APPROVED

How do you decide benin vs. malignant? Metastasis! Even if it has the histological characteristics of a benign tumor, if it metastasizes it is cancer!

NEOPLASIA (4)

Tumor-Host Interactions and Systemic Effects of Neoplasms

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NEOPLASIA (IV)

Goals and Objectives

1. Describe process of invasion, metastasis, and angiogenesis
2. Discuss host immunologic reaction to tumors and the concept of immune surveillance
3. Describe systemic effects of cancer and why functional differentiation of tumors can be useful clinically.
4. Compare the TNM and AJCC staging systems for cancer

Invasion and Metastasis

PATHWAYS OF METASTASIS (review)

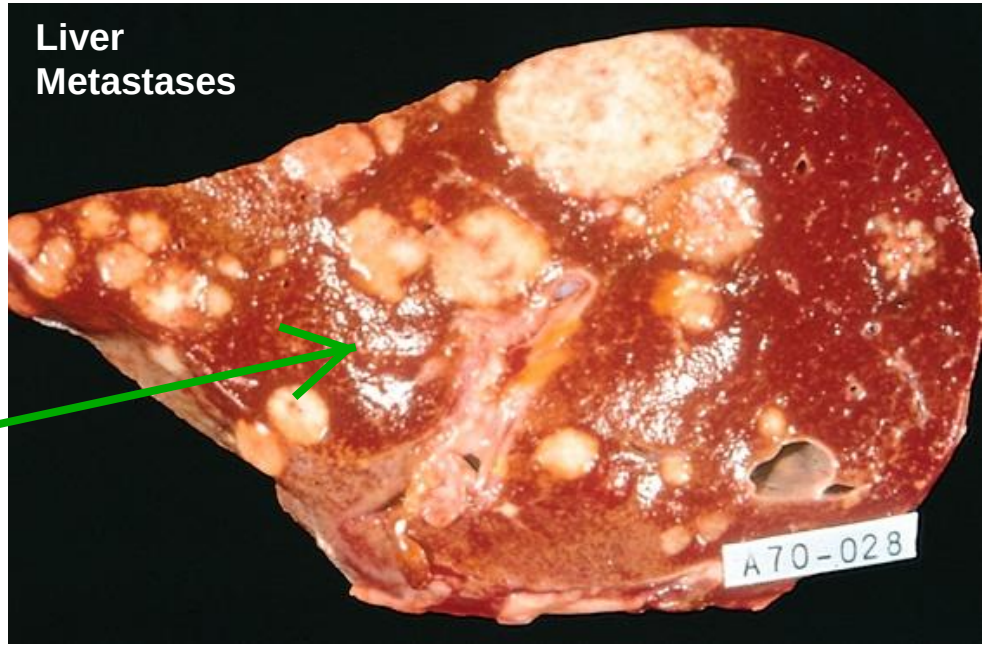
1. Seeding body cavities (peritoneum, pleura, meninges)
2. Lymphatic spread
3. Hematogenous spread
   - Liver
   - Lung
   - Brain
   - Bone

Ovarian cancers often seed the peritoneum

Proximal lymph nodes are often the first place to look for metastases. These are the 'N' in TNM staging

GI tumors often end up here due to portal system

Systemic venous circulation drains to lung capillary bed



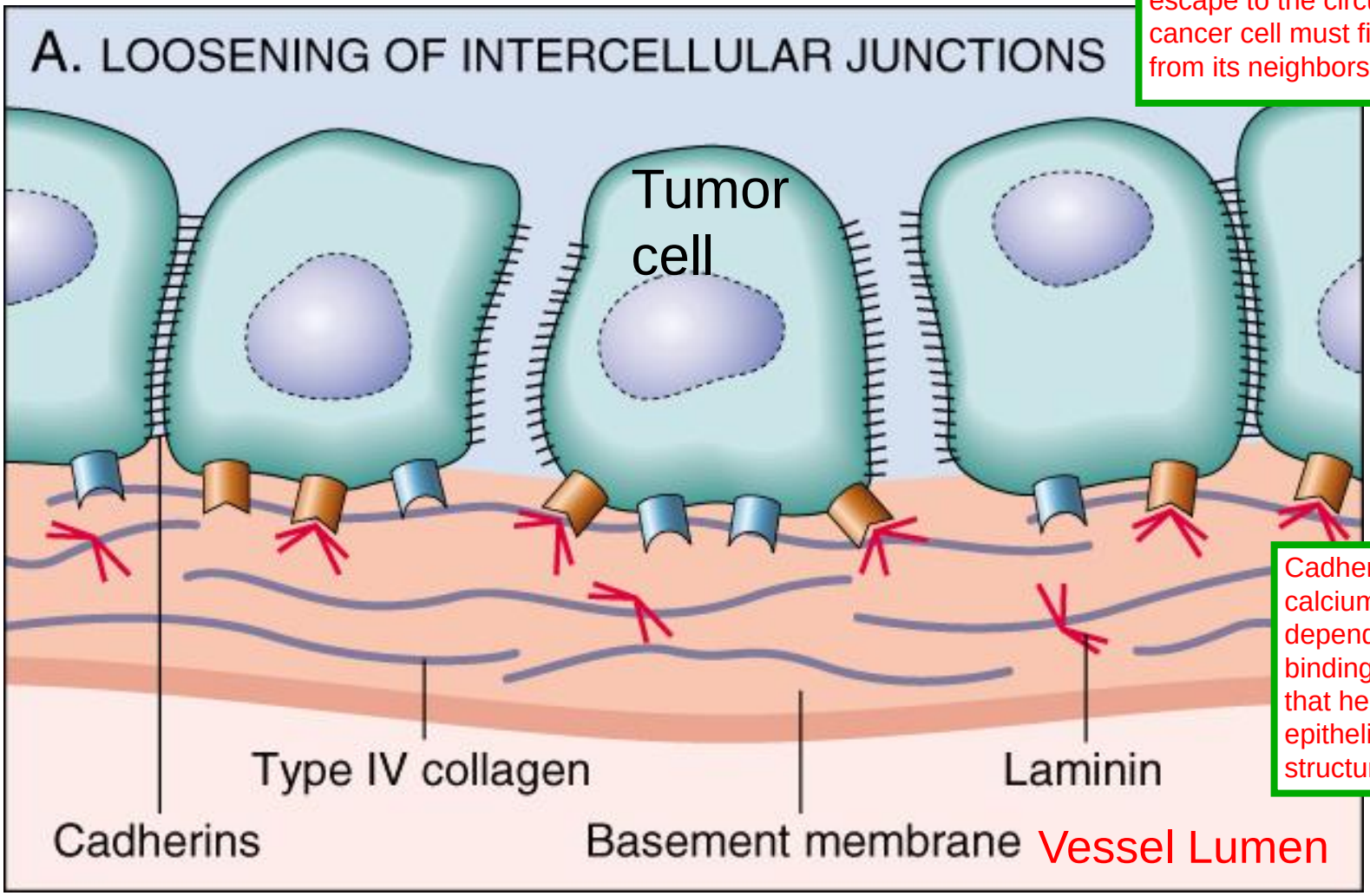
This multifocal tumor pattern is a hallmark of metastatic growth. It would be very strange to see so many primary tumors in this pattern

The good news is:
METASTASIZING IS HARD WORK!

