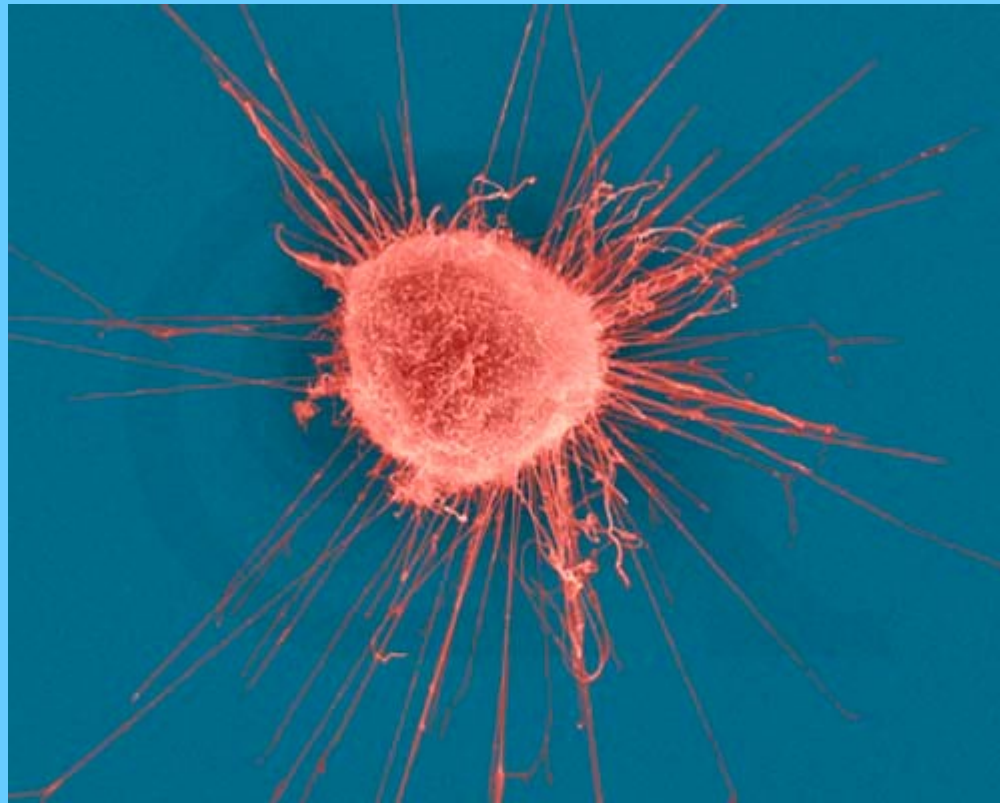


# Some Notes On Cancer Metastasis, Inter Alia By Doc GP



# STAGING & GRADING

- A few notes on determining prognosis.
- You may have heard these words or seen them on a relative's report.
- This is what it means.

# Grading vs. Staging

- **GRADING** IS THE HISTOLOGIC DEGREE OF DIFFERENTIATION AND ANAPLASIA OF THE TUMOR
  - A HISTOLOGIC DETERMINATION
- **STAGING** IS OFTEN COMBINATION OF CLINICAL OBSERVATION, IMAGING AND PATHOLOGY
  - DETERMINES EXTENT OF DISEASE
  - USUALLY STAGING MORE IMPORTANT THAN GRADING

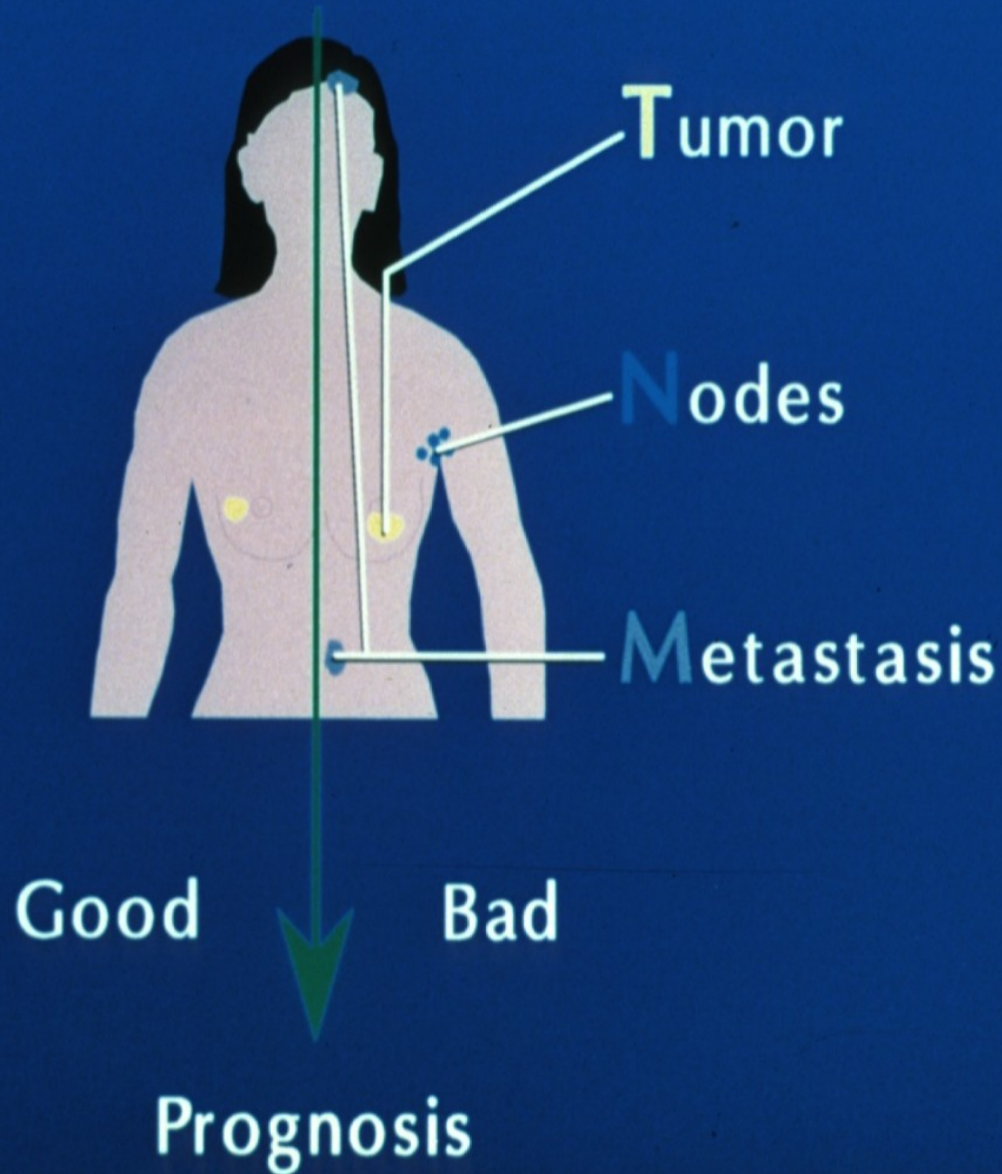
# STAGING OF CANCER

- **DETERMINATION OF THE EXTENT OF THE PATIENTS DISEASE**
  - **SIZE OF TUMOR**
  - **REGIONAL SPREAD**
  - **LYMPH NODE METASTASES**
  - **DISTANT METASTASES**

# STAGING

STAGE 0	DCIS, LCIS (5yr Survival <b>92%</b> )
STAGE 1	Less than 2cm, LN negative ( <b>87%</b> )
STAGE 2	<ul style="list-style-type: none"><li>• Less than 5cm, Axillary LN +, not fixed (<b>75%</b>)</li><li>• Greater than 5cm, LN Negative</li></ul>
STAGE 3	Any size, w Skin involvement, LN + ( <b>46%</b> )
STAGE 4	Distant Metastases ( <b>14%</b> )

# TNM CLASSIFICATION



- **Prognosis becomes worse if there are  
NODES or and METASTASES**

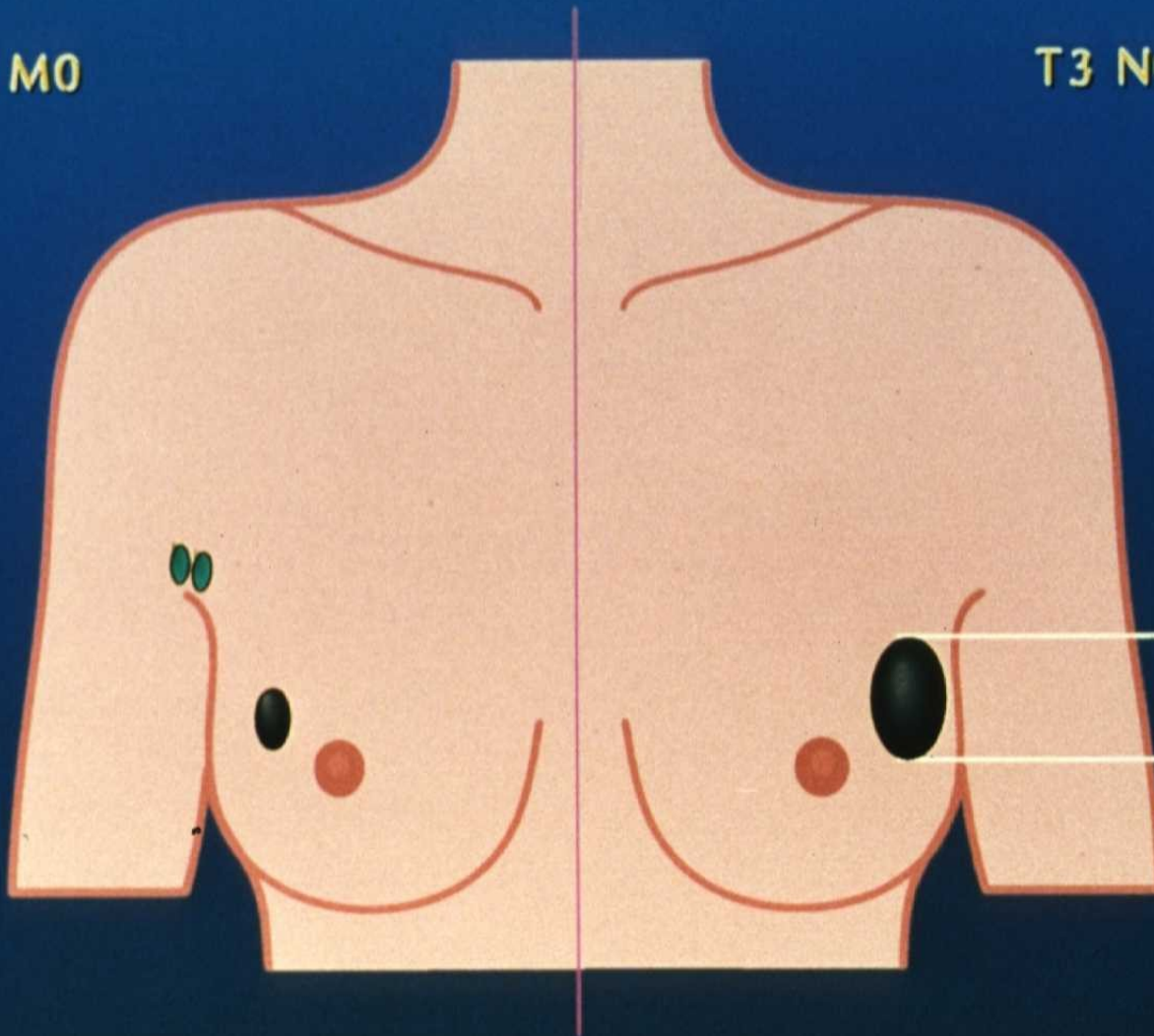
# BREAST CANCER

## STAGE II B DISEASE

T2 N1 M0

T3 N0 M0

**T2**  
 $2 \text{ cm} < T \leq 5 \text{ cm}$



**T3**  
 $T > 5 \text{ cm}$

**N1** = metastasis to movable ipsilateral axillary lymph node(s)  
(p) N1a, N1b



- **-A 75-year-old female with a long history of cigarette smoking is found to have a small tumor at the periphery of her right upper lobe. Initially, the tumor was believed to be a Stage I carcinoma (T1 N0 M0), but after surgery it is found to be Stage II (T1 N1 M0). What is found at surgery that changed the staging?**
- A. Involvement of the chest wall
- B. Tumor size greater than 3 cm
- C. Tumor at the carina
- D. Small cell histology
- **E. Positive bronchial lymph nodes**

Gene expression profile nearly identical between primary cancer and lymph node metastasis

- mRNA from human breast tumors from primary tumor and lymph node metastasis in same patients were collected
- Gene expression profiles were almost identical suggesting that **the molecular program of a primary tumor is generally retained in its metastases.**

