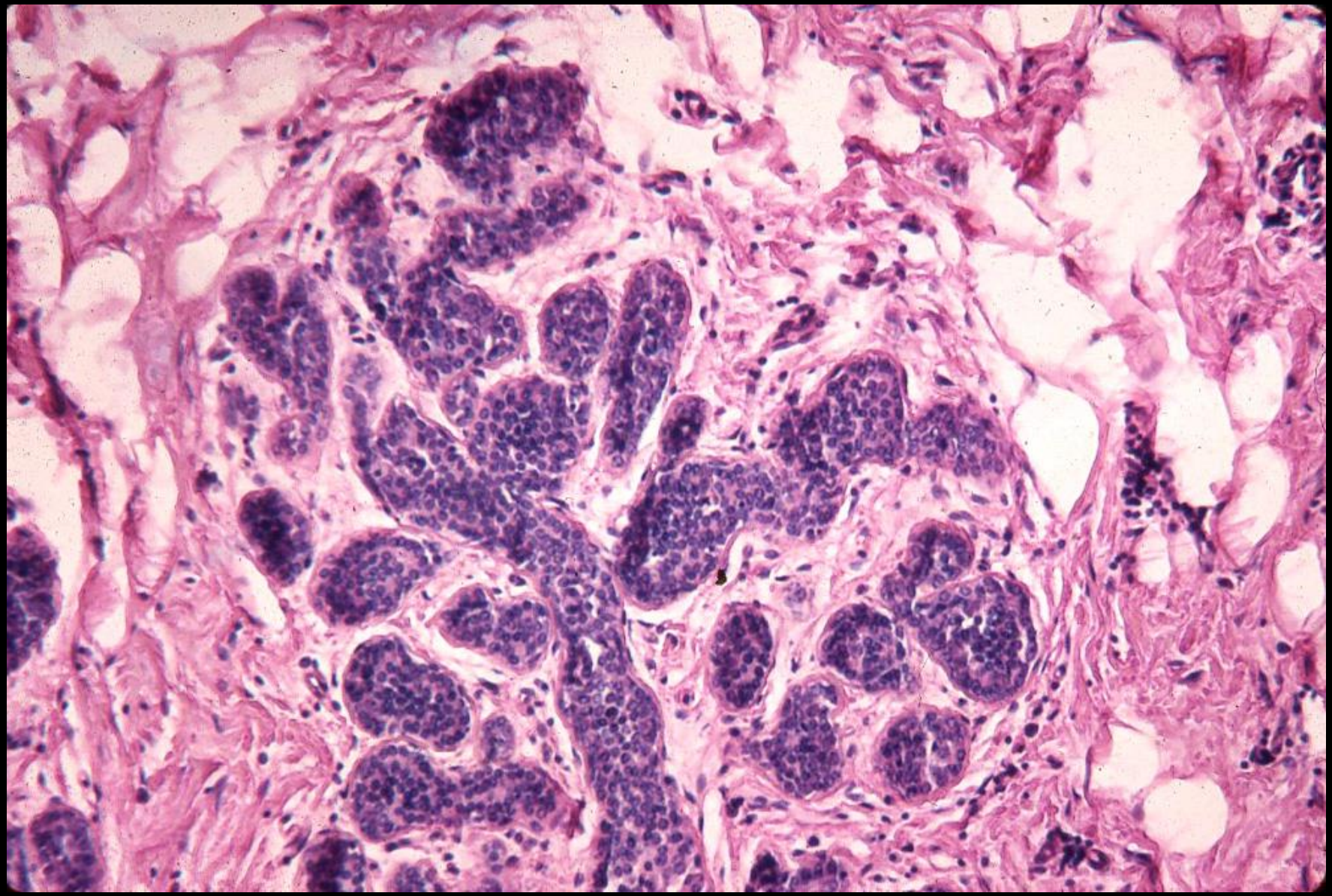


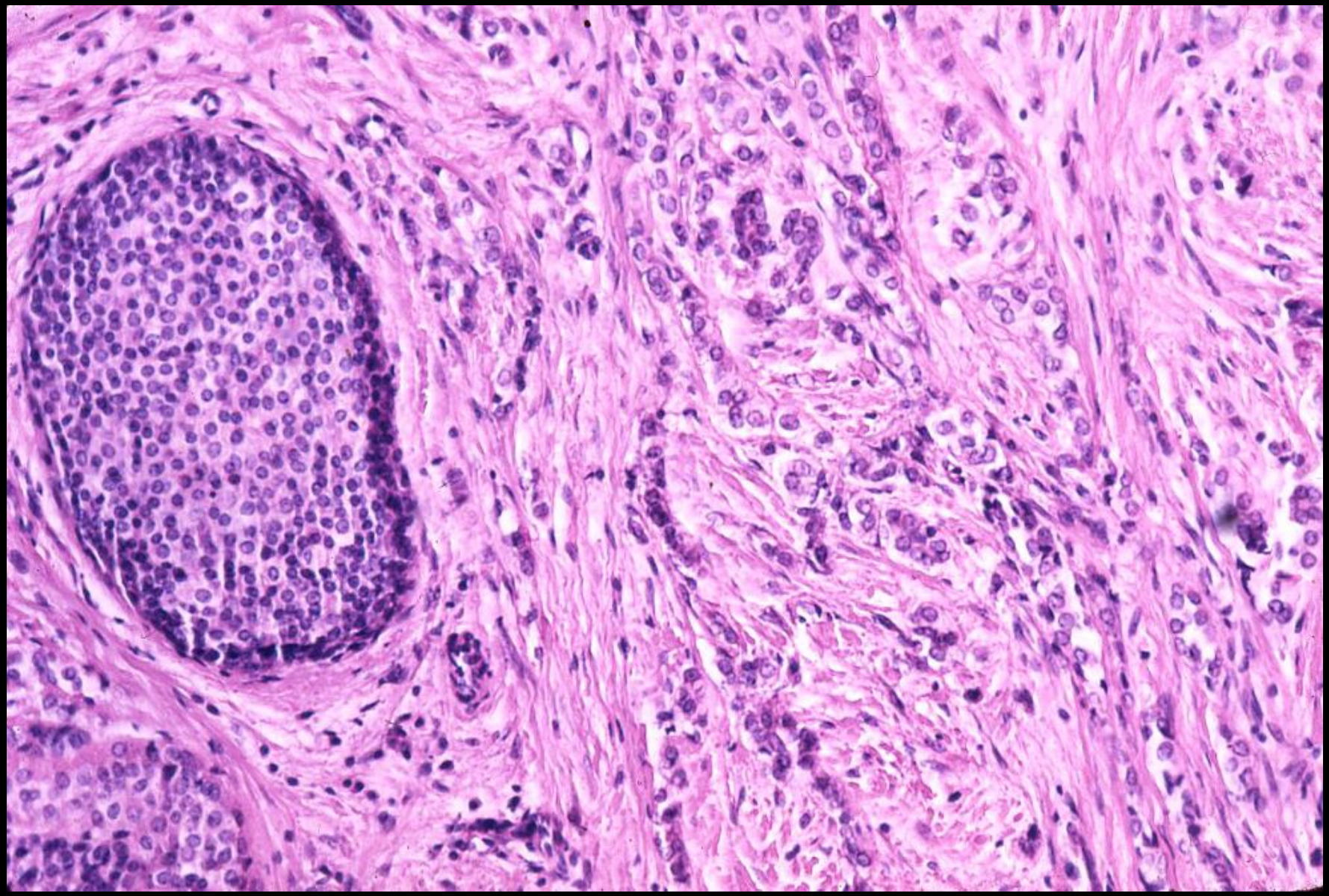












The Problem

- Breast cancer is a highly heterogeneous and complex set of diseases
- Breast cancer complexity elements: Risk factors (epi, germ line/ inherited, histology…SNP), diagnosis, biology (hallmarks of cancer), prognostic and predictive markers, treatment, follow-up and evolution. And of course prevention