There are many barriers to successful metastasis…

MOLECULAR MECHANISM OF INVASION OF EXTRACELLULAR MATRIX (ECM)

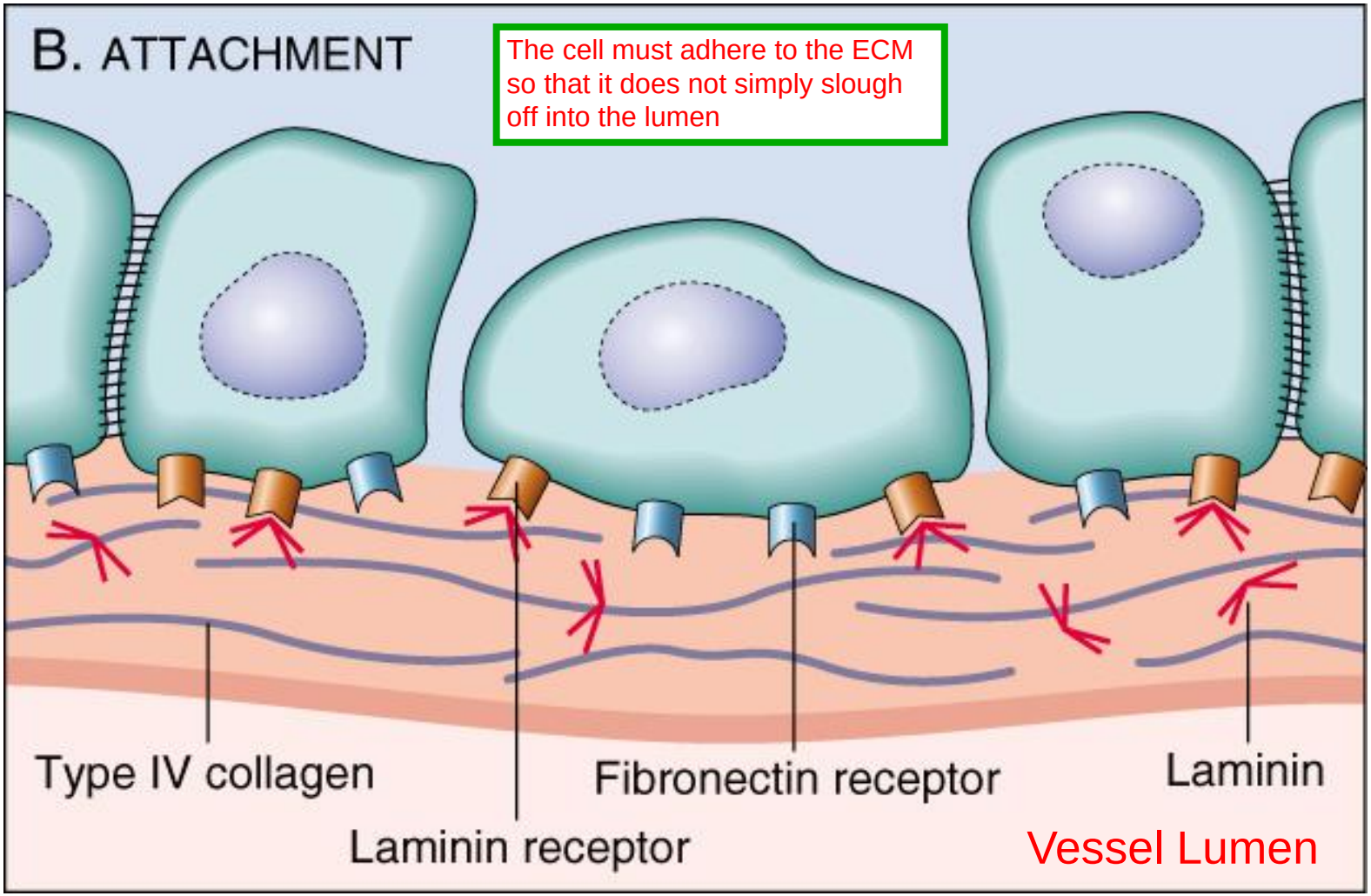
All cells interact with the cell and ECM around them. To escape to the circulation, a cancer cell must first separate from its neighbors.



Cadherins are calcium-dependant cell-cell binding proteins that help hold epithelia in sheet structures

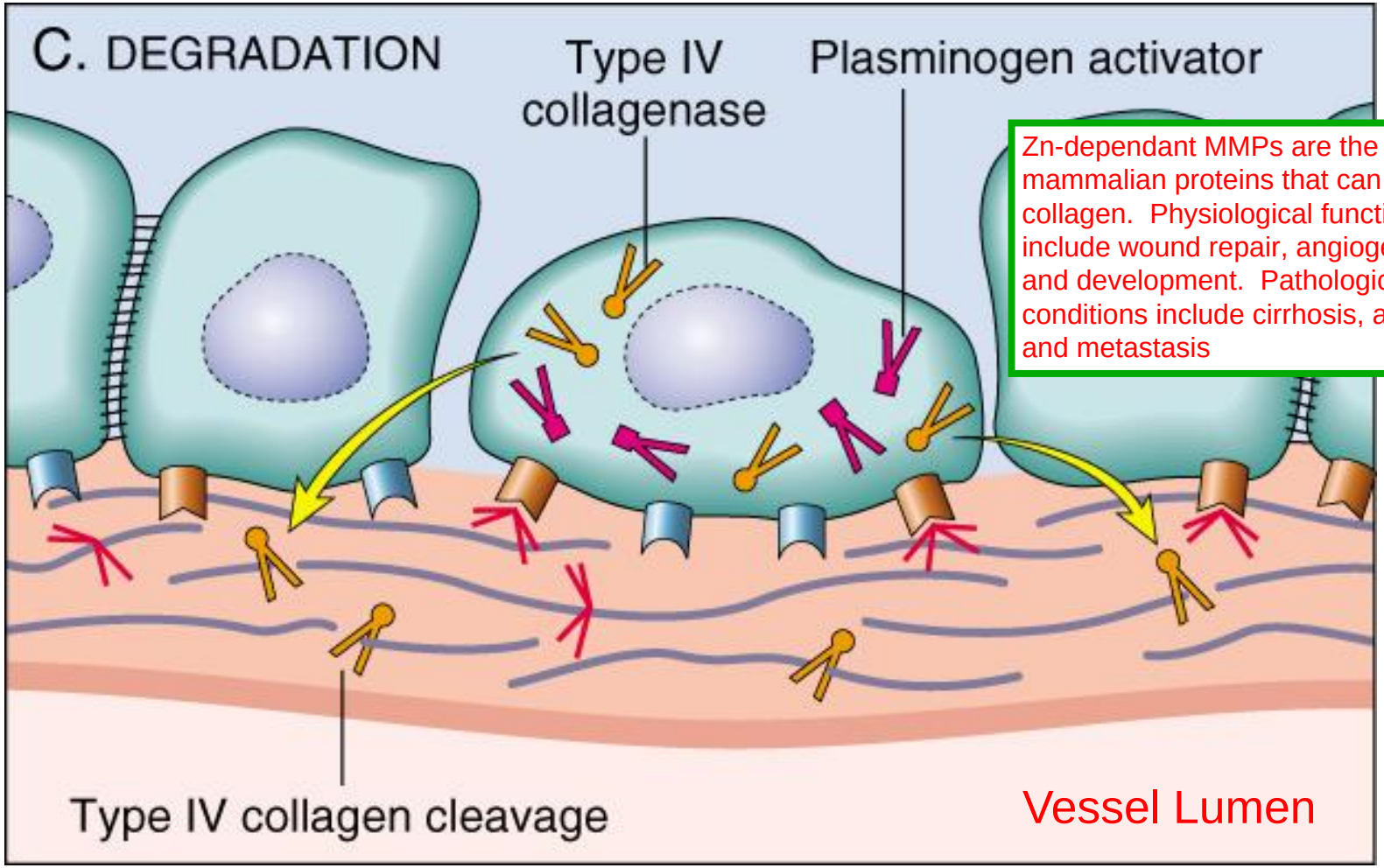
Reduce expression of adhesion molecule E-cadherins

