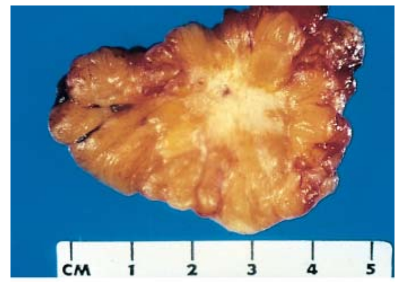
NEOPLASIA
Robbins Basic Pathology Chapter 5
M.E. Bauman, M.D.

Nomenclature

Neoplasia =



Tumor:

Oncology =

Cancer =
(Fig 5-9)

Parenchyma:

Stroma:

Desmoplasia (scirrhous, page 165):

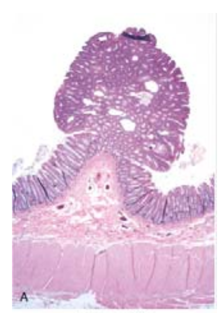
Benign tumors

-oma

adenoma cystadenoma

papilloma

polyp sessile/pedunculated (Fig 5-1)

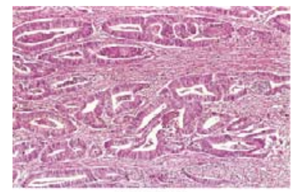


Malignant tumors

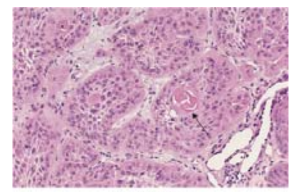
sarcoma

carcinoma

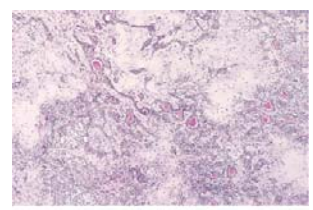
adenocarcinoma



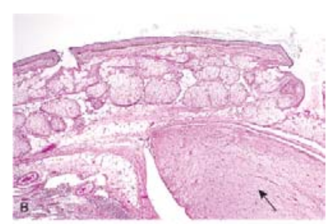
squamous cell carcinoma (Fig 5-3)



mixed tumors (benign or malignant) (Fig 5-2)



Teratoma



Misnomers

Hamartoma =

Choristoma =

Heterotopic tissue

Review Table 5-1 Nomenclature of Tumors

Characteristics of Benign and Malignant Neoplasms

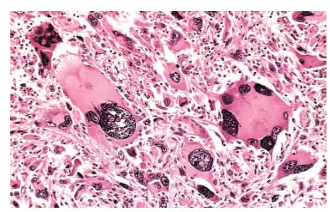
Validity of benign vs. malignant classification: Malignancy is a multistep process

Four fundamental features of malignancy:

1. Differentiation and Anaplasia

well differentiated/poorly differentiated

anaplasia =
(Fig 5-4)



pleomorphism =

hyperchromasia =

mitoses

loss of cellularity polarity

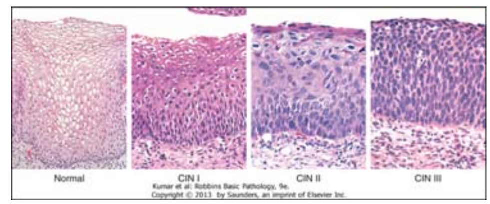
dysplasia =

loss of cellular uniformity

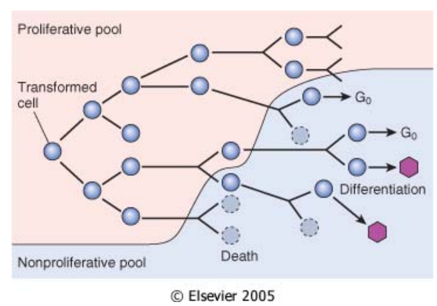
architectural disarray

reversibility

carcinoma in situ (figure not in book)



2. <u>Rates of Growth</u> (Figure not in book)



doubling time of tumor cells*
(* indicates material not in text)