The Solution…comprehensive analysis

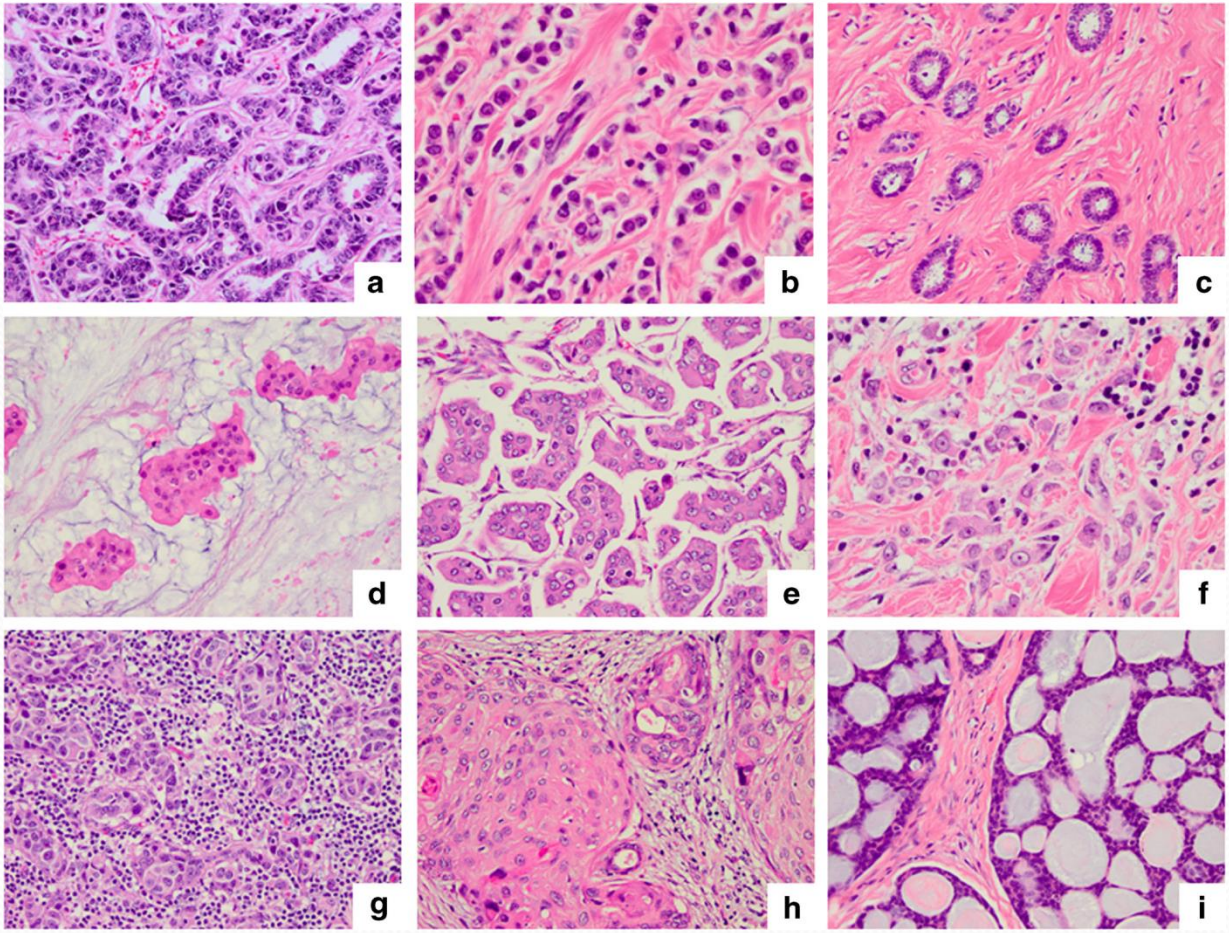
- Characterization of breast cancer traditionally relied on histologic diagnosis and classification, grading, immunohistochemical and limited copy number profile (ER, PR, Her-2, Ki-67), staging (TNM), and in the last two decades increasingly molecular characterization (multi-omic approach). These characteristics may be mapped to various complexity elements i.e. prognosis, therapy….

The challenge…

- The challenge is to create an integrated representation that will enhance our understanding and impact the disease course.
- As such, classification of breast cancer attempts to define the heterogeneity and allow for constricting/reducing the heterogeneity of a class thus defining a convergent phenotype i.e. commonly behaving and responsive tumors.