MOLECULAR MECHANISM OF INVASION OF EXTRACELLULAR MATRIX (ECM)



Receptor-mediated attachment to the matrix proteins, laminin in the basement membranes and fibronectin in the interstitial ECM.

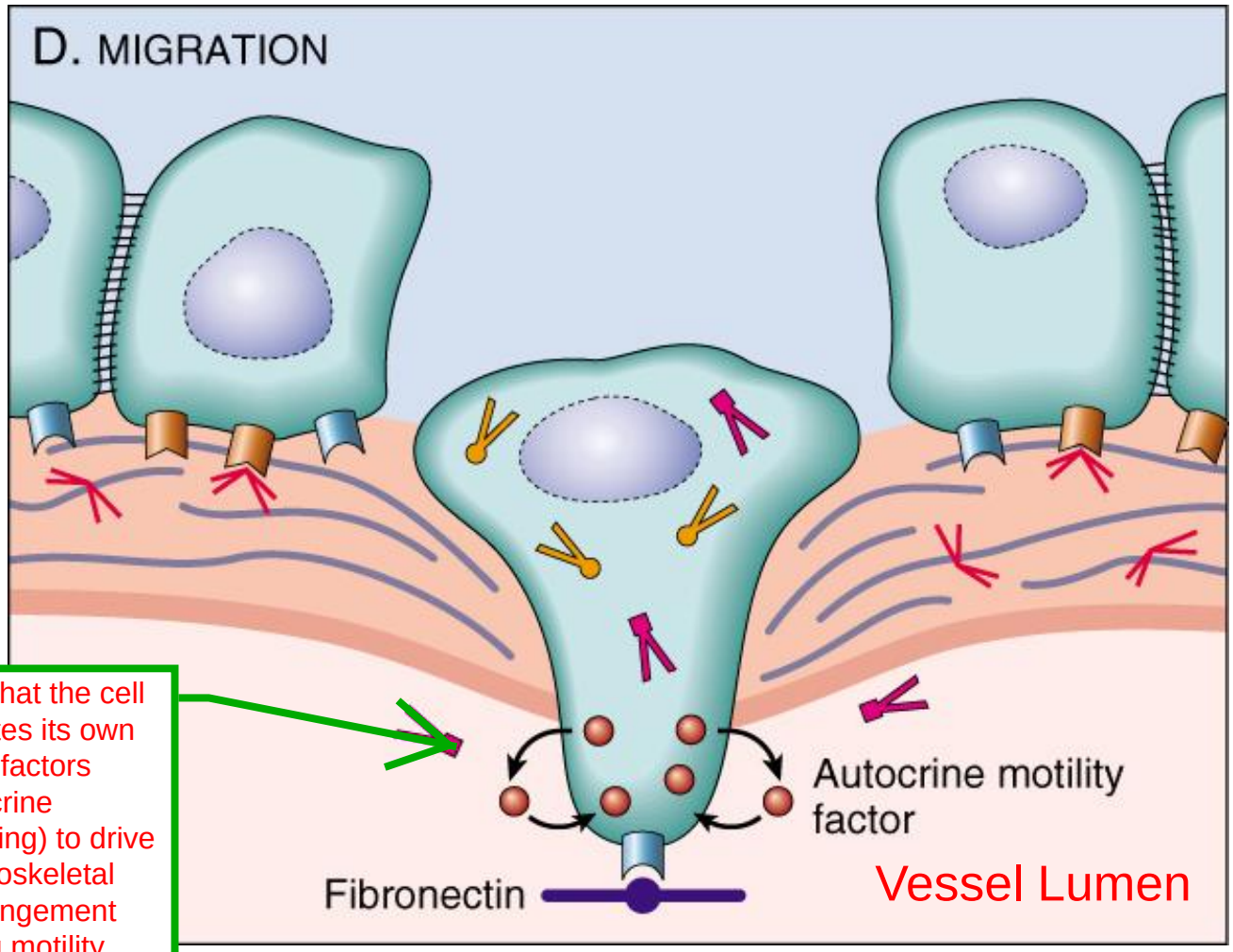
MOLECULAR MECHANISM OF INVASION OF EXTRACELLULAR MATRIX (ECM)



Zn-dependant MMPs are the only mammalian proteins that can degrade collagen. Physiological functions include wound repair, angiogenesis, and development. Pathological conditions include cirrhosis, arthritis, and metastasis

Use proteases, such as matrix metalloproteinases (MMPs) to digest matrix proteins, degrade basement membrane.

MOLECULAR MECHANISM OF INVASION OF EXTRACELLULAR MATRIX (ECM)



The opposite process as leukocyte diapedesis during inflammation

The whole process of moving from an intact epithelium to a motile cell is termed 'epithelial to mesenchymal transition' (EMT), a common event during embryonic development that, in adult tissues, is a major aspect of metastasis.