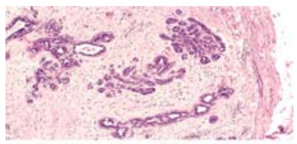
growth fraction of tumor cells*

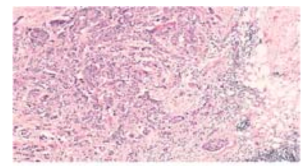
tumor cell heterogeneity*

cancer stem cell hypothesis:

3. <u>Local invasion</u>

cohesive expansile mass vs. infiltration into adjacent tissue





(Figures 5-7 through 5-10)

Encapsulation

uterine leiomyoma

dermal hemangioma

4. <u>Metastasis</u> (pl. metastases) =
(Fig 5-11)

local invasion vs. metastasis

pathways of spread

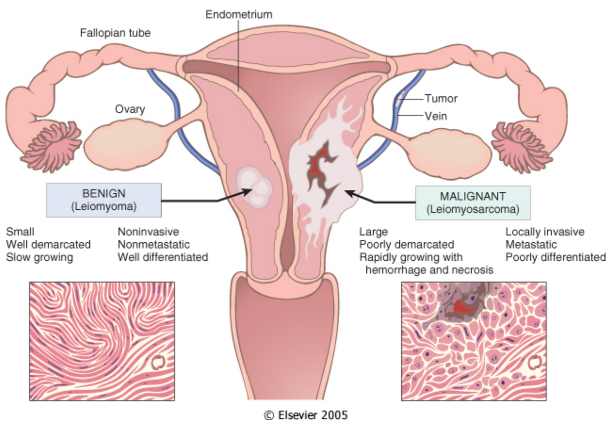
1.

2.

"sentinel lymph node"

3.

(Fig 5-12)



Epidemiology

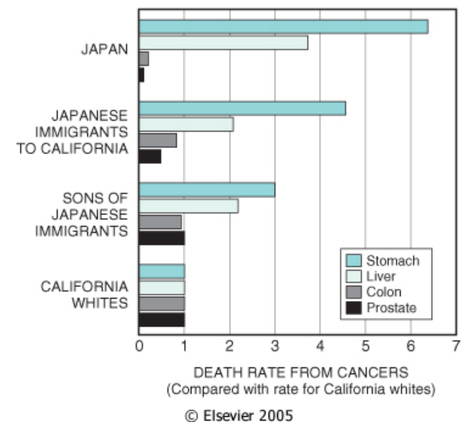
Epidemiology =

Cancer incidence

Incidence		**Mortality**	
Male	Female	Male	Female
1.	1.	1.	1.
2.	2.	2.	2.
3.	3.	3.	3.

Geographic and environmental variables
(Figure not in book)

Environmental factors are the predominant cause of the most common sporadic cancers.



Age
Cancer incidence increases with age/accumulation of somatic mutations.

Pediatric malignancies cause ~10% of deaths in children < 15 years of age:

Heredity
At least 90% of cancers are sporadic; three categories of familial/inherited cancers:

1. Autosomal Dominant Cancer Syndromes

    Mechanism:

    e.g.

2. Autosomal Recessive Syndromes of Defective DNA Repair

    Mechanism

    e.g.

3. Familial Cancers of Uncertain Inheritance
    e.g.

<u>Acquired Preneoplastic Lesions</u>
Cellular replication in "fertile soil"

Carcinogenesis: The Molecular Basis of Cancer

Tumors are a clonal expansion of acquired or inherited non-lethal cellular genetic changes.

Four classes of normal regulatory genes:

1. Growth-promoting proto-oncogenes

2. Growth-inhibiting tumor suppressor genes
    Haploinsufficiency:

    Governors:

    Guardians:

    Mutator phenotype:

3. Genes regulating apoptosis
4. Genes regulating DNA repair

Genetic Lesions in Cancer

Oncogenic genetic changes may be subtle (point mutations, insertions, deletions) or large enough to produce karyotypic changes.