# What is cancer metastasis?

- **Cancer defines a population of cells that have lost their normal controls of growth and differentiation and are proliferating without check.**
- **Metastasis is the process by which a tumor cell leaves the primary tumor, travels to a distant site via the circulatory system, and establishes a secondary tumor.**

# What Finally Kills the cancer Patient?

**Pneumonia:** Infection (most?), neutropenia, aspiration  
immunosuppression, airway obstruction, narcotic suppression

**Sepsis:** Gram negative shock

**Hemorrhage:** Thrombocytopenic patient (CNS, Gut)

**Pulmonary Thromboemboli:** Kill many bedridden

**Renal Failure:** Tumor Infiltration, Ureteral Obstruction

**Iatrogenic Disease:** Post Surgical, Radiation, ChemoTX

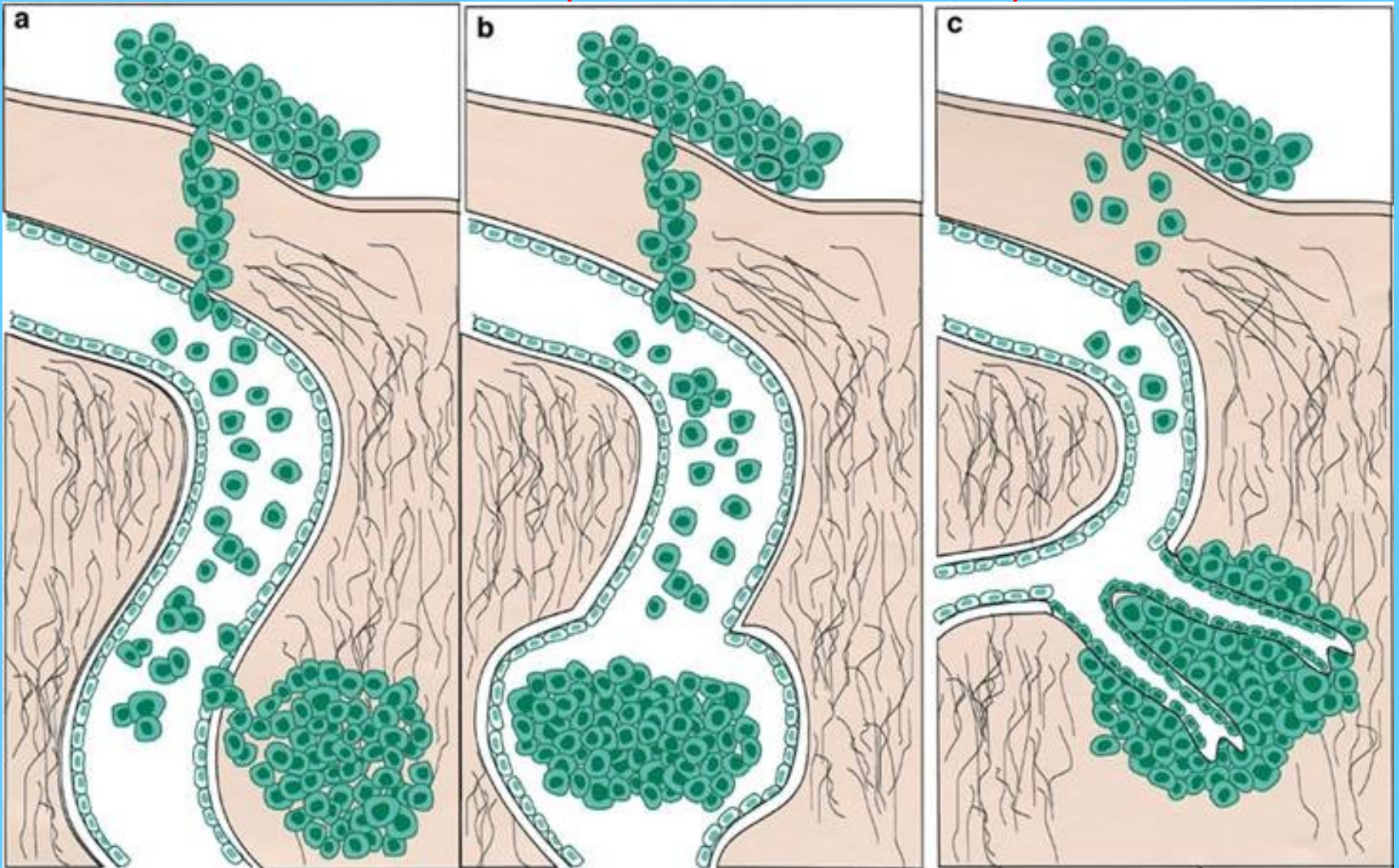
**Concurrent Vital Organ Disease:** COPD, ASHD

**Suicide/Active Euthanasia:** Br.Med.J 312:1431, 1996

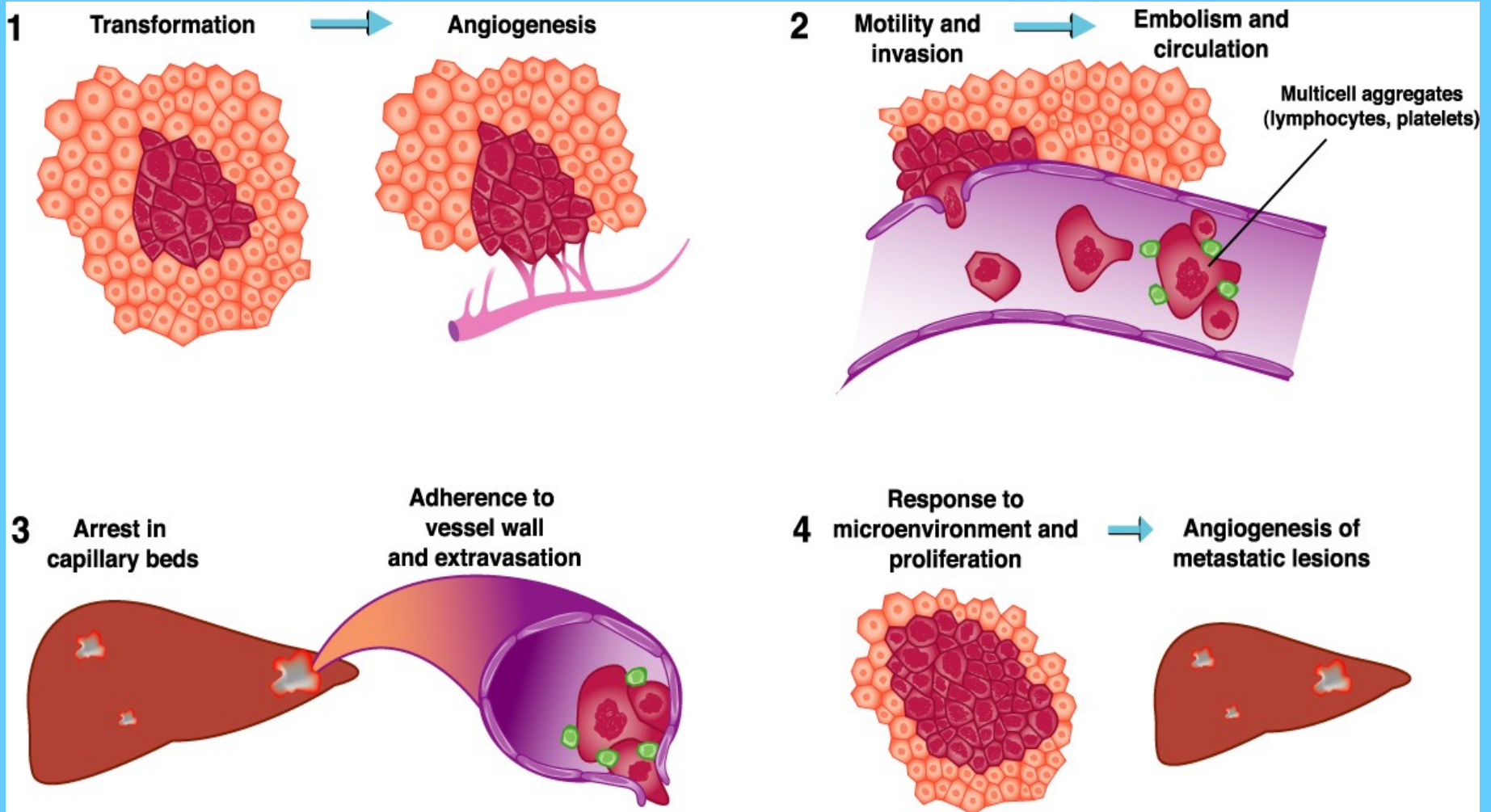
# Metastasis

- is the cause of death in >90% of cancer patients
- the cause of significant pain and suffering
- signifies that a cancer is usually incurable
- signifies a need for effective systemic therapy- local therapies usually not effective
- is the least well understood of all stages of carcinogenesis

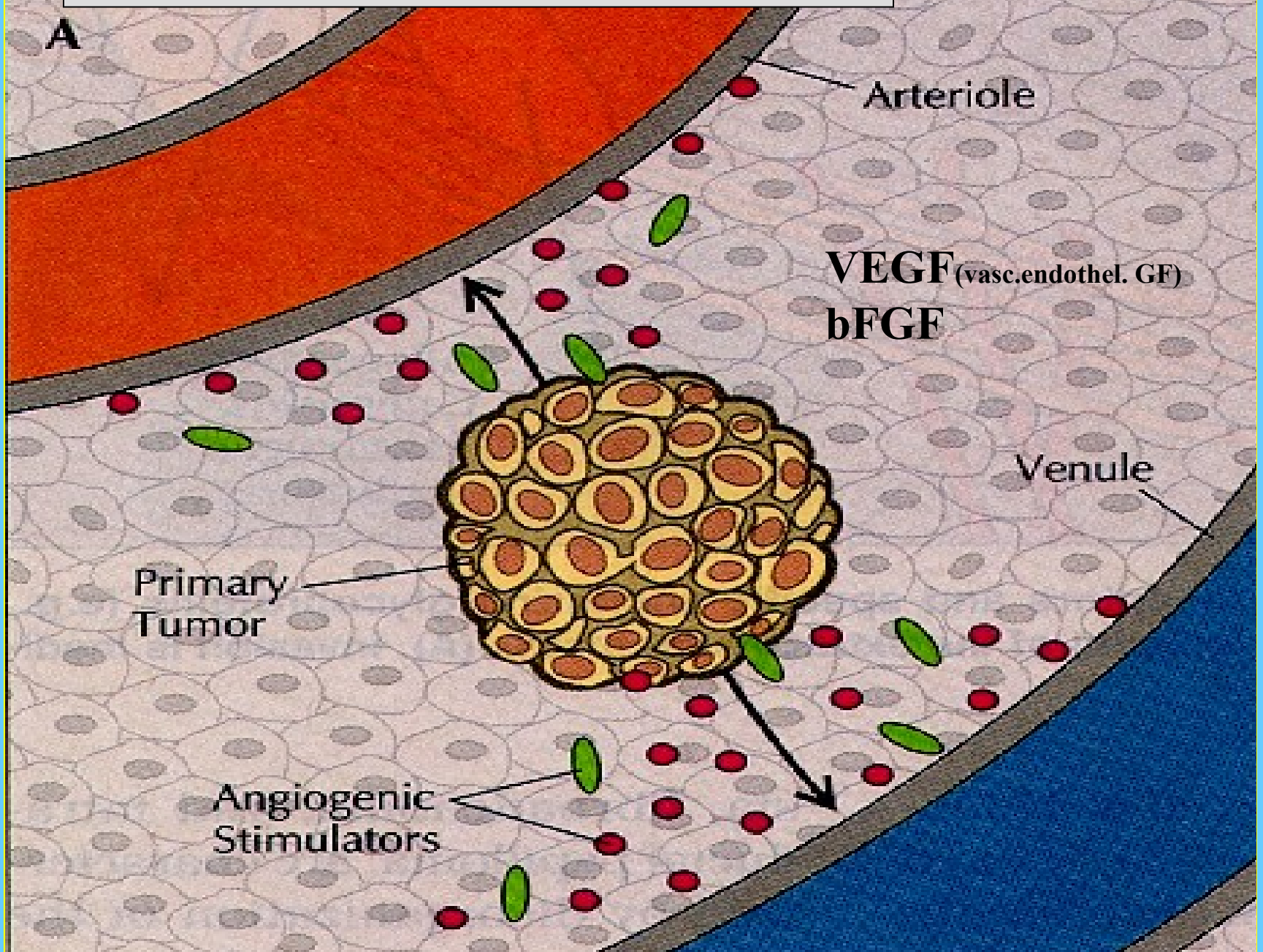
# Cancer entering the blood stream and being carried elsewhere ( cancer metastasis)