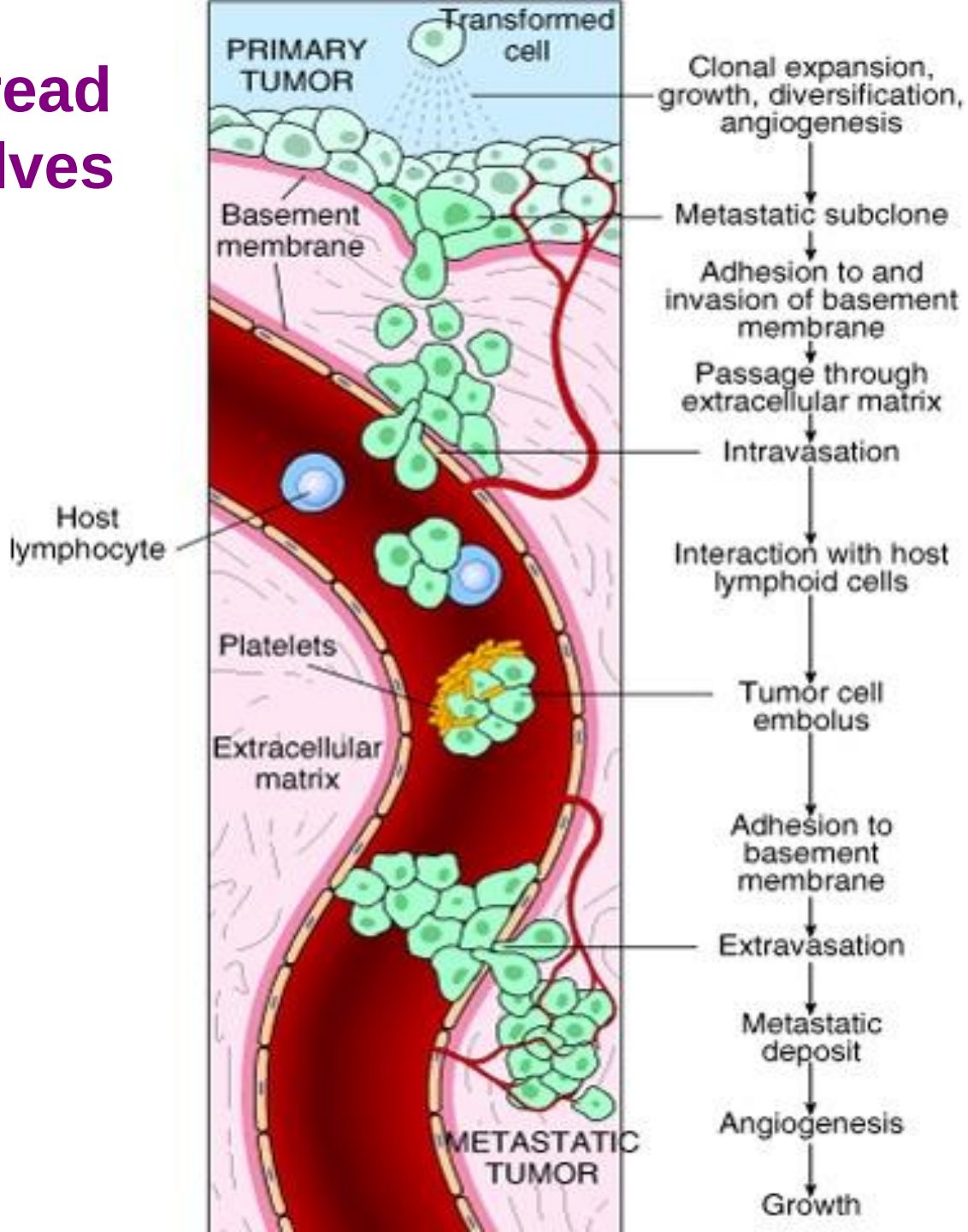
Note that the cell secretes its own tropic factors (autocrine signaling) to drive its cytoskeletal rearrangement during motility.

secrete factors to enhance tumor cell motility and migration

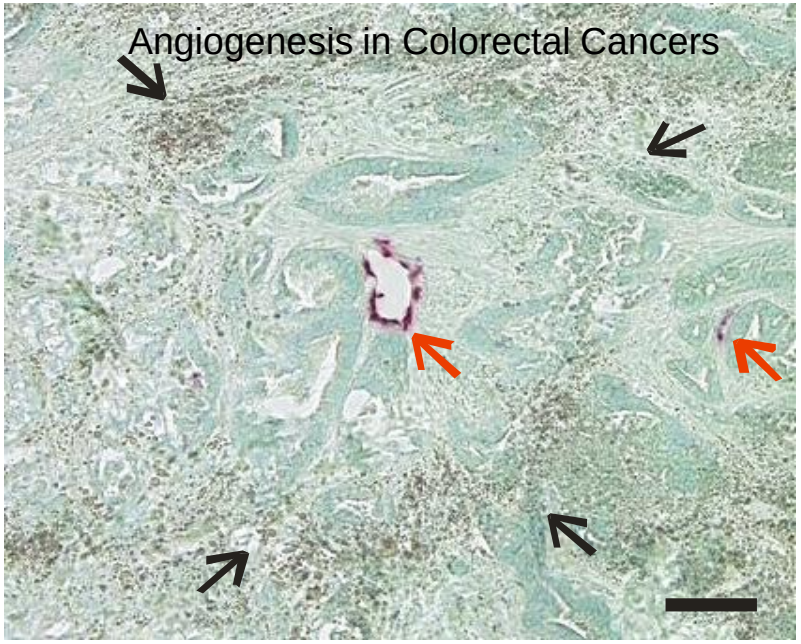
Hematogenous spread of tumor cells involves many steps.

Once the tumor cell or cells make it into the lumen, they form a tumor embolus. These can interact with lymphoid cells and platelets in the bloodstream

To begin a metastatic colony, the tumor cells must undergo mesenchymal-to-epithelial transition (MET)



Angiogenesis in Cancer



- Tumors must develop a blood supply from the surrounding tissues in order to grow.
- In the absence of vascularization, tumor nodules can grow to only 1-2 mm.

This is the basis for anti-angiogenic cancer treatment such as VEGF inhibitors

- Some tumors make angiogenesis factors (VEGF, HIF)

Remember, the tumor parenchyma is typically under significant hypoxic stress, so HIF will be very strongly expressed. Even when angiogenesis does occur, the newly formed vessels tend to be poorly formed and leaky

Tumor Angiogenesis is an Attractive Therapeutic Target

- Tumor endothelial cells are molecularly distinct from "normal" or static endothelial cells
- Readily accessible to therapeutic agents in the blood
- Tumor endothelial cells are genetically stable and should not develop resistance
- **Bevacizumab** (trade name **Avastin**, Genentech/Roche) is a monoclonal antibody against vascular endothelial growth factor-A (VEGF-A).
  - Currently used for colon, lung, breast kidney, ovarian, and brain cancers

Note that this is not as true for the brain--getting drugs past the blood-brain barrier is a major clinical problem

Tumor vascular cells (stroma) are NOT neoplastic, so they tend not to develop therapeutic resistance the way hyper-mutable tumor parenchymal cells do. If you can starve the tumor of its blood supply, it should (ideally) begin to die off and shrink

Unfortunately, this doesn't spare GOOD angiogenesis. Wound healing is affected, is common side effects are hypertension and bleeding risk

EVIDENCE THAT METASTASIS REALLY IS HARD WORK…

1. Many patients with cancer have circulating tumor cells in their blood, but never go on to develop distant metastases. EMT has occurred, but MET has not
2. Even patients with thousands of circulating tumor cells typically develop only a handful of metastatic sites.
3. Patients with cancer can have small numbers of tumor cells in their lymph nodes (“isolated tumor cells”), yet have a prognosis identical to patients with negative lymph nodes.


GALAPAGOS ISLANDS

Host Defense—Anti-tumor Immunity

>100 years since role of immune system in defending against cancer was first suggested.

The immune system can recognize and attack neoplastic cells.

Smaller but significant increases in non-viral neoplasms indicates that some aspect of the immune system is protective against oncogenesis

Evidence of Immune Response

1. **Immunosupressed patients have markedly higher incidence of many cancers**
   - Vast increase (up to 1000x) in viral-related tumors (HPV, EBV, Kaposi's) and skin cancers.
   - Smaller increases (2-5x) in non-viral related tumors (colon, lung, melanoma, sarcoma, etc).