<u>Karyotypic Changes in Tumors</u>

Balanced translocations (Fig 5-14)

Burkitt lymphoma

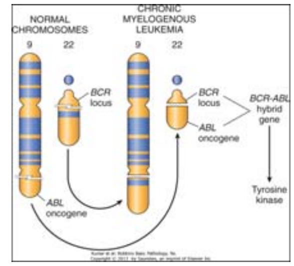
t(8;14) MYC on 8 → 14 adjacent to IgH

Follicular lymphoma

t(14;18) BCL2 on 18 → 14 adjacent to IgH

Chronic Myelogenous Leukemia

t(9;22) ABL on 9 → 22 adjacent to BCR



Deletions

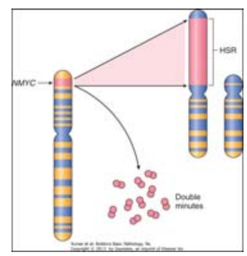
Karyotypic and molecular deletions

Tumor suppressor genes commonly affected

LOH:

Gene amplifications

Double minutes and homogeneously staining regions (HSR) (Fig 5-15)



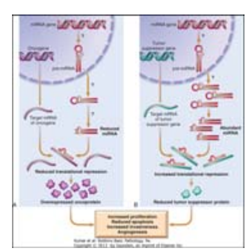
Neuroblastoma: NMYC

Breast carcinoma: HER2/NEU (ERBB2)

Aneuploidy =

<u>MicroRNAs and Cancer</u> (Fig 5-16)

Non-coding single stranded RNA inhibiting translation of target mRNAs



Reduced miRNA targeting oncogenes:

Increased miRNA targeting tumor suppressor genes:

(See also Chapter 6, Fig 6-1 with text for RISC, siRNAs, and lncRNAs.)

Epigenetic Modifications and Cancer

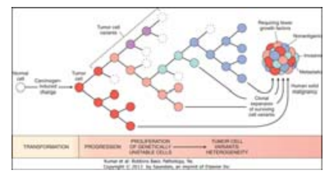
Epigenetics: Changes in gene expression secondary to posttranslational modifications of histones and DNA methylation

Tumor suppressor genes silenced by hypermethylation of promoter sequences

The epigenetic state of a particular cell (its epigenetic context) determines its response to growth and differentiation signals.

Carcinogenesis: A Multistep Process

Tumor progression:
(Fig 5-17)

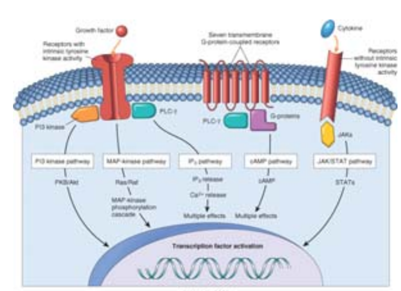


Monoclonal origin to a mass of extremely heterogeneous constituent cells:

Hallmarks of Cancer

Fundamental changes in cell physiology which together comprise the malignant phenotype

Self-Sufficiency in Growth Signals



Physiologic cell proliferation (Figure not in book)
1. Binding of growth factor to its specific receptor on cell membrane
2. Transient activation of growth factor receptor activating signal transducing proteins on inner leaflet of membrane
3. Transmission of transduced signal to nucleus by secondary messengers or by a cascade of signal transduction molecules to activate transcription
4. Induction of nuclear regulatory factors for DNA transcription
5. Progression of cell cycle resulting in cell division

Growth factors

Paracrine → autocrine synthesis of soluble growth factors

e.g. Glioblastoma: PDGF and PDGF receptor

Growth Factor Receptors and Non-Receptor Tyrosine Kinases

Mutation or overexpression of growth factor receptors

e.g. Breast carcinoma: *HER2/NEU* amplification

Rx: anti-HER2/NEU antibody (Herceptin)

Downstream Signal-Transducing Proteins

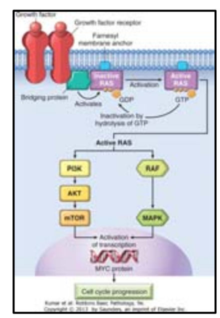
RAS Protein (Fig 5-19)

EGF or PDGF activates quiescent GDP RAS → activated GTP RAS.