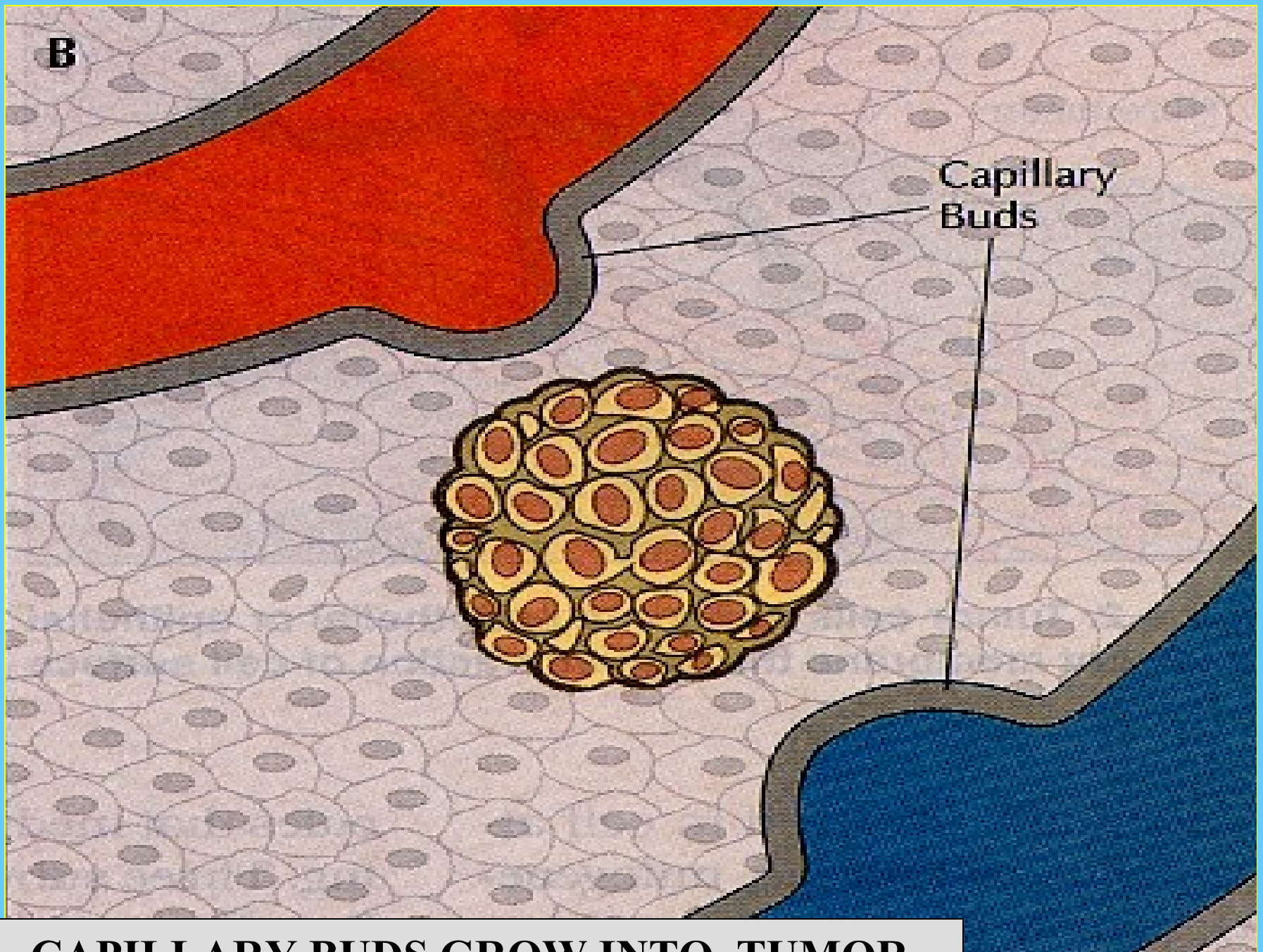
# Role of Angiogenesis (blood vessel formation) in Primary and Metastatic Tumors



# TUMOR FOMENTS ANGIOGENESIS

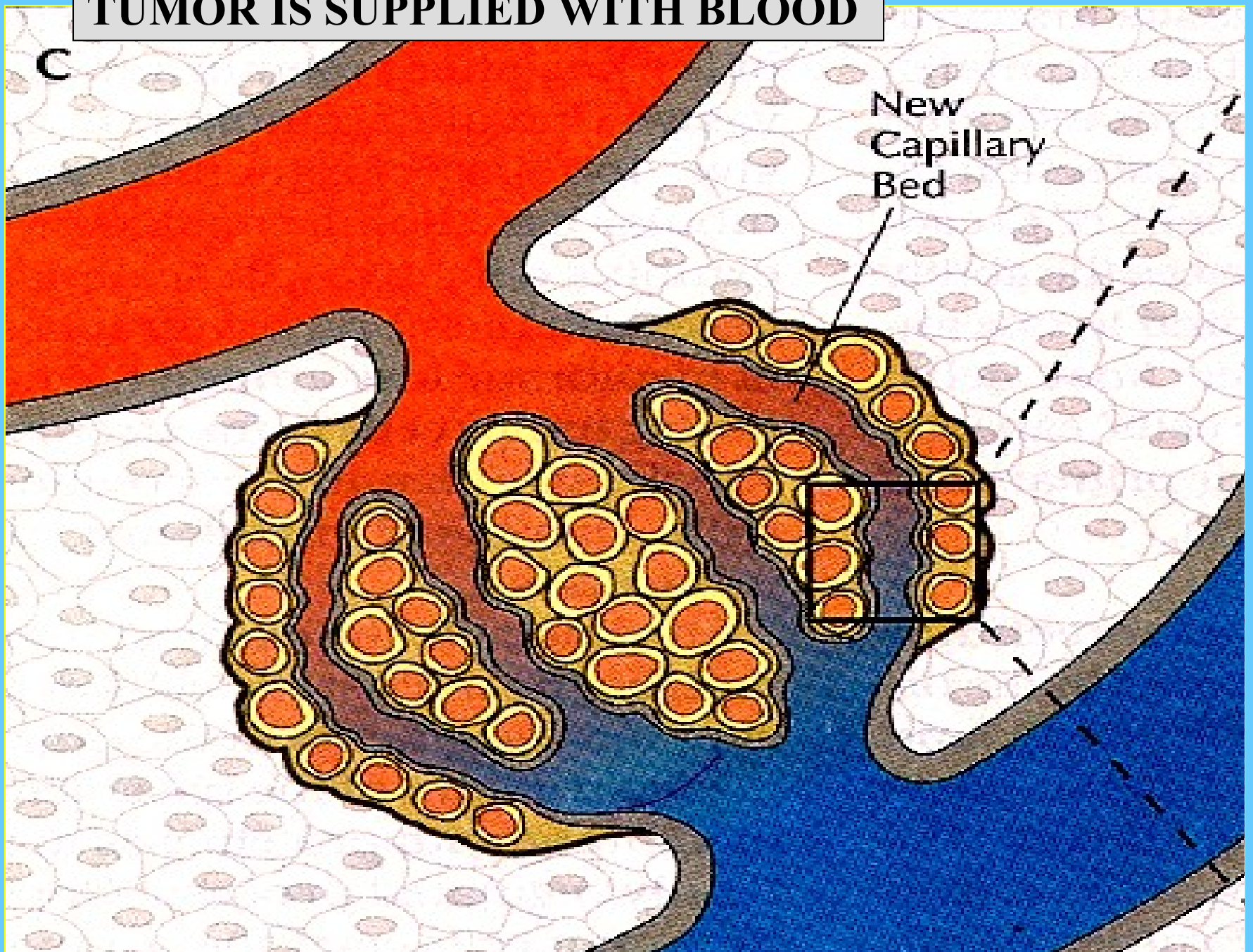






**CAPILLARY BUDS GROW INTO TUMOR**

# TUMOR IS SUPPLIED WITH BLOOD



# Preferential metastatic sites

Primary tumour	Common distant site (s)
Breast' adenocarcinoma	Bone, brain, adrenal
Prostate adenocarcinoma	Bone
Lung small cell carcinoma	Bone, brain, liver
Skin cutaneous melanoma	Brain, liver, Bowel
Thyroid adenocarcinoma	Bone
Kidney clear cell carcinoma	Bone, liver, thyroid
Testis carcinoma	Liver
Bladder carcinoma	Brain
Neuroblastoma	Liver, adrenal

# Incidence of Bone Metastases in Cancers

Incidence of  
Bone Metastases (%)

- **Myeloma** **95-100**
- **Breast** **65-75**
- **Prostate** **65-75**
- **Thyroid** **60**
- **Bladder** **40**
- **Lung** **30-40**
- **Renal** **20-25**
- **Melanoma** **14-45**

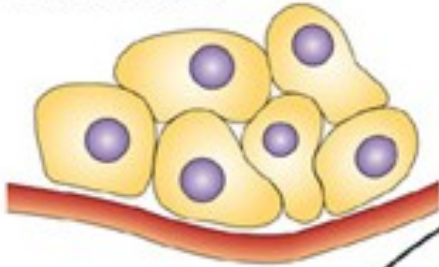
# Determining factors

- Appropriate **growth factors** or **extracellular matrix environment**
- Compatible **adhesion sites** on the endothelial luminal surface
- Selective **chemotaxis** at which the organ producing some soluble attraction factors to the tumor cells

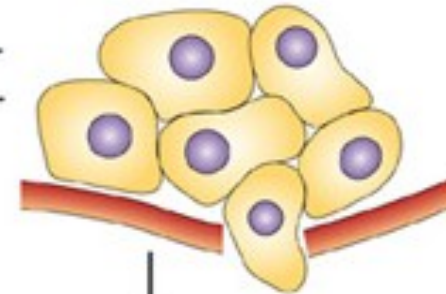
# 5 major steps in metastasis

- 1. Invasion and infiltration of surrounding normal host tissue with penetration of small lymphatic or vascular channels;**
- 2. Release of neoplastic cells, either or single cells or small clumps, into the circulation;**
- 3. Survival in the circulation;**
- 4. Arrest in the capillary beds of distant organs;**
- 5. Penetration of the lymphatic or blood vessel walls followed by growth of the disseminated tumor cells**