Viral oncogenesis review:
--
HPV 16, 18- cervical cancer - viral factors E6 and E7 interfere with tumor suppressors p53 and Rb to drive cell cycle
--
EBV - Burkitt's lymphoma, Hogkin's lymphoma, nasopharyngeal carcinoma - transforms B cells
--
HHV-8 - Kaposi's sarcoma - AIDS-associated
--
Note that that there are higher rates of hepatocellular carcinoma in Hep B/C chronically infected patients

Evidence of Immune Response

Hybrid proteins that result from translocation are sufficiently different that they are recognized as non-self

2. Cancer patients develop measurable immune responses to tumor antigens

- **Products of mutated oncogenes or tumor suppressor genes, eg. EGFRvIII, BCR/ABL**
- **Overexpressed or aberrantly expressed protein, eg. *c-erbB2***
- **Oncogenic virus protein**
- **Oncofetal antigens**
  - a-fetoprotein (AFP) in yolk sac tumors and hepatocellular carcinomas
  - carcinoembryonic antigen (CEA) in colonic carcinomas
- **Altered cell-surface glycolipids and glycoprotein**
- **Cell type-specific differentiation antigens, eg. CD10**

Fetal antigen proteins are typically expressed only during prenatal development but for whatever reason tumor cells often decide to reactivate them. A reminder that in a lot of ways tumor cells are reverting to a 'developmentally active' state.

particularly lymphomas

Evidence of Immune Response

3. **Lymphocytes seen histologically in and around cancers ("Tumor Infiltrating Lymphocytes")**
   – When present, usually = improved prognosis).

Evidence of Immune Response

4. Well documented examples of some cancers undergoing complete regression, even when metastatic (melanoma in particular)

- Site of tumor replaced by lymphocytes and macrophages

Condensed list:
--
1. Immunosuppressed patients have a higher rate of developing both viral and 'normal' cancers
--
2. Cancer patients have measurable immune responses to tumor antigens
---> Tumor antigens include fusion proteins (Bcr-abl in CML), overexpressed proteins (c-erbB2), viral proteins, fetal proteins, etc.)
--
3. Lymphocytes may be observed histologically around tumor sites
--
4. Spontaneous regression is histologically associated with lymphocyte and macrophages at the former tumor site

“Immune Surveillance” Theory

- **Very early cancers usually eliminated by immune system**
- **To be successful, a tumor must evade the host immune system (“immune escape”)**

If not, then we'd all have the cancer rate of immunosuppressed patients

Cancer Immunity

- In theory, has the potential to eliminate cancers with minimal side effects
- Has been focus of intense research
- Holy grail—a “Cancer Vaccine”
  - Many have tried…none have succeeded (yet!)

Tumor Antigens—Many Potential Targets

- Products of mutated oncogenes and fusion proteins
- Mutated self protein
- Overexpressed or aberrantly expressed self protein (growth factor receptors, etc)
- Viral proteins (for the few viral-related cancers)

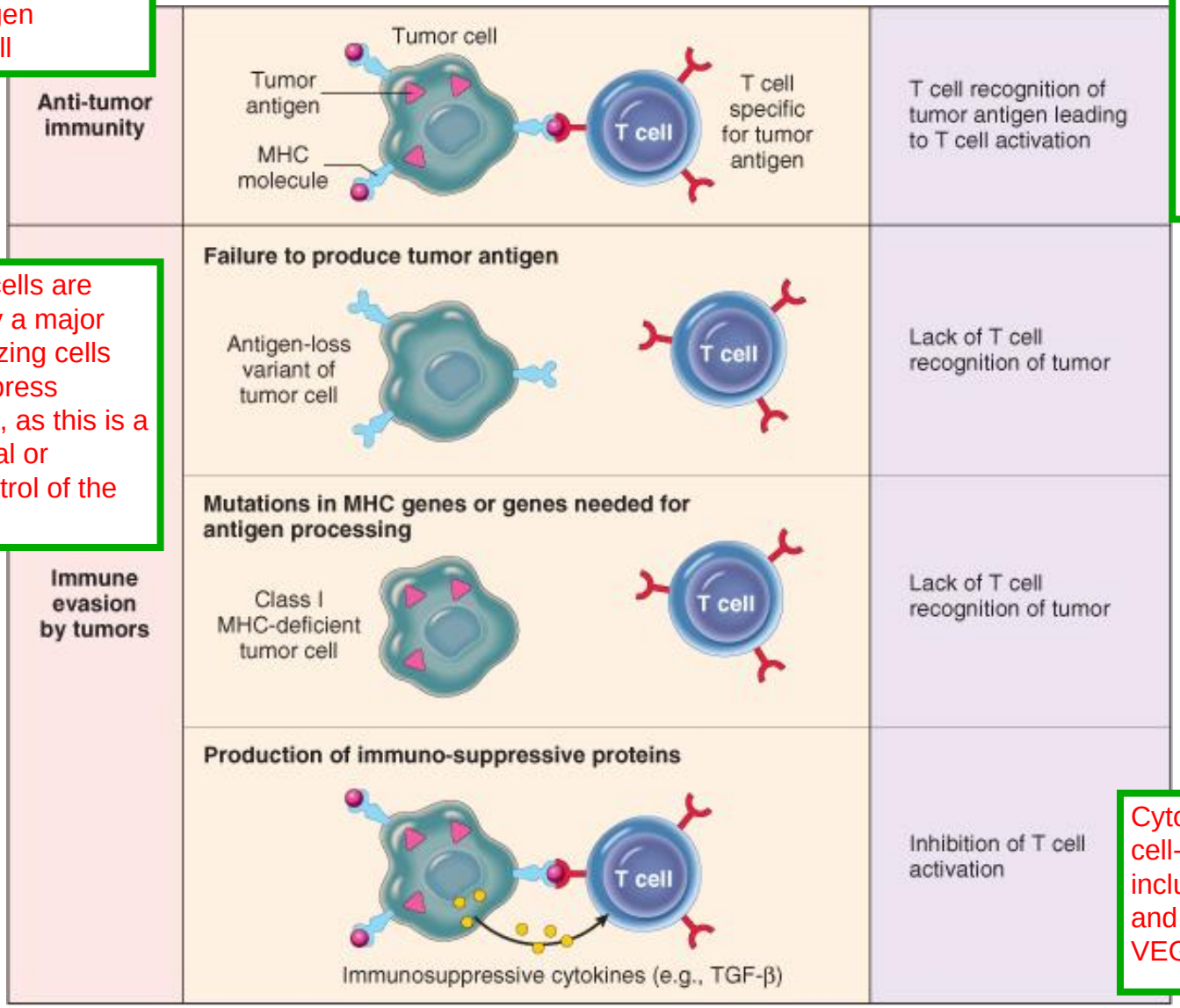
Same list as before.