GTP RAS stimulates downstream regulators of proliferation via RAF or PI3K pathway.

GTPase hydrolyzes GTP RAS → quiescent GDP RAS.

GTPase activity is activated by GTPase-activating proteins.



RAS point mutations lead to decreased GTP hydrolysis
(Colon and pancreatic adenocarcinomas)

RAF or PI3K mutations lead to increased proliferation
(Melanomas)

GTPase-activating protein mutations lead to increased proliferation
(NF-1 in familial neurofibromatosis)

ABL Protein

A non-receptor-associated tyrosine kinase signal transduction molecule
BCR-ABL hybrid protein has constitutive tyrosine kinase activity
Imatinib mesylate (Gleevec)

Oncogene addiction:

Nuclear Transcription Factors

MYC, MYB, JUN, FOS, and REL regulate cyclins.

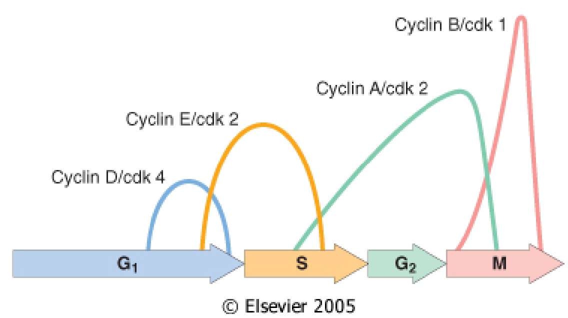
MYC

activates cyclin-dependent kinases (CDKs)
represses cyclin-dependent kinase inhibitors (CDKIs)
upregulates aerobic glycolysis (Warburg effect)
increases utilization of glutamine
Burkitt lymphoma t(8;14)
NMYC neuroblastoma
LMYC lung small cell carcinomas

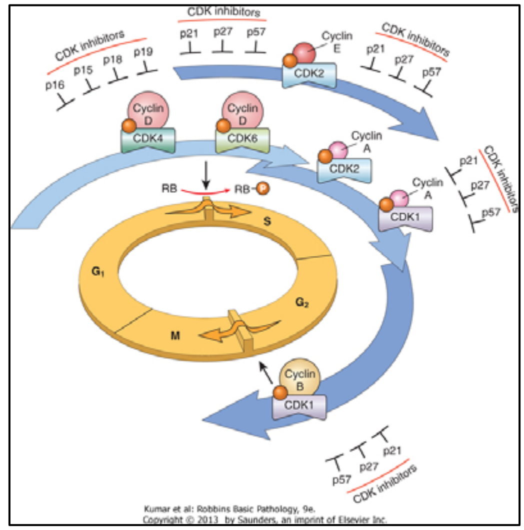
Cyclins and Cyclin-Dependent Kinases

The Normal Cell Cycle (Figure not in book)

Progression through the cell cycle is orchestrated by cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (CDKIs)



Cellular quality control check points (Fig 5-20)



G_1-S:

G_2-M:

Alterations in Cell Cycle Control Proteins in Cancer Cells

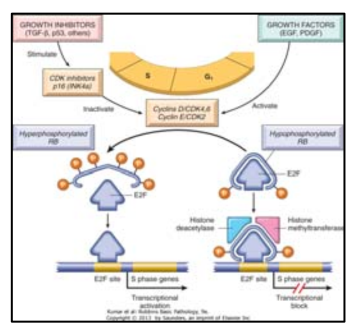
Cyclin D overexpression

CDK4 amplification

CDKI disabling

Senescence:

Apoptosis:



<u>Insensitivity to Growth Inhibitory Signals</u>

RB Gene: Governor of the Cell Cycle

Two-hit hypothesis: both normal alleles inactivated

Familial cases: one inherited defective gene + somatic mutation

Sporadic cases: two somatic mutations

The cell cycle is regulated, in part, by RB as follows:

-The transition from $G_1 \rightarrow S$ requires cyclin E/CDK2 complexes
-Production of cyclin E requires E2F family of transcription factors
-Active hypophosphorylated RB binds E2F, prohibiting transcription of cyclin E
(RB is a cellular brake at the G_1/S restriction point)