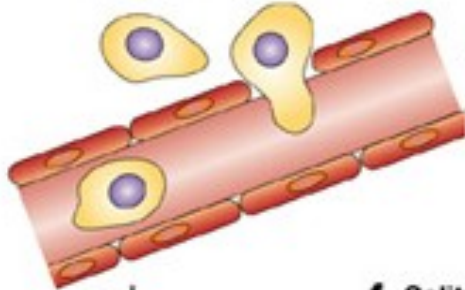
**a** *In situ* cancer



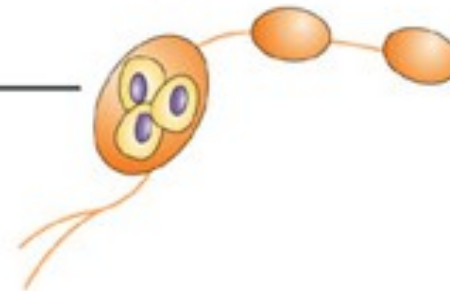
**b** Invasion of the tumour border



**d** Intravasation of the circulatory system  
Survival, transport



**c** Lymphatic spread



**e** Arrest  
Extravasation

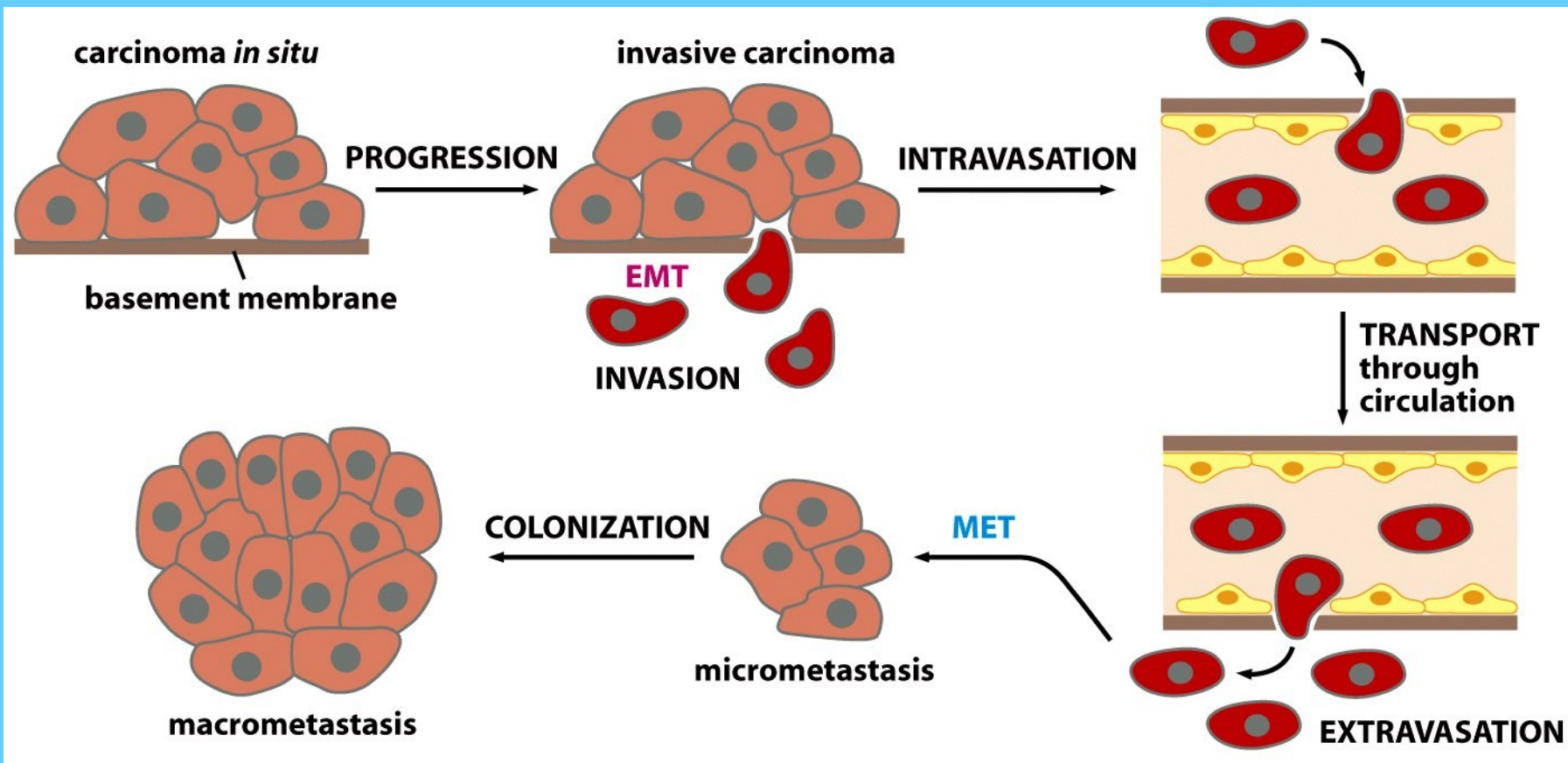


**f** Solitary dormant cells  
Occult micrometastases



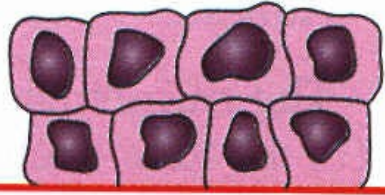
**g** Progressive colonization  
Angiogenesis



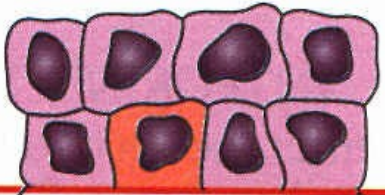




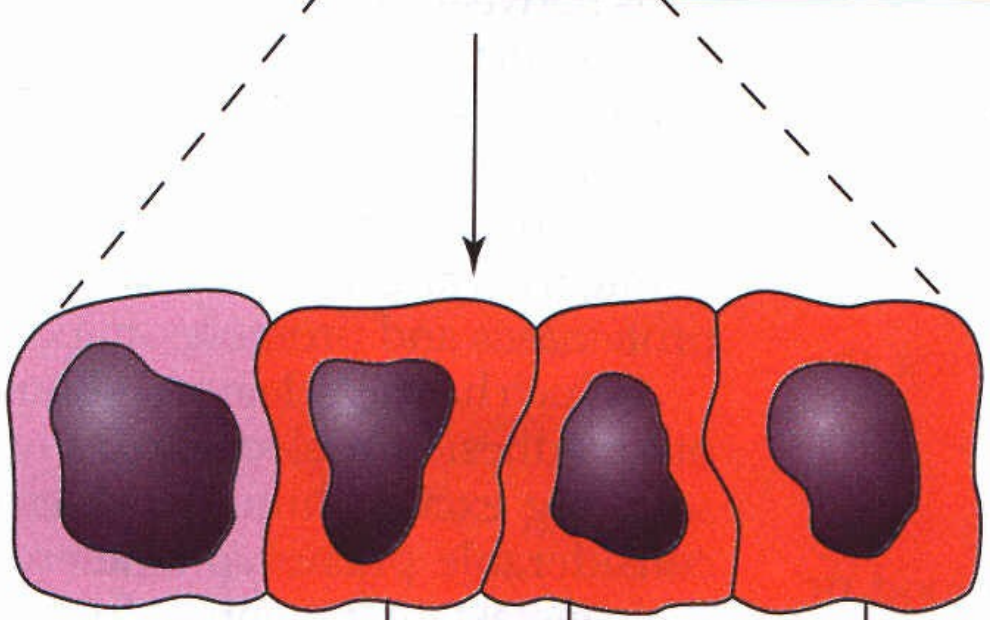
Basement  
membrane



**Carcinoma in situ**



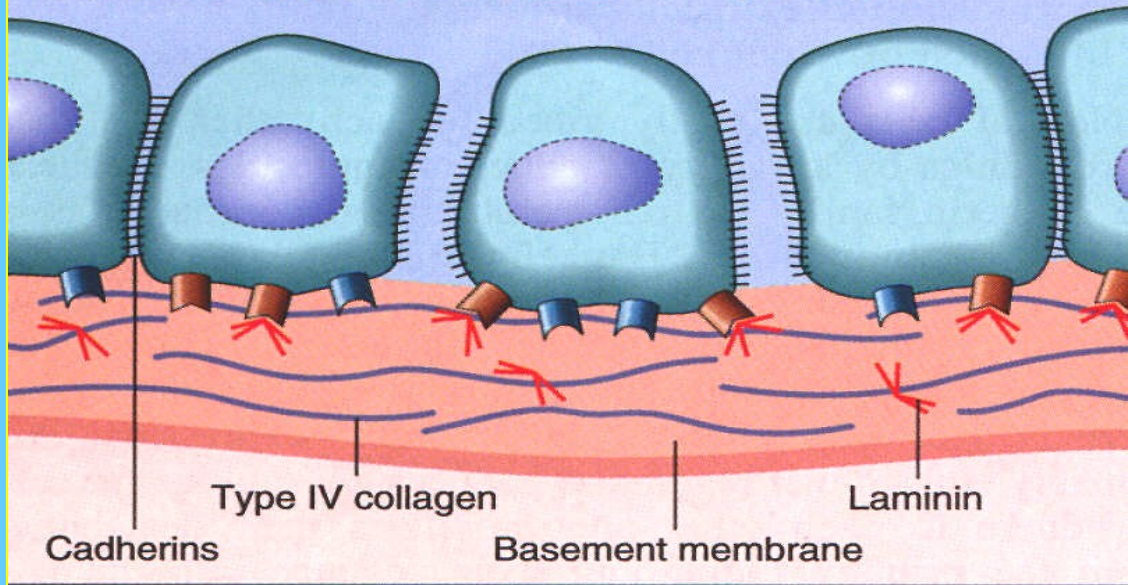
**A cancer cell becomes capable of invasion (expresses surface adhesion molecules)**



**Tumor cell adhesion molecules bind to underlying extracellular matrix**

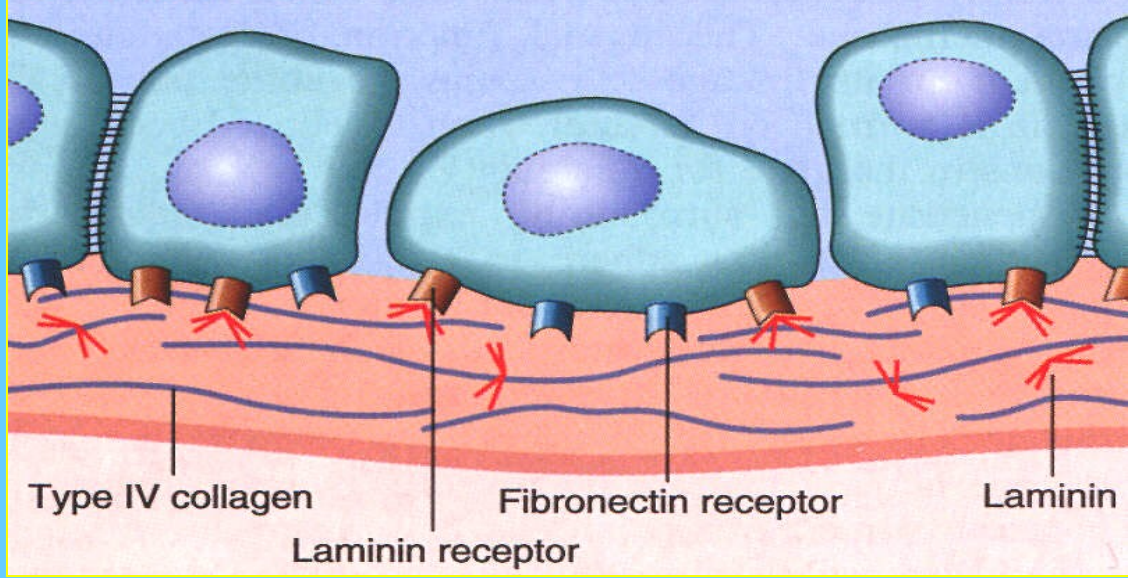


**A. LOOSENING OF INTERCELLULAR JUNCTIONS**

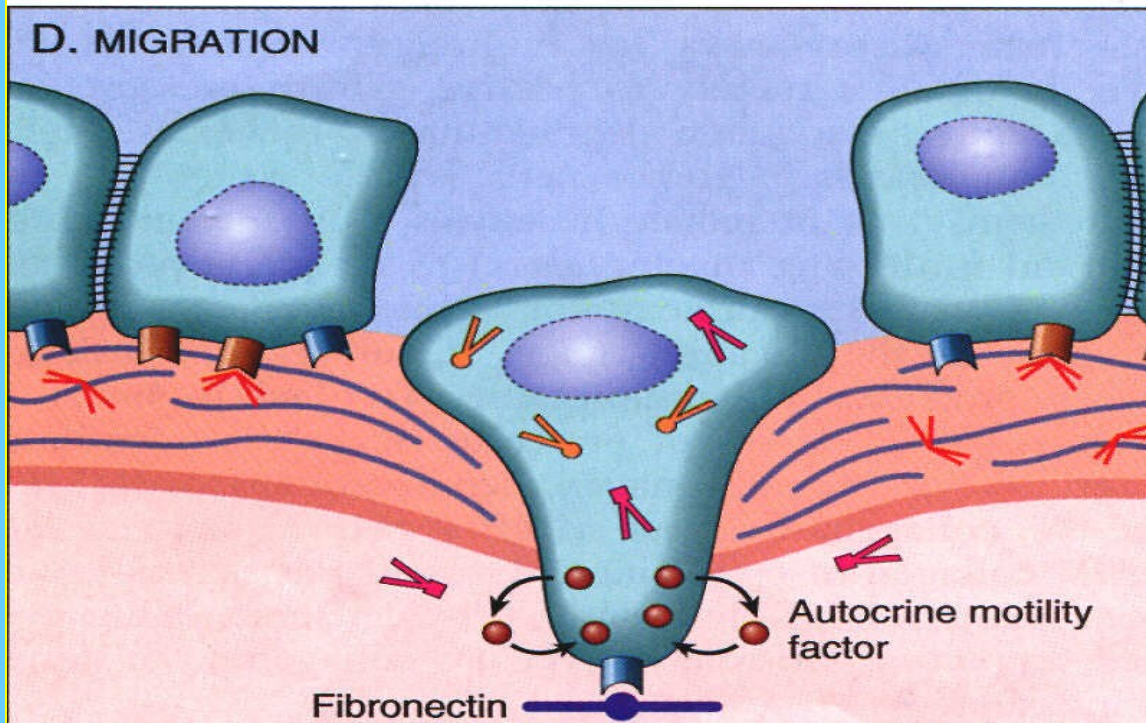
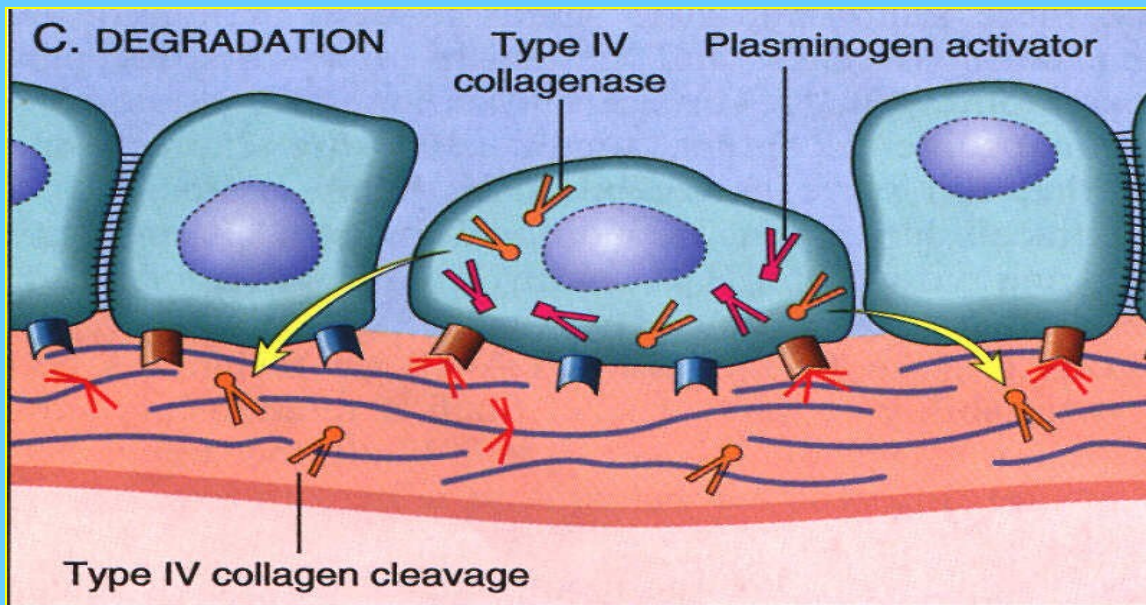


