Cancer Biology

Lecture 2

Fall 2018

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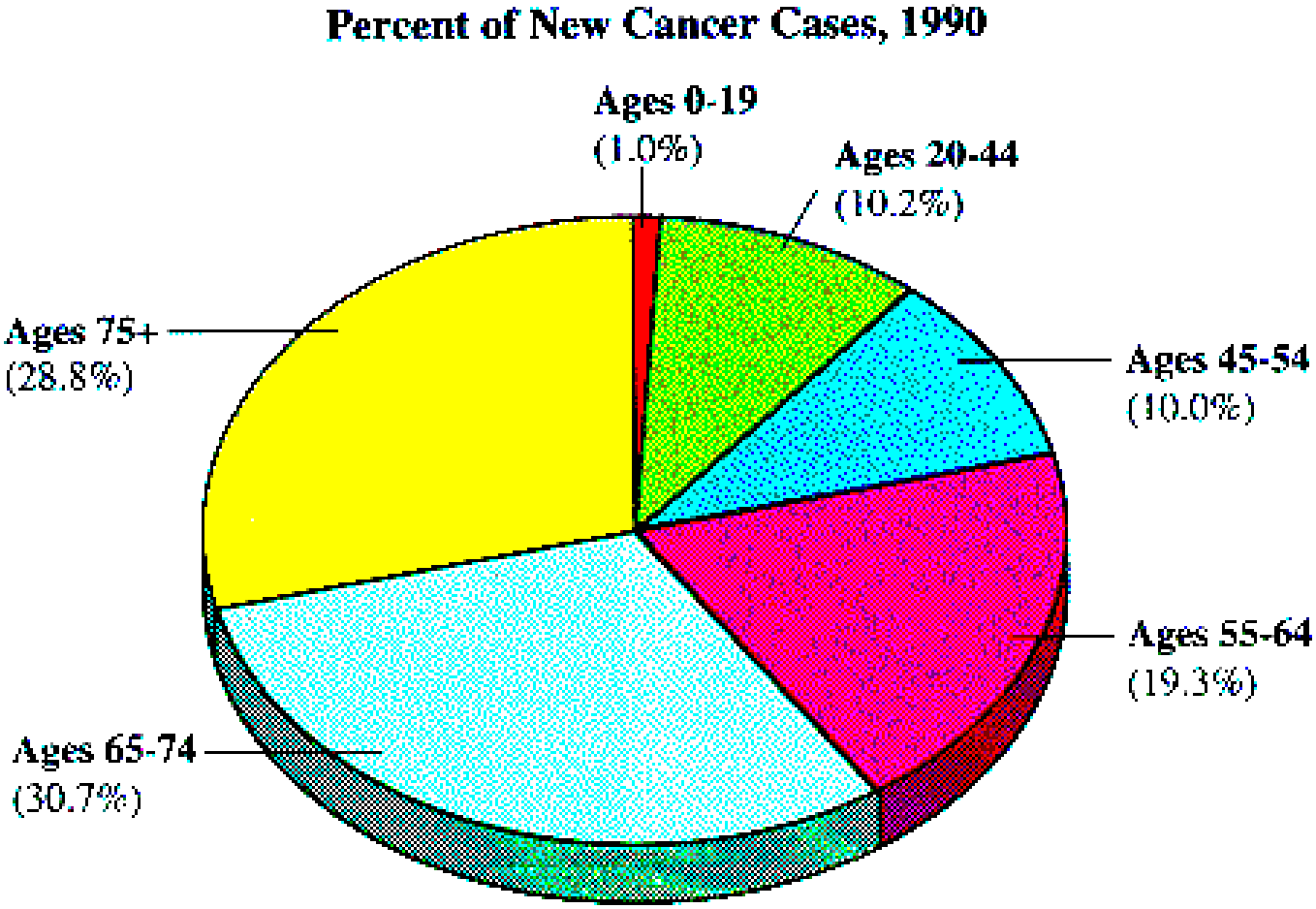
Cancer Incidence by Age

The contrast in cancer incidence by age is striking. Americans aged 65 and older face 10 times the risk of developing cancer compared with those under 65. The near-doubling in the annual number of new cancer cases for all ages – from an estimated 625,000 cases in 1970 to 1,170,000 cases in 1993 – is largely due to the increasing population size and especially the disproportionate increase in the older population.