But also many mechanisms by which tumor cells evade immune system

Steps of immune activation:
1. Produce antigen
2. Present antigen
3. Activate T cell

Steps of immune evasion:
1. Suppress antigen expression
2. Disrupt MHC I signaling system
3. Express immunosuppressive cytokines

Note that NK cells are thought to play a major role in recognizing cells that do not express enough MHC I, as this is a hallmark of viral or oncogenic control of the cell



Cytokines that suppress cell-mediated immunity include TGF-b, IL-10, and, conveniently, VEGF

Examples of Immune Therapies in Routine Use

One of the first examples of 'personalized' medicine - genotyping a patient's tumor for Her2/neu overexpression determines whether Herceptin is indicated

- **Monoclonal antibodies**
  - **Herceptin (trastuzumab): anti-Her2/neu antibody, used for breast cancers that overexpress growth factor receptor Her2/neu due to gene amplification**
  - **Rituximab: Anti-CD20 antibody, used for B-cell lymphomas**

Not useful for multiple myeloma, though, as plasma cells don't express CD20

- **Immune adjuvants**
  - **BCG (a weakened TB strain used normally for immunizations), used for bladder cancer**

Mechanism unclear, it's just thought to 'prime' the local immune system to a state where it will begin recognizing/fighting the tumor

- **Cytokines**
  - **Interferon: Kidney cancer, melanoma**

Examples of Immune Therapies in Routine Use

- **Donor vs. host (donor leukocyte infusion):**
  - **After bone marrow transplant, infuse donor white cells—they attack host cells as foreign tissue (leukemias)**
- **"Vaccine"**
  - **Sipuleucel-T (Provenge), host dendritic cells from blood cultured in vitro with sample of patient's tumor to induce immunity (prostate cancer)**

Same idea as graft-vs-host disease (BAD), only the host is presumably more histocompatible than the host's cancer (again, due to tumor antigens), so only the cancer cells get attacked. Clever!

The limiting step here is APC recognition of the tumor antigen. This process can be facilitated through various laboratory methods in vitro. Once the APCs are set, they can be transplanted and activate the immune response more effectively.

Expensive and not all that effective, so far.

Effects of Neoplasia on the Host

Great reason to remember anatomy - many effects of tumors are purely architectural

***Local symptoms*: Location, location, location!** Compression of surrounding tissues may cause chronic symptoms such as jaundice, or acute symptoms caused by either rupture or infarction.

***Symptoms of metastasis*: Location, location, location!** Enlarged lymph nodes, cough and hemoptysis, hepatomegaly (enlarged liver), bone pain, fracture of affected bones and neurological symptoms from brain metastases

Most common metastatic sites (three L's, two B's): lymph nodes, lung, liver, brain, bone

***Systemic symptoms*:** weight loss, poor appetite, fatigue and cachexia, excessive sweating, anemia, effects of endocrine secretory products, and specific paraneoplastic phenomena.

More on this coming up...

Systemic Symptoms of Cancer

There are a wide variety of effects that cancers can have systemically, remote from the sites of tumor

CACHEXIA IN CANCER

Formal definition: decreased lean body mass that cannot be reversed nutritionally; presents with marked atrophy of skeletal muscle

Anorexia, weight loss, weakness and anemia

Some correlation with tumor burden but imperfect. Not caused by the nutritional demands of the tumor.

Molecular basis is unclear but cachectin (tumor necrosis factor) which is a macrophage product may play a role.

EXTREMELY COMMON IN CANCER—ONE OF THE MOST COMMON PRESENTING SYMPTOMS OF CANCER IS UNINTENTIONAL WEIGHT LOSS.

Note: cachectin is just another name for TNF-alpha. Everything you learned about it for immunology still applies. The differences in presentation are a result of acute/high levels in local inflammation vs. chronic/low levels in cancer

CACHEXIA IN CANCER

1/3RD OF CANCER DEATHS DUE TO CACHEXIA, RATHER THAN DIRECTLY DUE TO THE TUMOR BURDEN ITSELF.

If a patient presents with unexplained, unintentional weight loss, immediately think cancer

Cachexia can disqualify patients for chemotherapy as well

Paraneoplastic Syndromes

Acromegaly as a result of GH expression from a pituitary tumor would NOT be a paraneoplastic syndrome, because pituitary cells normally express GH

- Definition: Symptom complexes 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.
- 10% of patients with cancer
- Important because they can be 1st manifestation of cancer, and in some patients can be major cause of morbidity or even death.
- These phenomena are mediated by humoral factors excreted by tumor cells or by an immune response against the tumor. Some are better understood than others.

Examples of Paraneoplastic Syndromes

- **Endocrinopathies** ectopic hormone expression

Again, a tumor of the adrenal cortex that caused Cushing's syndrome would NOT be a paraneoplastic syndrome

Cushings Syndrome (excess cortisol)

- Secretion of ACTH, lung cancers

- Hypercalcemia—most common

Pathology connection: hypercalcemia results in metastatic calcification. Dystrophic calcification occurs in degenerated or necrotic tissue such as scars.

  - Secretion of parathyroid horm
    protein, TGF-alpha, TNF

PTH-RP is not exactly PTH, but it has a similar function

- Polycythemia (too many red cells)

  - Secretion of erythropoietin

Kidney cancers are particularly known for this

Examples of Paraneoplastic Syndromes

- **Nerve and Muscle Disorders**

Autoimmune, rather than hormonal, in etiology

  - "Neuromyopathic syndromes"
    - Peripheral neuropathies, cerebellar degeneration, polymyositis—autoimmune etiology
  - Myasthenia
    - Autoantibody inhibits function of neuromuscular junction—profound weakness

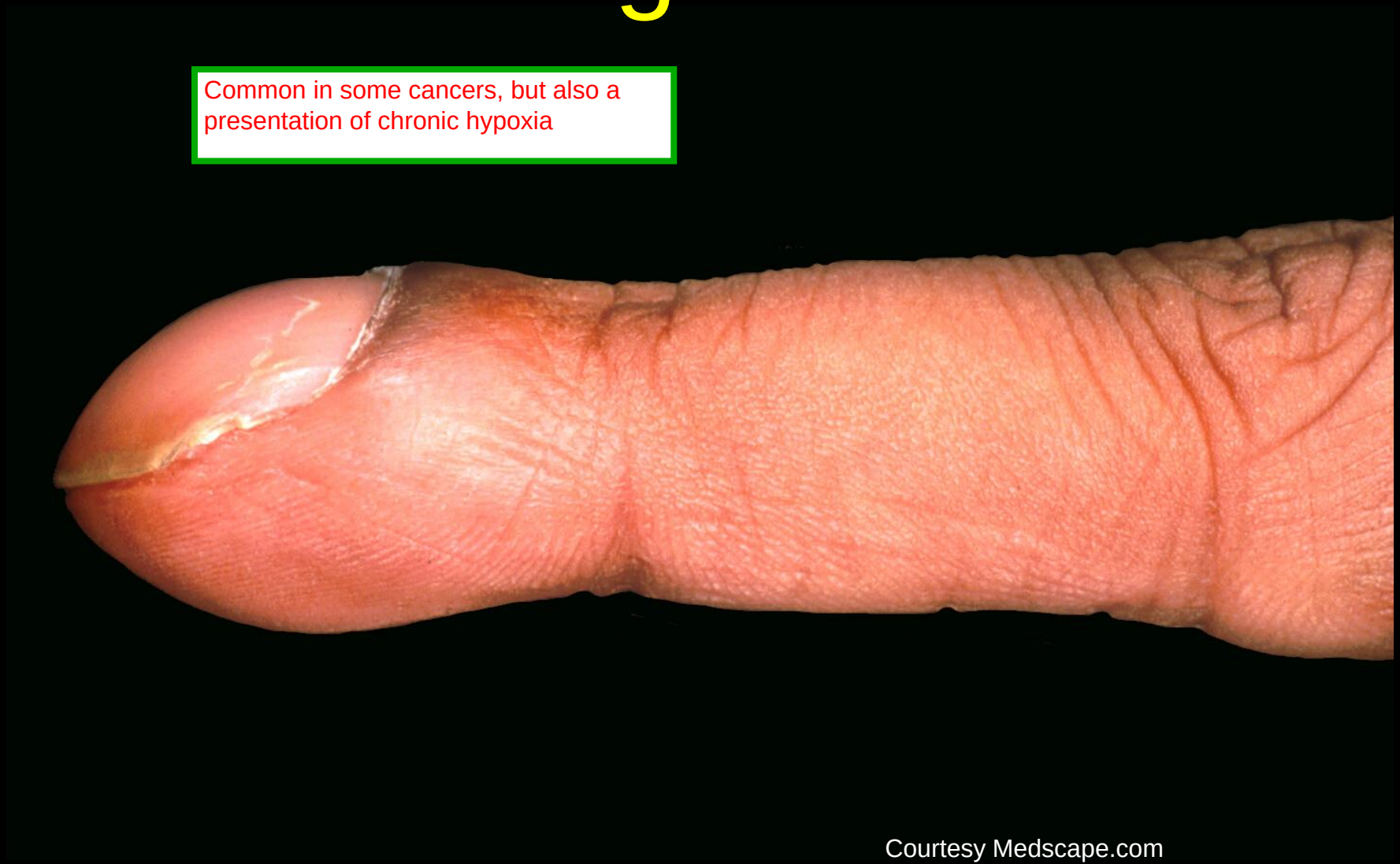
Mimics myasthenia gravis (autoimmune attack against nAChR)