**Detachment**

**B. ATTACHMENT**

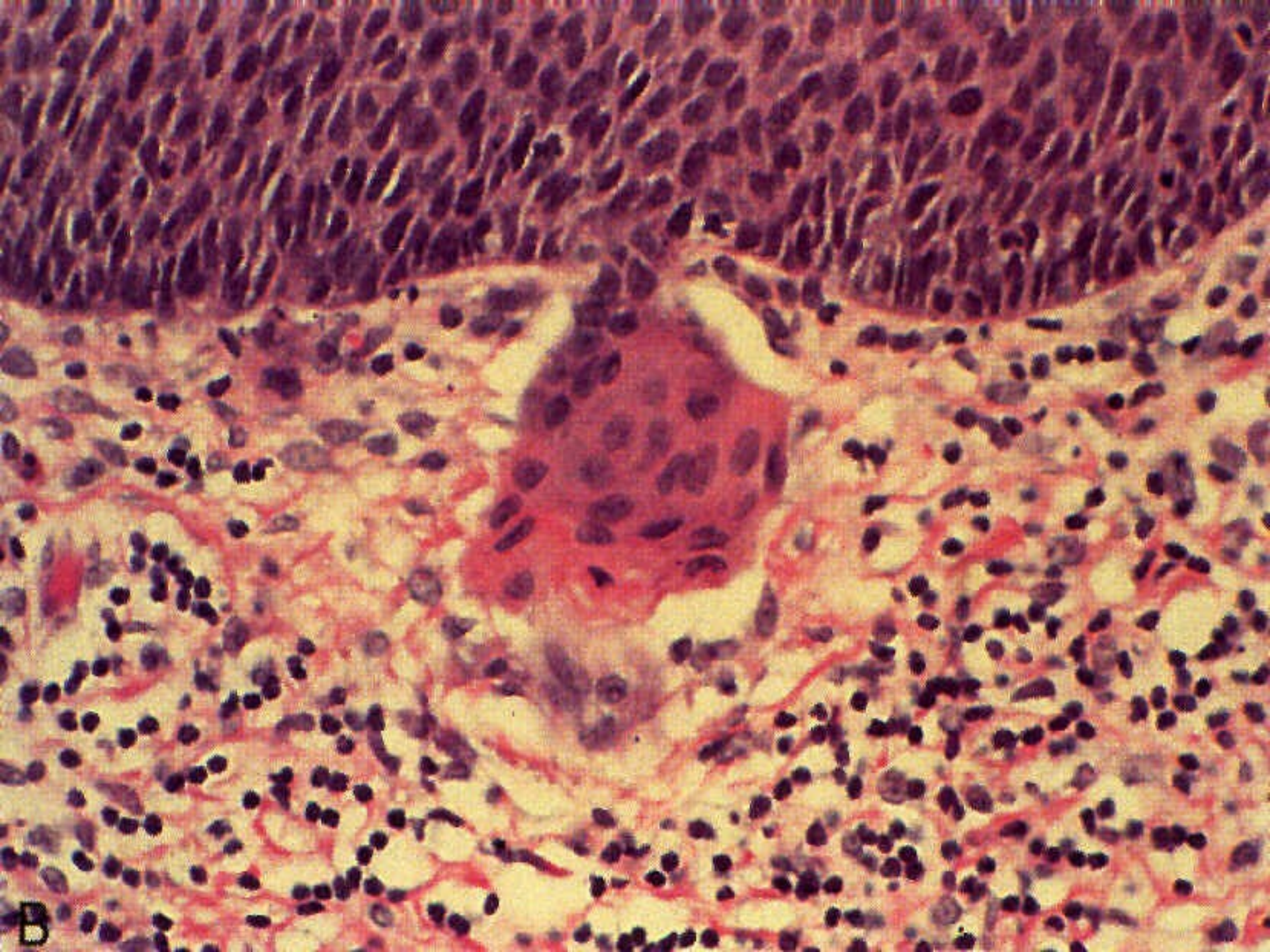


**Attachment  
to Matrix**

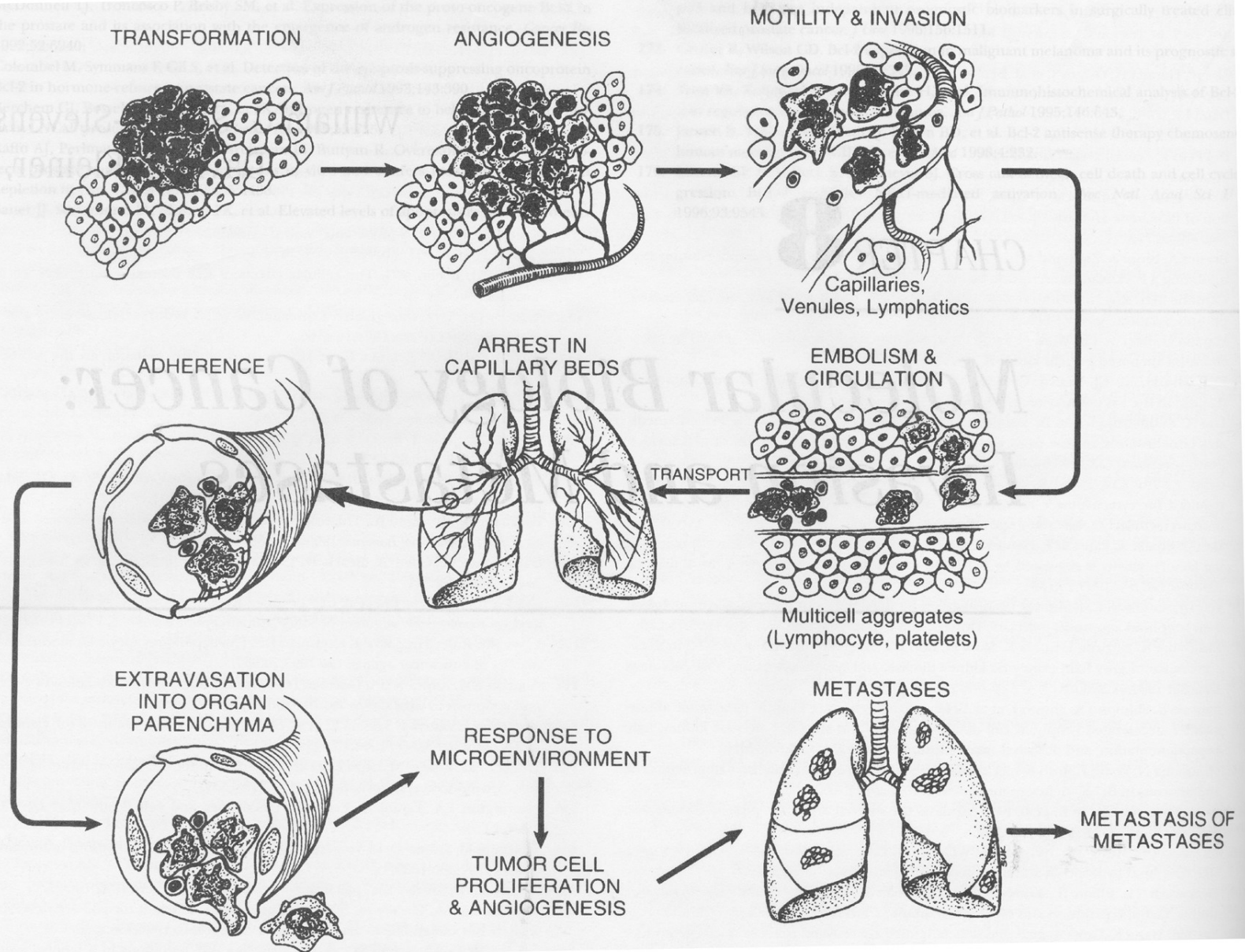


**Degradation**  
**3 classes proteinases:**  
 serine-cathepsin D  
 cysteine-plasminogen  
 activator  
 Type IV collagenase

**Migration**



B



## **LYMPHATIC SPREAD :**

initial dissemination of carcinomas  
follows natural routes of drainage

- (1) enters lymph node through capsular sinus, tumor cells must proliferate within node, invade internal structure, and then eventually give rise to secondary metastases draining through hilar lymphatics to the next node in the chain.

## **HEMATOGENOUS SPREAD :**

initial dissemination of sarcomas

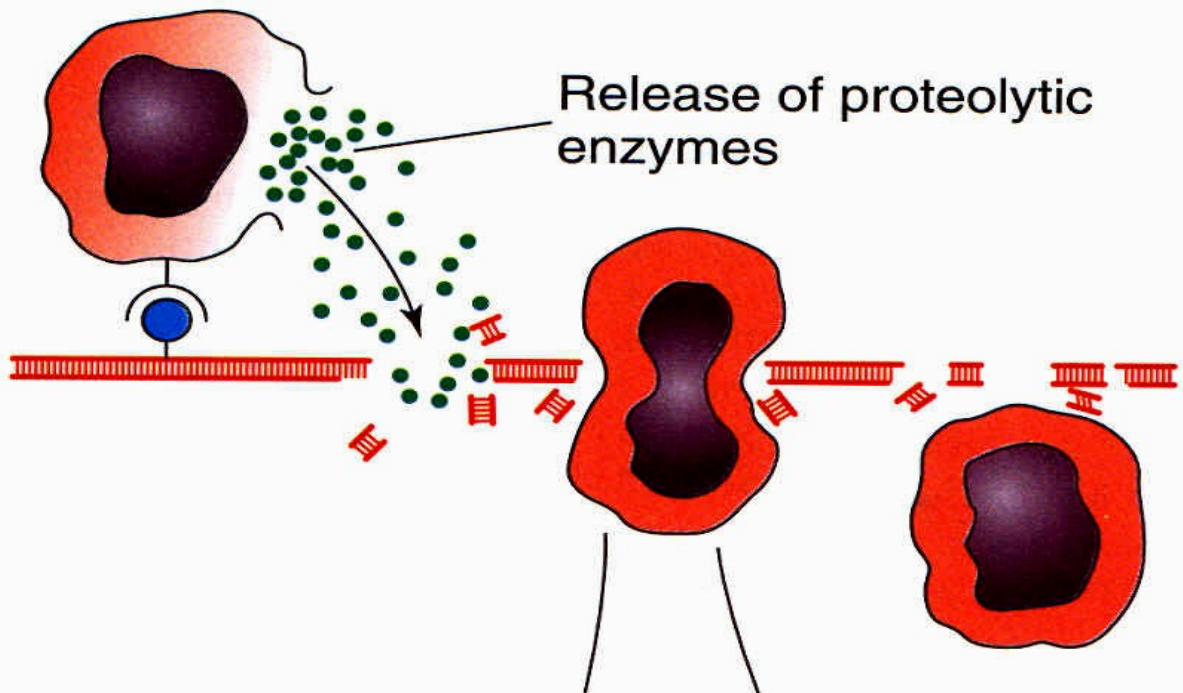
late for all tumors after penetrate pulmonary capillary beds

early for gastrointestinal tumors which follow the portal vein to the liver

Renal cell carcinoma and Liver adenocarcinoma both favor venous invasion early.