-Mitogenic signals produce cyclin D and activate cyclin D-CDK4/6 complexes
-Cyclin D–CDK4/6 complexes phosphorylate RB,
releasing E2F, allowing transcription of cyclin E
(Cyclin D promotes cell proliferation)

Mutational activation of CDK4:

Overexpression of cyclin D:

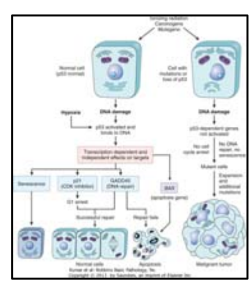
Mutational inactivation of CDKIs:

Oncogenic DNA virus binds RB:

TP53 Gene: Guardian of the Genome

TP53 is one of the most commonly mutated genes in human cancers
P53 t½ = 20 minutes, targeted for destruction by MDM2 protein
With cellular stress, post-translation modifications of p53, escaping MDM2

p53 activates transcription of hundreds of genes: (Fig 5-23)
-cell cycle arrest by CDKN1A (p21) transcription (thus inhibiting cyclin-CDK complexes and preventing RB phosphorylation)
-induced expression of DNA repair genes (GADD45)
-induced senescence
-induced apoptosis (BAX)



-production of miRNAs (inhibiting translation of proliferative genes)

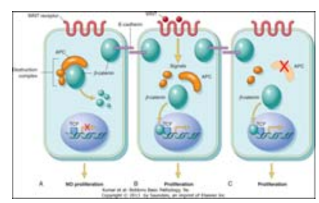
Oncogenic DNA viruses bind p53:

Transforming Growth Factor-β Pathway

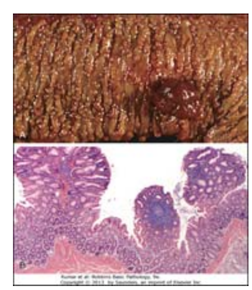
TGF-β is a potent inhibitor of proliferation
Transcriptional activation of CDKIs
Repression of growth-promoting genes, e.g. MYC, CDK2
100% of pancreatic cancers have a mutation in the TGF-β signaling pathway

Contact Inhibition, NF2, and APC

Cell-cell contact inhibition mediated by cadherins via Neurofibromin-2 (NF-2) and Adenomatous Polyposis Coli (APC) gene products (Fig 5-24)

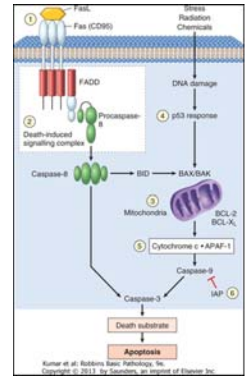


-APC protein regulates the stability and function of β-catenin, both components of the WNT signaling pathway.
-Abnormal APC → increased β-catenin mediated transcription of cell cycle proliferative genes
-Abnormal APC → thousands of adenomatous colon polyps (familial adenomatous polyposis syndrome) (Fig 14-35)



Evasion of Cell Death

Accumulation of neoplastic cells from activation of growth-promoting oncogenes, inactivation of growth-suppressing genes, and mutations in genes regulating apoptosis (Fig 5-25)



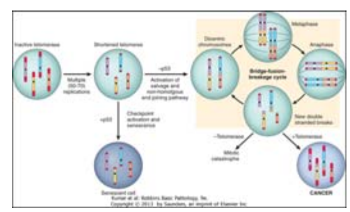
Review pages 18 – 23 for Apoptosis and Autophagy, and skim pages 189-190.