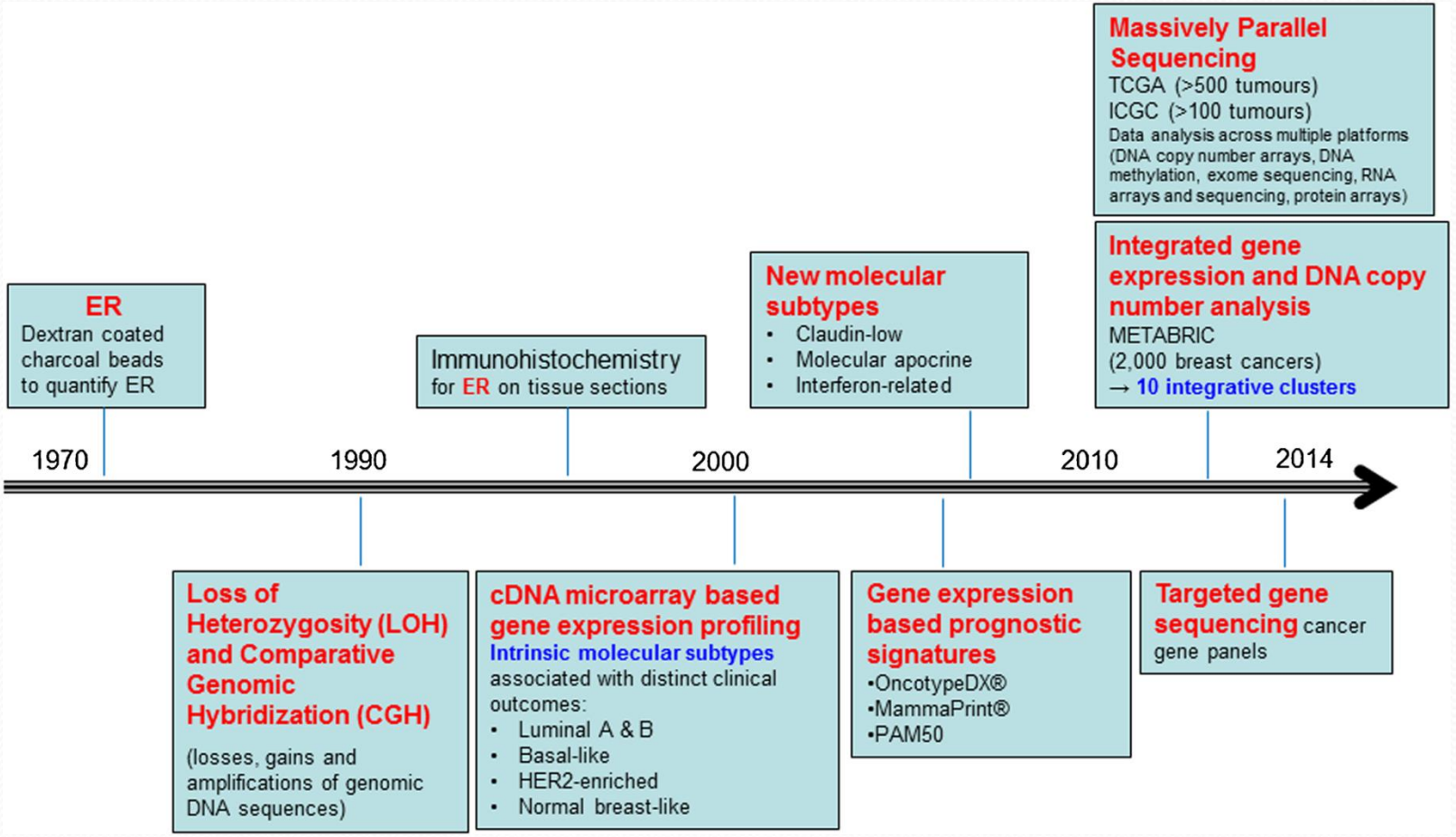
Breast cancer by Histology WHO defined 21 subtypes

D. Vuong …Virchows Arch (2014) 465



Molecular characterization

D. Vuong …Virchows Arch (2014) 465



Summary

- Cancer is a genetic and epigenetic phenomenon
- May arise from any cell type, manifesting as benign, borderline or malignant
- Classified based on histologic, immunohistochemical and molecular features.
- Requires understanding of intrinsic tumor characteristic and extrinsic tissue microenvironment

Outlook in the face of complexity

The emergence of light initially is blinding/confusing until you adjust to the newly revealed reality. That reality may be more complex/or just different than your previous conception, akin to the transition in the early part of the last century from a Newtonian world to Quantum mechanical based world. However it has the benefit s of providing an ever clearer picture of reality.

The combination of the underlying biology, technology, luck, false discovery , hypothesis generation and validation capacity are front and center and will determine how soon we can exploit this knowledge and reach the promised land…