Hematogenous metastases will be found in the first capillary bed that captures the large malignant cells.

- (1) Malignant epithelial cells are huge, 80 or more microns and cannot pass through capillaries
- (2) Usually Liver for portal drainage
- (3) Lung for organs that drain into main venous system



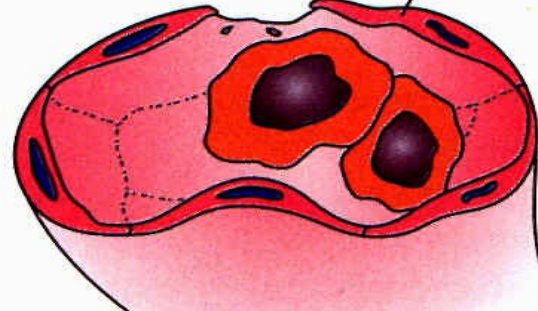
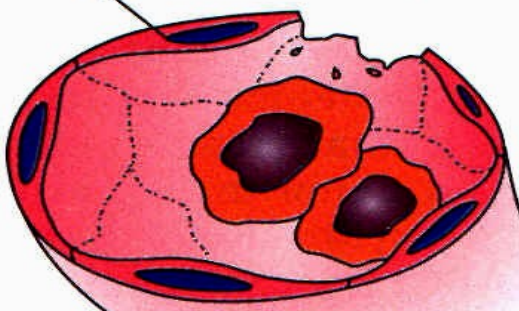
Release of proteolytic enzymes

**Tumor cells disrupt and invade extracellular matrix**

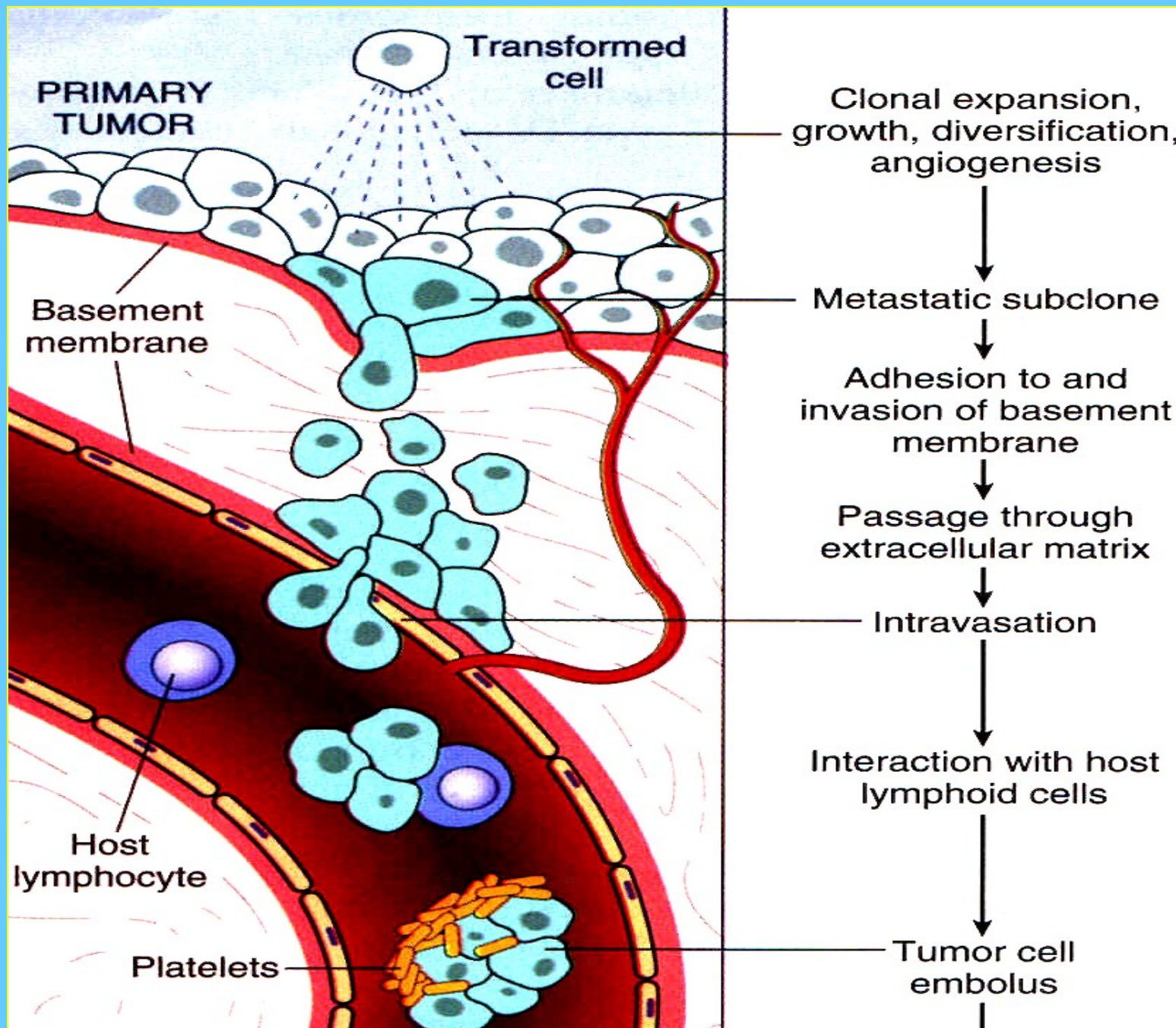
Repeated binding to and dissolution of extracellular matrix

Blood vessel

Lymphatic



**Tumor cells metastasize by way of blood vessels or lymphatics**





# Metastasis Formation is Highly Inefficient

- 0.01% of highly metastatic cells form tumor foci after intravenous injection.
- 1cm<sup>3</sup> size tumor has 10<sup>9</sup> cells. 10<sup>6</sup> cells will be shed into the circulation each day.
- >95% of all breast cancer patients have detectable circulating tumor cells.
- Metastases from renal cell carcinoma, melanoma, colon cancer and breast cancer can lie dormant for 15-20 years
  - Angiogenesis inhibition, immune status, hormonal changes, new mutations.

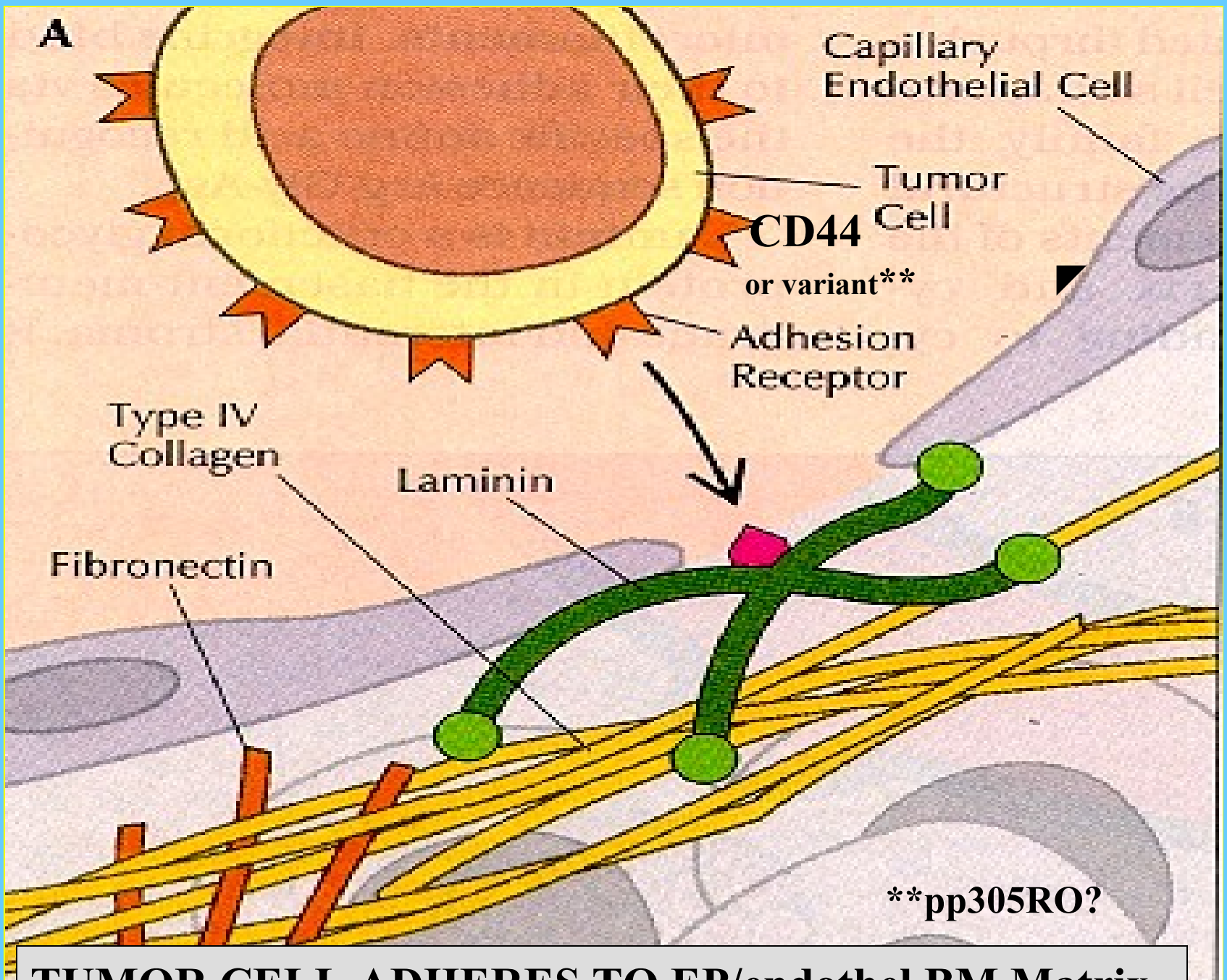
# Stages in Metastasis

- **Early stage:**
  - Tumor cells must decrease cell and matrix adhesion to escape from primary tumor
- **Later stage:**
  - Tumor cells need increased adhesiveness to ECM and other cells to arrest and extravasate at distant site.

**“...vulnerable to destruction...NK cells, adaptive immune defenses.....” RO**

**“...vast majority of tumor cells do not survive their journey in the blood stream, and less than 0.1% remain to establish a new colony.....”**