Limitless Replicative Potential

Review pages 26 – 30 for cellular aging. (Fig 5-26)

Telomere =

Telomerase:



Development of Sustained Angiogenesis

Skim this section.
1 – 2 mm maximum zone for diffusion of oxygen, nutrients, and waste

Tumor vasculature is abnormal:

Vascular Endothelial Growth Factor (VEGF):

Thrombospondin-1 (TSP-1):

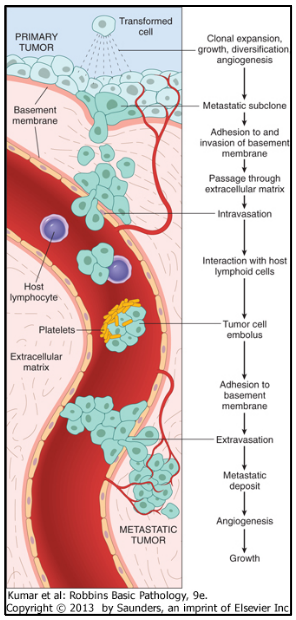
Targeted Rx:

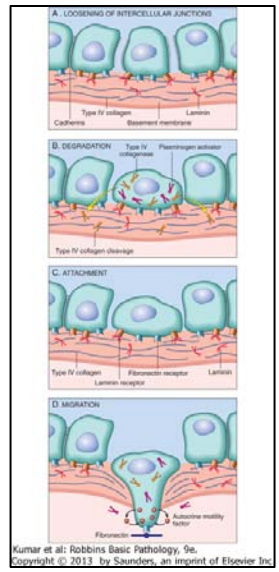
<u>Ability to Invade and Metastasize</u>

Skim this section.
Loss of E-cadherin function in almost all carcinomas.

Invasion of tumor cells requires proteolytic enzymes.

Review figures 5—27 and 5-28

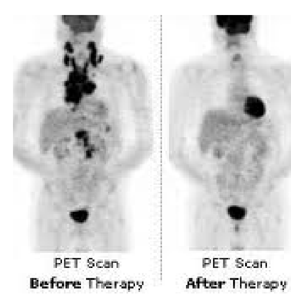




<u>Reprogramming Energy Metabolism</u>

Warburg metabolism in fetal and cancer cells:

PET scans with ^{18}F-fluorodeoxyglucose (Figure not in book)



Evasion of Immune System
(See Immune Surveillance below)

Genomic Instability as an Enabler of Malignancy

Defects in DNA repair proteins increase the risk for malignancy

Hereditary Nonpolyposis Colon Cancer Syndrome (HNPCC)
- Defects of one or more of at least four genes of DNA mismatch repair
  - Faulty DNA “spell checkers” or proofreaders

- Microsatellite Instability (MSI):

Xeroderma Pigmentosum
- Defects of several proteins of nucleotide excision repair
  - Inability to excise cross-linked pyrimidine residues generated by UV sunlight damage
  - Risk of cancers of sun-exposed skin

Diseases with Effects in DNA Repair by Homologous Recombination
- Defects of homologous recombination DNA repair system
- Bloom syndrome, Ataxia-telangiectasia, Fanconi anemia

Cancers Resulting From Mutations Induced by Regulated Genomic Instability: Lymphoid Neoplasms

In adaptive immunity, B and T cells rearrange their antigen receptor genes (VDJ regions)

Errors during receptor gene assembly are responsible for many lymphoid neoplasms (details in chapter 11 to follow)

<u>Tumor-Promoting Inflammation as Enabler of Malignancy</u>

Chronic inflammation secondary to infection or to autoimmune response leads to compensatory proliferation and regeneration of cells

Inflammation in response to tumors may release tumor-promoting growth factors

Rx: cyclooxygenase-2 for colon cancer prevention and treatment

<u>Multistep Carcinogenesis and Cancer Prevention</u>

Cancer results from an accumulation of multiple mutations

Etiology of Cancer: Carcinogenic Agents

Three classes of carcinogenic agents causing genetic damage

<u>Chemical carcinogens</u>

Skim this section

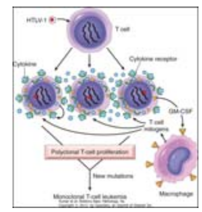
Sir Percival Pott: "Take a bath!"