Examples of Paraneoplastic Syndromes

- **Bone and soft tissue**
  - Hyerptrophic osteoarthropathy and clubbing of the fingers
    - “arthritis of cancer”—unknown cause.

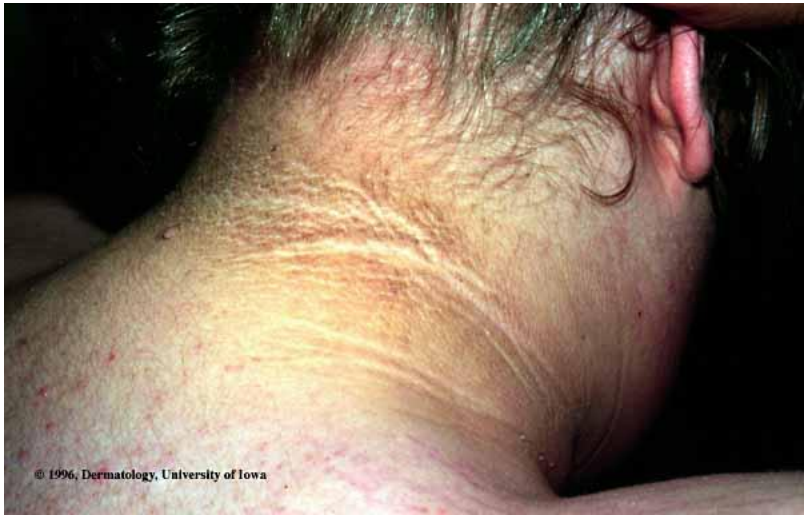
Clubbing

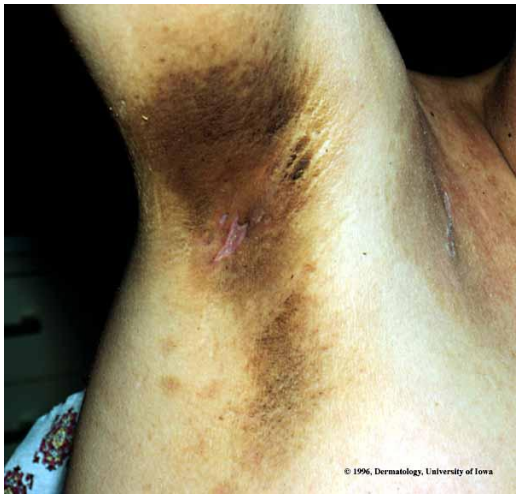
Common in some cancers, but also a presentation of chronic hypoxia



Courtesy Medscape.com

DERMATOLOGIC PARANEOPLASTIC SYNDROME





Acanthosis nigricans

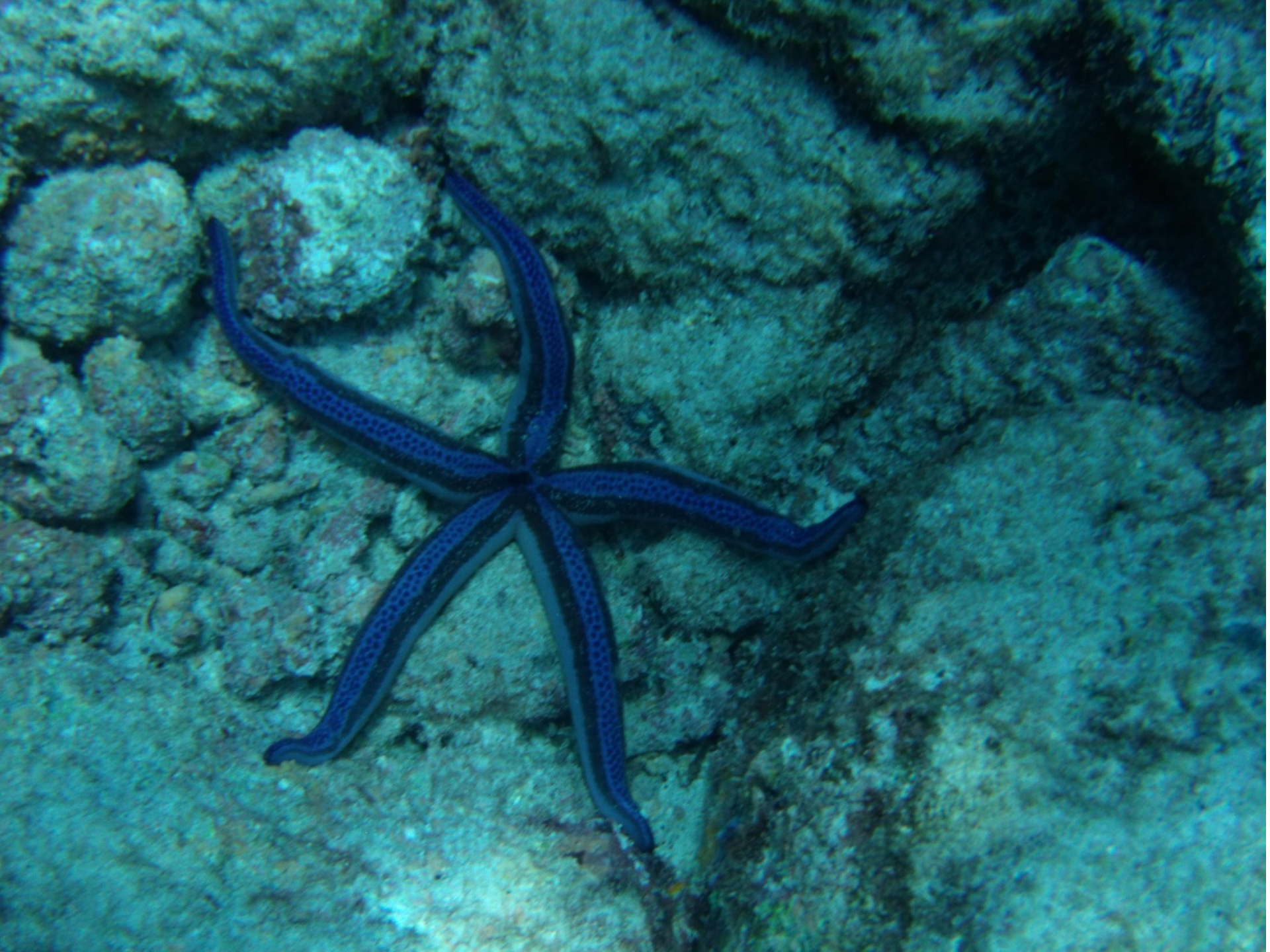
Can happen in patients with gastric, lung and uterine carcinomas