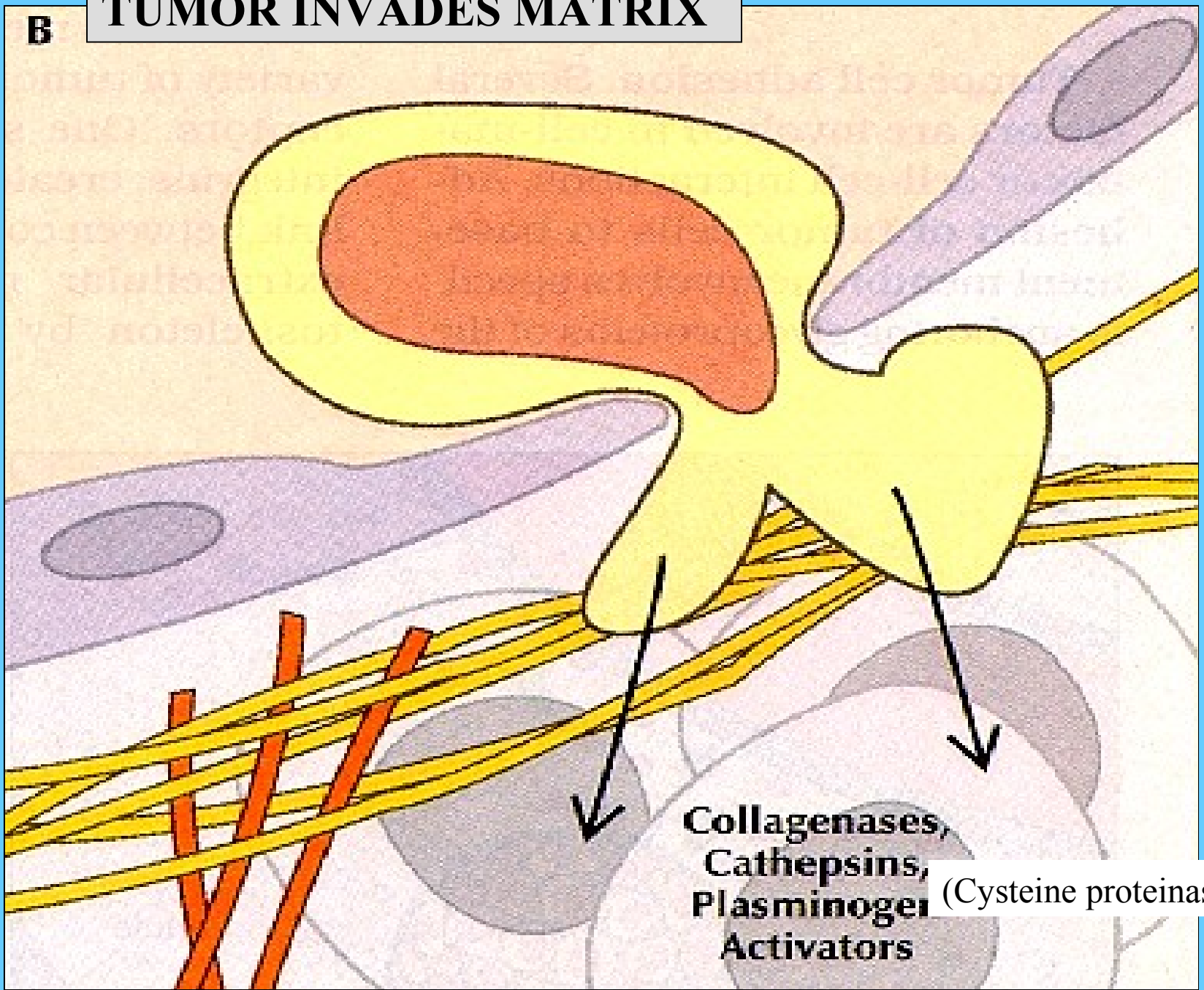
**Rubin & Farber**



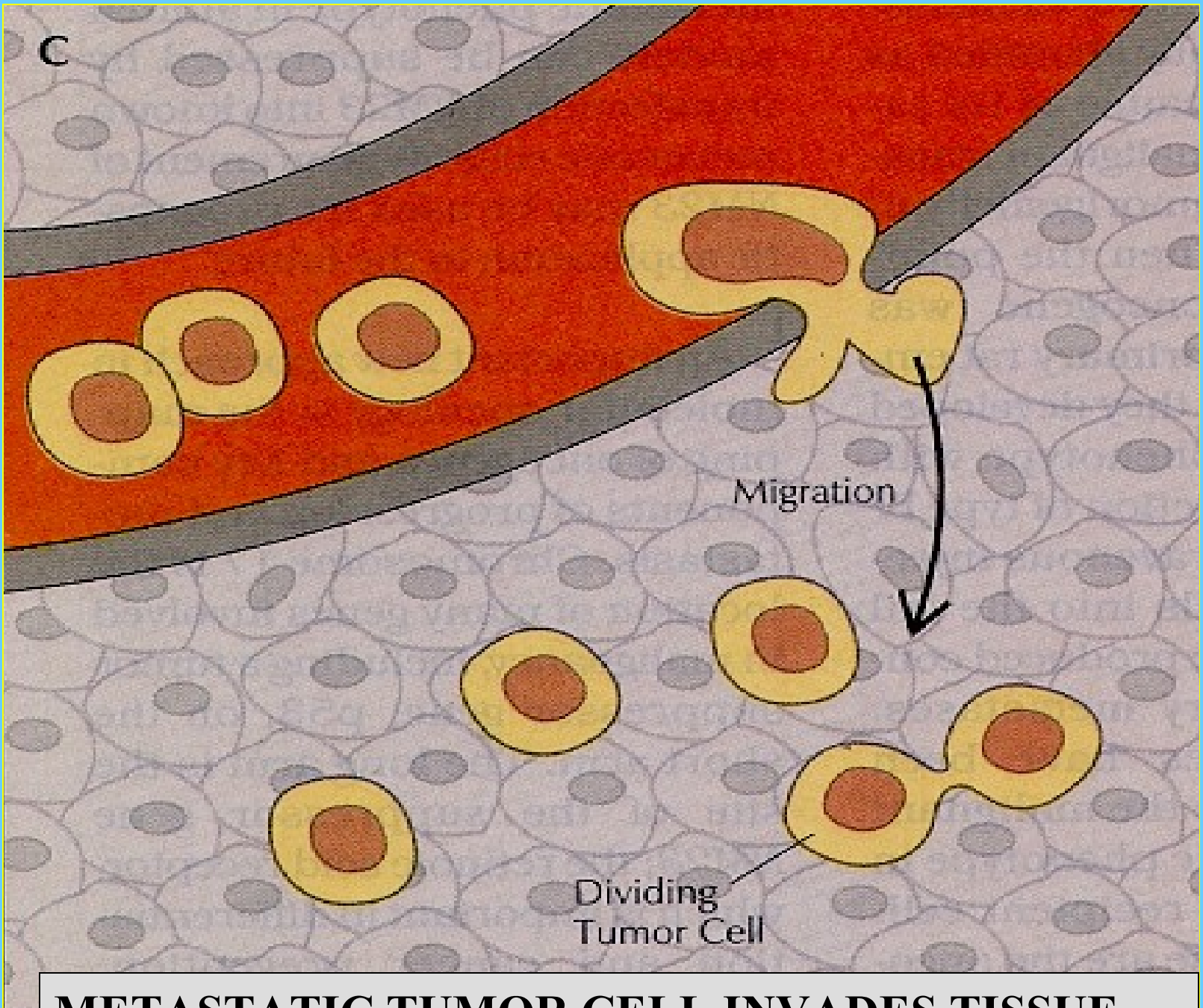
**TUMOR CELL ADHERES TO EP/endothel BM Matrix**