Direct acting agents, procarcinogens requiring metabolic activation, and naturally occurring agents (Table 5-4)

<u>Radiation carcinogenesis</u>
Skim this section
UV sunlight, x-rays, nuclear fission, radionuclides
Nagasaki and Hiroshima: leukemias, thyroid, breast, colon and lung cancers

<u>Viral and Microbial Oncogenesis</u>
Skim this section

Oncogenic RNA viruses
- Human T Cell Lymphotropic Virus-1 (HTLV-1)
  - T-cell leukemia/lymphoma in Japan and Caribbean
  - CD4 tropism, cytokine and receptor proliferation → autocrine
  - T cell proliferation, 20-50 year latency until malignancy



Oncogenic DNA viruses
- HPV Human Papilloma Virus
  - Types 1,2,4,7: squamous papillomas (warts)
  - Types 6,11: genital warts (low risk), nonintegrated, episomal
  - Types 16,18: cervical squamous cell carcinoma (high risk), random integration into host genome, genomic instability; oncoproteins E6 and E7 bind to and neutralize RB and p53, respectively

- EBV Epstein-Barr Virus
  - Attaches to complement receptor CD21 on B cells
  - Infectious mononucleosis
  - Burkitt lymphoma in endemic African form, nasopharyngeal carcinoma in China, subset of Hodgkin lymphoma, lymphomas in immunosuppressed patients (More to follow in chapter 11)

HBV Hepatitis B Virus
With HCV (a single stranded RNA virus) associated with 70% of hepatocellular carcinomas
Epithelial cell proliferation in a background of chronic inflammation
(More to follow in chapter 15)

Helicobacter pylori
Peptic ulcers, gastric adenocarcinoma, gastric lymphoma
MALToma: Mucosa Associated Lymphoid Tumor

Host Defense Against Tumors: Tumor Immunity

Immune Surveillance:

Tumor antigens
Skim this section

Products of mutated oncogenes, tumor suppressor genes, other mutated genes, overexpressed or aberrantly expressed cellular proteins, antigens of oncogenic viruses, oncofetal antigens, cell surface glycolipids and glycoproteins, cell type specific differentiation antigens

Oncofetal antigens: carcinoembryonic antigen (CEA), alpha fetoprotein (AFP)

Mucins: CA-125, CA-19-9

Cell type specific differentiation antigens: CD20

Antitumor Effector Mechanisms
Skim this section

MHC class I molecules recognized by CD8+ cytotoxic T lymphocytes
Natural Killer cells, Macrophages, Humoral mechanisms

Immune surveillance and Immune Evasion by Tumors
Skim this section

Increased incidence of cancer in immunosuppressed patients

Evasion of surveillance by antigen negative tumor variants, reduced histocompatibility molecules, immunosuppression

Clinical Aspects of Neoplasia

Effects of Tumor on Host
Location:

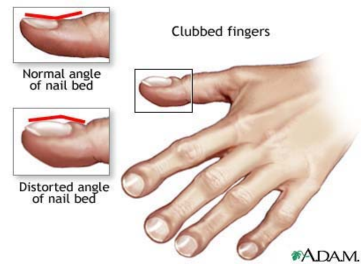
Cancer Cachexia:

Paraneoplastic Syndromes (Table 5-5)

Hypercalcemia

Cushing syndrome

Hypertrophic osteoarthropathy (Figure not in book)



<u>Grading and Staging of Cancers</u>

Grading

Staging

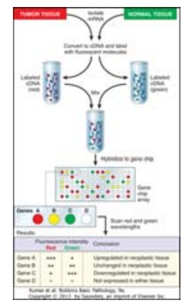
<u>Laboratory Diagnosis of Cancer</u>

Skim this section

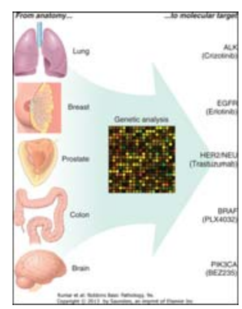
Morphologic methods, Tumor Markers, Molecular Diagnosis

Molecular Profiling of Tumors

Expression Profiling (Fig 5-35)



Whole Genome Sequencing (Fig 5-36)



Driver mutations

Passenger mutations