Immunologic, secretion of EGF

Skin changes can appear before discovery of cancer

Examples of Paraneoplastic Syndromes

- **Vascular disorders**
  - Trousseau syndrome
    - Venous thrombi--Hypercoagulability, uncertain cause.
  - Non-bacterial thrombotic endocarditis
    - Unknown mechanism.



Functional Differentiation of Neoplasms

Neoplasms often continue to make the normal products of the tissue of origin

Functional Differentiation

- Pituitary, thyroid, adrenal, etc. neoplasms -- hormones
- Breast and Gyn tumors -- estrogen and progesterone receptors

Estrogen receptor status is VERY important for breast cancer prognosis and treatment - tamoxifen is a common drug that targets ER

- Trophoblastic tumors -- B-HCG
- Prostate – Prostate specific antigen (PSA)

Functional Differentiation

- Some tumors "revert" to making proteins characteristic of embyologic development
- "**Oncofetal proteins**"
  - CEA (Carcinoembryonic antigen)
  - AFP (Alpha-fetoprotein)

These proteins are NOT expressed in healthy adult tissues. Thus, they make good biomarkers for neoplasia (although not pathognomonic)

Functional Differentiation

Can help us DIAGNOSE neoplasms

- Hormone products can be detected in blood or in biopsies.
- Tissue specific products can be identified in blood or in biopsies (PSA, CA-125, CEA, etc).

Functional Differentiation

Can help us TREAT neoplasms

- Receptors can be treatment targets (tamoxifen for breast cancer, ER)
- Radioactive iodine, thyroid cancer

Local, specific delivery of high doses of radiation possible since the thyroid takes up most of the iodine in the body

Cancer Diagnosis

- People with suspected cancer are often first investigated with medical tests. These commonly include blood tests, X-rays, CT/MRI scans and endoscopy.
- Clinical history, risk factors, occupational exposures, family history is important.
- Diagnosis of malignancy ultimately is by histology
  - Biopsy or excision
  - Fine needle aspiration
  - Cytology of fluids (ascites, pleural fluid, urine, CSF, etc)
- Histologic features discussed in neoplasia 1.

When was the last time you did a D/Dx that cancer didn't appear on?

Tumor cells can slough off into fluids

Cancer Diagnosis

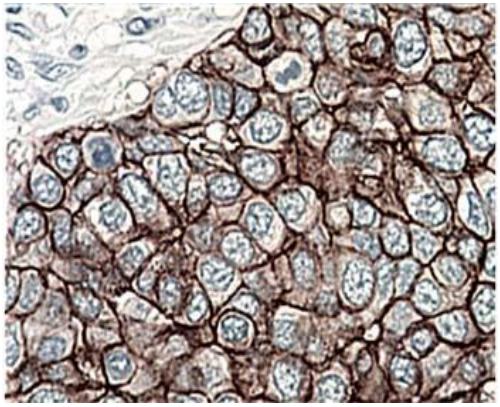
Immunohistochemistry

applying known antibodies to tissue sections to detect tumor antigens

- Categorization of undifferentiated malignant tumors
- Categorization of leukemias and lymphomas

basically no way to ID these by morphology

- Determination of site of origin of metastatic tumors
- Detection of molecules that have prognostic or therapeutic significance



Immunohistochemical stain for HER2/neu
Breast cancer

Staging Of Cancer

- **Standardized way of classifying disease progression**
- **Critically important for:**
  - **Prognosis and treatment**
  - **Comparison to literature**

Staging of Cancer

- **Stage is based on:**
  - **Size of the primary tumor and/or extent of local invasion**
  - **Extent of spread to regional lymph nodes**
  - **Presence or absence of distant metastases**

NOT GRADE.
Grade is a purely histologic characteristic
Stage is a purely anatomic characteristic

Staging of Cancer

Two major systems:

- UICC: Union Internationale Contre Cancer
- AJCC: American Joint Committee on Cancer Staging

UICC: TNM System

- **T**: Primary tumor size
  - T0 (in situ) to T4 (very large)
- **N**: Lymph node involvement:
  - N0 (no nodal involvement) to N3 (multiple involved lymph nodes)
- **M:** Distant metastases,
  - M0 (no distant metastases) to M1 and M2 (multiple metastases)

Size doesn't always correlate with pathology, but it's a decent approximation, especially when combined with the other categories

There's a big difference between proximal and distal lymph node involvement, so there are a few gradations

AJCC: STAGE I - IV

- **Stage I**
  - **Smallest tumors.**
- **Stage II, III**
  - **Larger tumors, more local spread.**
- **Stage IV**
  - **Metastases**

Straightforward, but not as nuanced. Used mainly for prognosis rather than detailed description of cancer

"Stage Grouping"

Each cancer has a table that "groups" TNM possibilities into the 4 AJCC stages

Every cancer is different! Don't spend too much time worrying about the specific numbers from this table, as it's just a 'generic' cancer.

AJCC	UICC		
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	Any	M0
Stage IV	Any	Any	M1

Grouping of different UICC numbers into stages is based on survival rate

If there is metastasis, it is stage IV. Size and node involvement do not matter if the tumor has already metastasized. The tumor has already demonstrated that it's a "bad actor" = Stage IV

Tumors with similar AJCC stage have similar survival

Cancer stage is critical for determining prognosis and therapy

Stage is usually the single most important predictor of survival

SUMMARY

1. Describe process of invasion, metastasis, and angiogenesis
2. Discuss host immunologic reaction to tumors and the concept of immune surveillance
3. Describe systemic effects of cancer and why functional differentiation of tumors can be useful clinically.
4. Compare the TNM and AJCC staging systems for cancer

Quick Review

Which of the following observations would indicate specifically a tumor that is large, but node-negative?

A. Grade 2 histology
B. CEA (carcinoembryonic antigen) found in blood.
C. Stage 2
D. Stage T3N0M0

Quick Review

Which of the following observations would indicate specifically a tumor that is large, but node-negative?

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B. CEA (carcinoembryonic antigen) found in blood.
C. Stage 2
D. Stage T3N0M0—CORRECT!!!

Quick Review

What is the difference between stage and grade?

A. Grade is determined entirely by microscopic examination
B. Stage includes information about tumor size, lymph node status, and distant metastases
C. Stage is usually the single most important predictor of cancer outcome
D. All of the above

Quick Review

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D. All of the above—CORRECT!

THE END

(Of your introduction to neoplasia!)