**B**

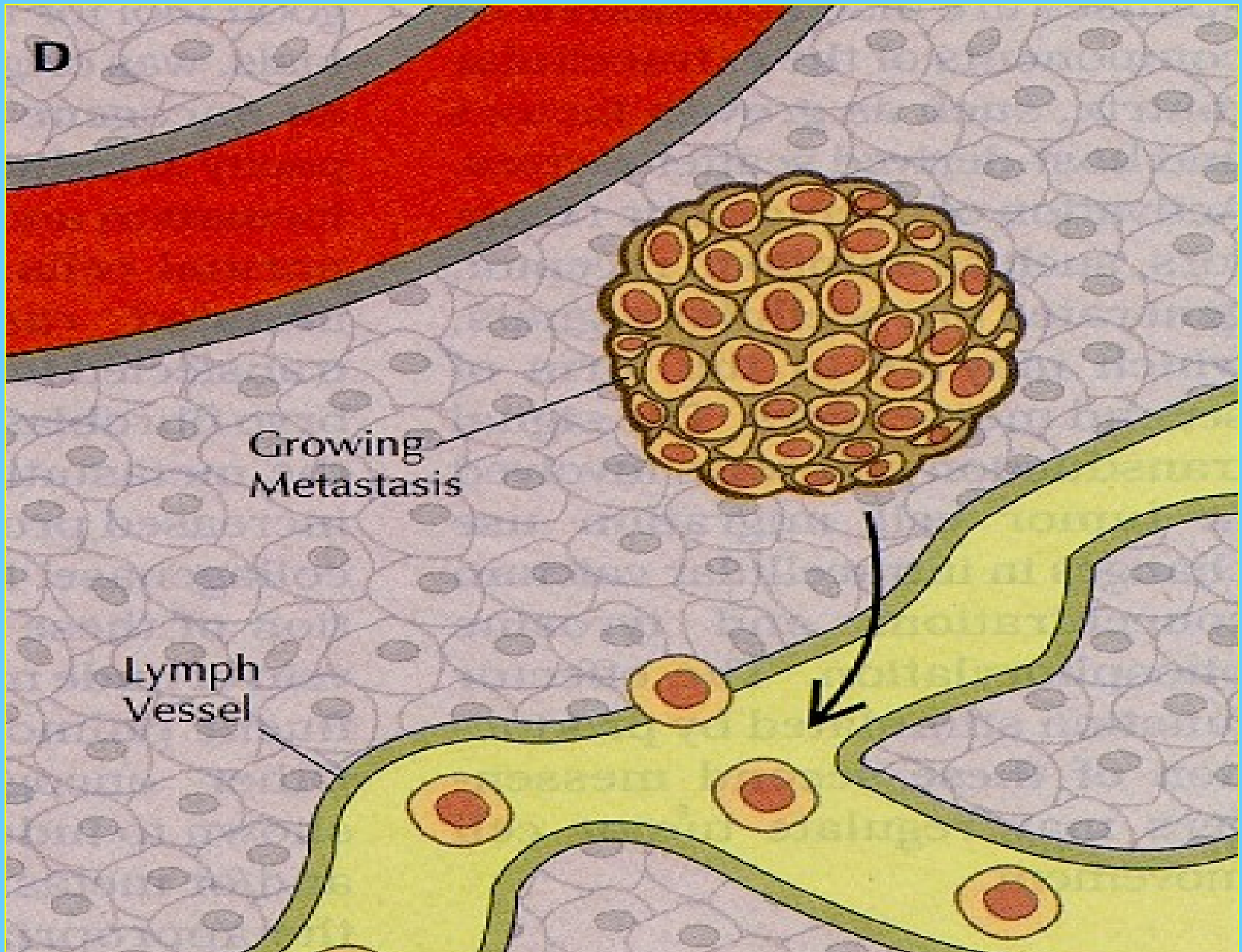
# TUMOR INVADES MATRIX



**Collagenases,  
Cathepsins,  
Plasminogen  
Activators** (Cysteine proteinase)

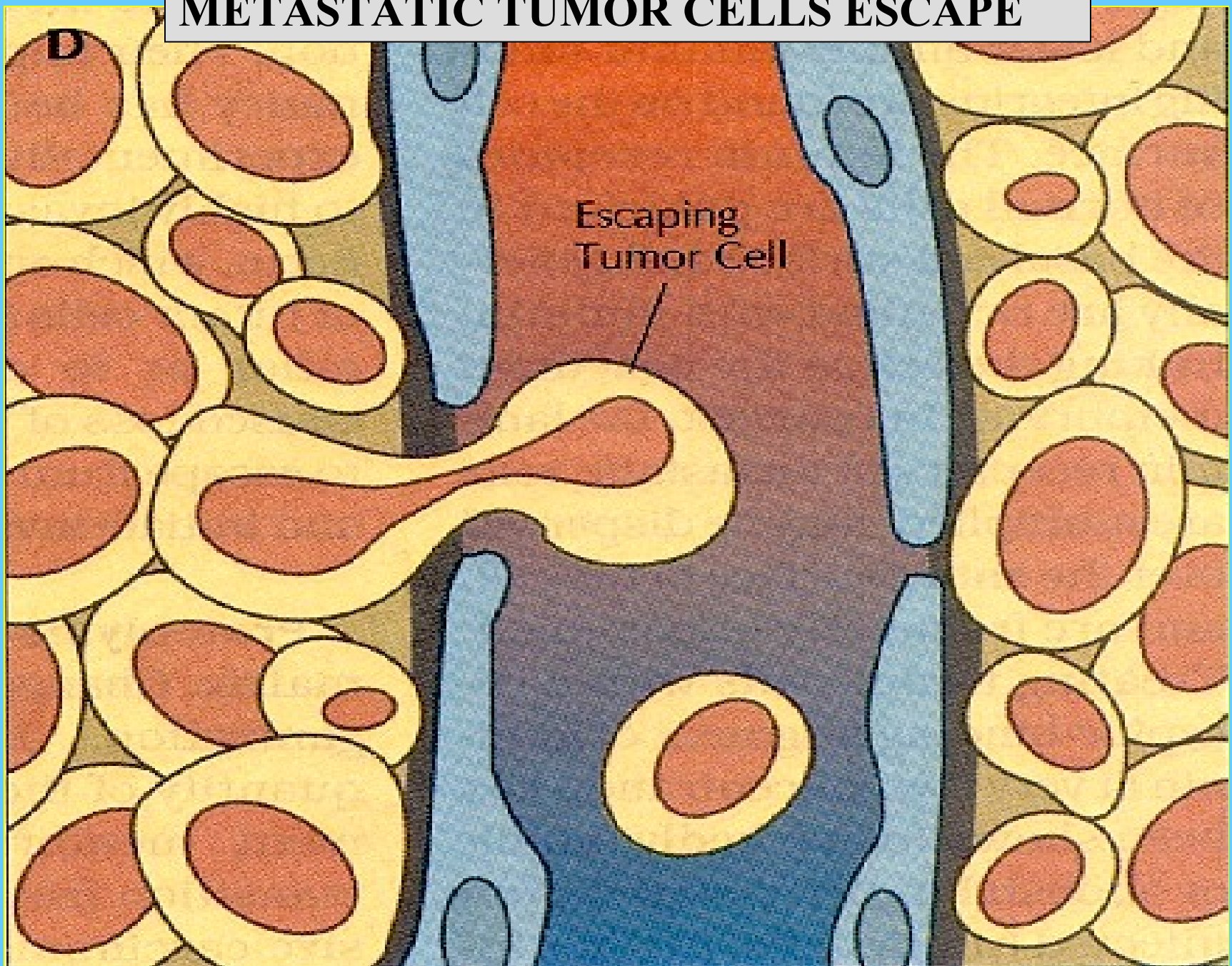


**METASTATIC TUMOR CELL INVADES TISSUE**

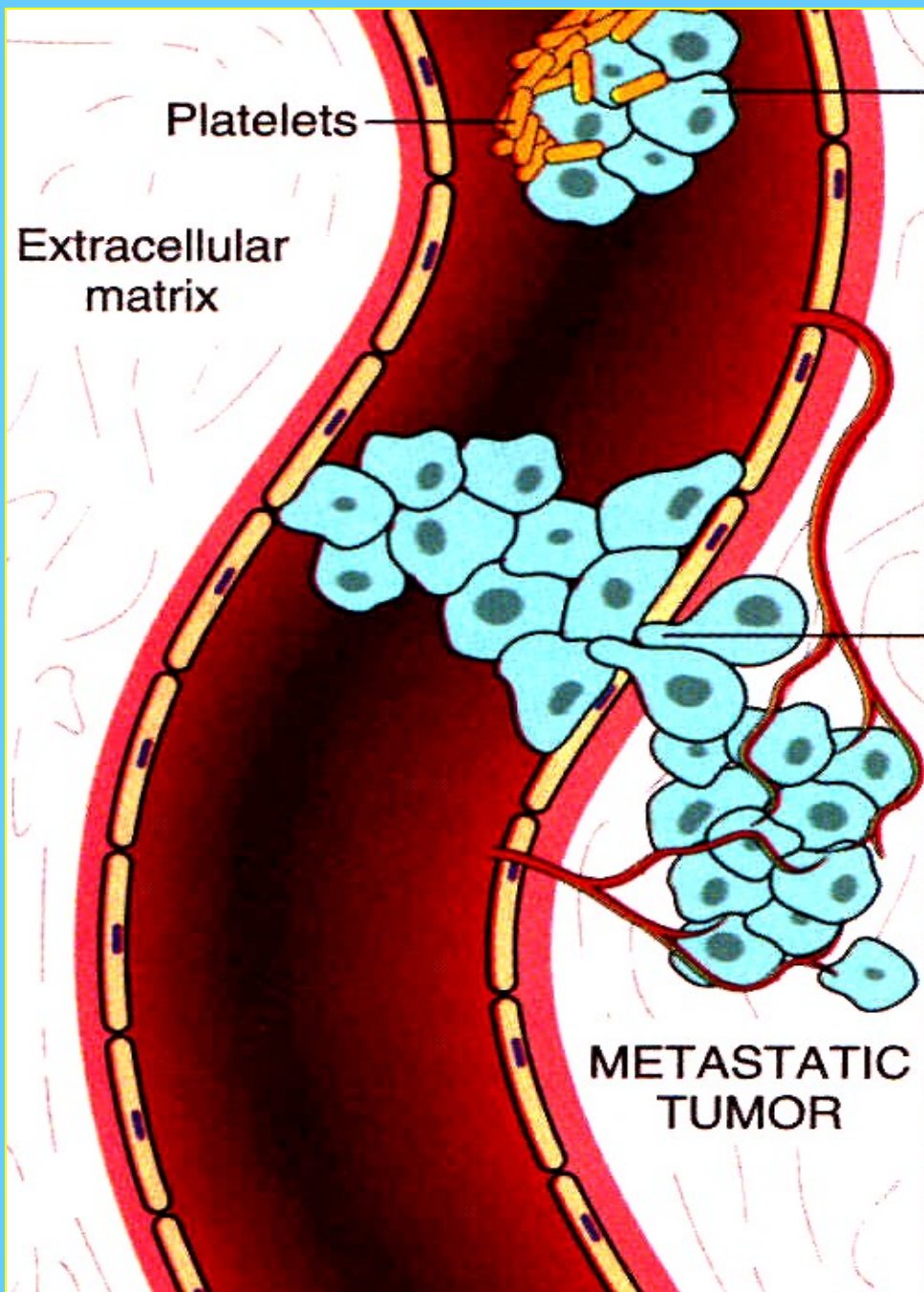


**METASTATIC TUMOR SPREADS TO LYMPHATICS**

# METASTATIC TUMOR CELLS ESCAPE







Tumor cell embolus

Adhesion to basement membrane

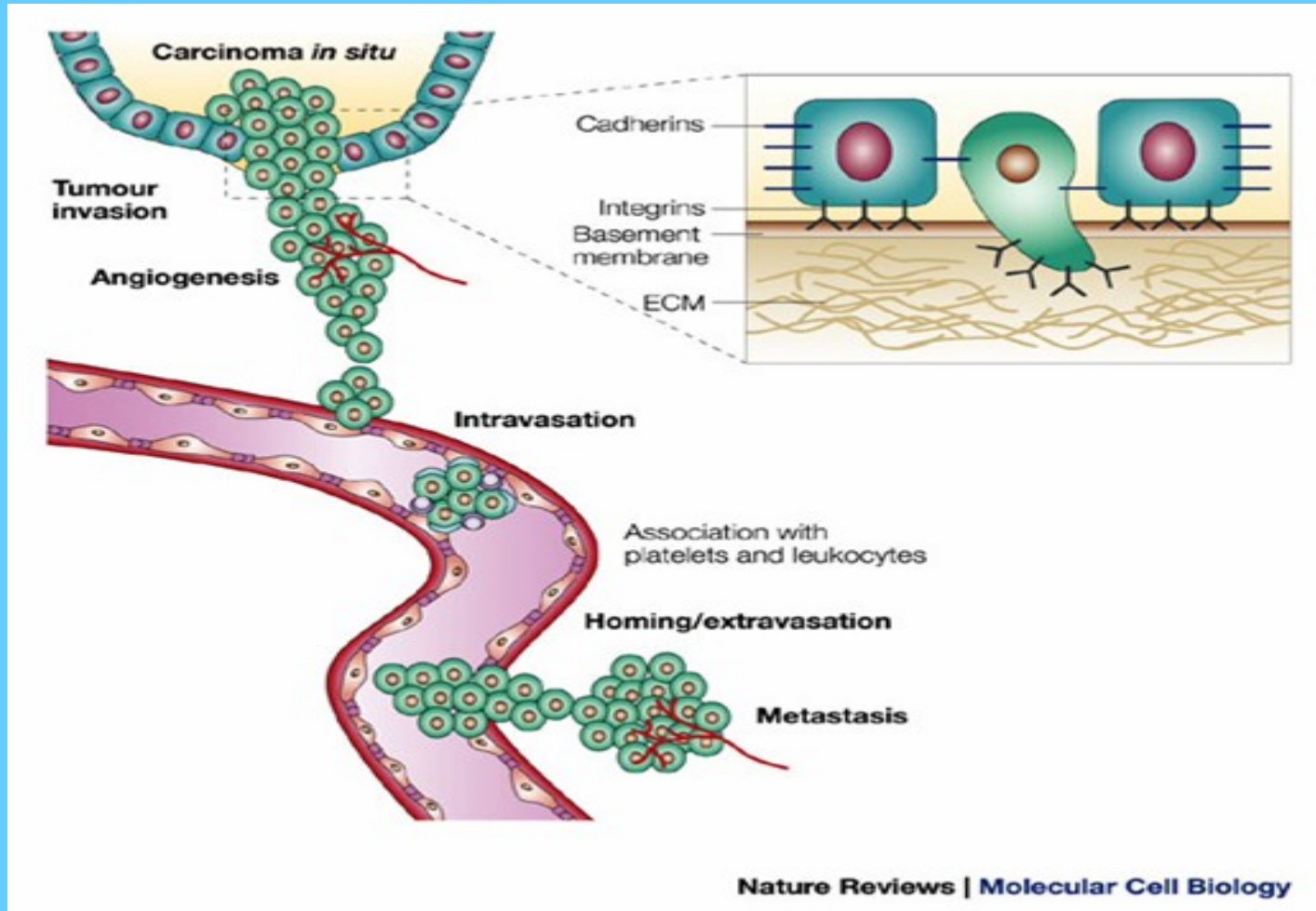
Extravasation

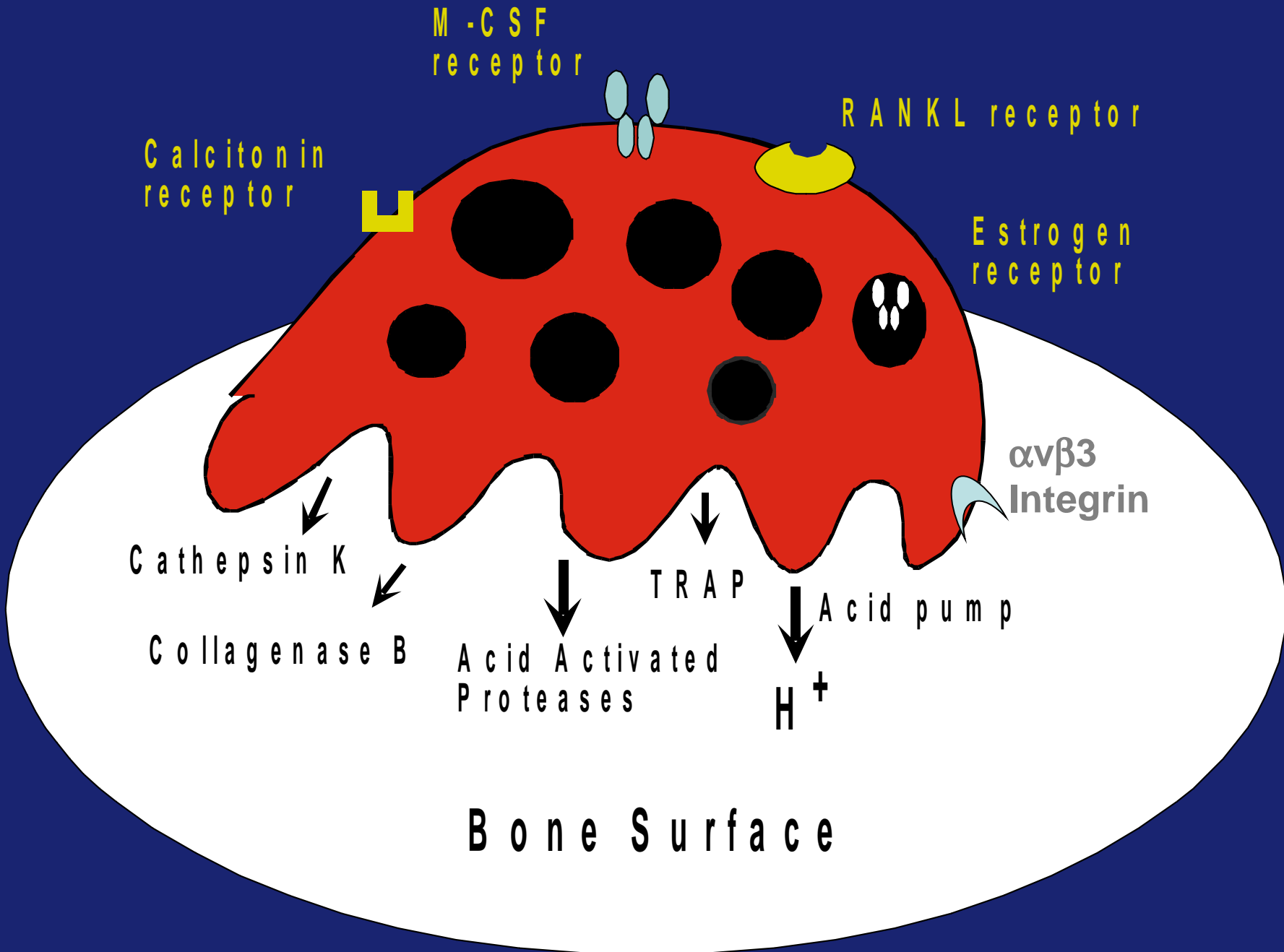
Metastatic deposit

Angiogenesis

Growth

# Cell adhesion and metastasis





M - C S F  
receptor

C a l c i t o n i n  
r e c e p t o r

R A N K L receptor

E s t r o g e n  
r e c e p t o r

αvβ3  
I n t e g r i n

C a t h e p s i n K

C o l l a g e n a s e B

T R A P

A c i d A c t i v a t e d  
P r o t e a s e s

A c i d p u m p

H<sup>+</sup>

B o n e S u r f a c e