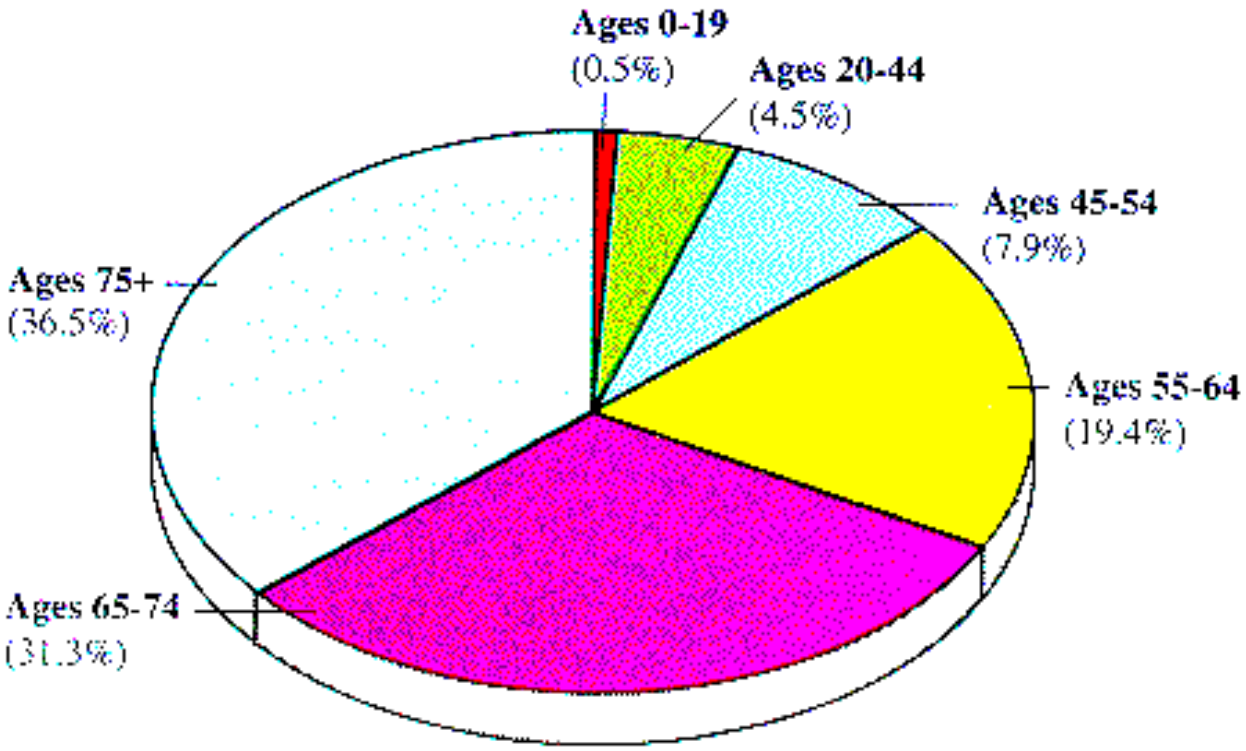
From JNCI, 1994

AgeStart.pcx

Cancer Mortality by Age

Americans age 65 and older account for about 67% of all cancer deaths nationwide. Mortality rates for all cancer sites combined (1986-90) were 75.4 per 100,000 persons under 65 and 1058.3 per 100,000 persons 65 and older. From 1973 to 1990, mortality rates decreased 0.2% per year for those under 65 and increased 0.9% per year for those 65 and older. The increase in the older group has been largely due to an increase in lung cancer deaths, although recent lung cancer mortality rates have leveled off among men.

Percent of All Cancer Deaths, 1990



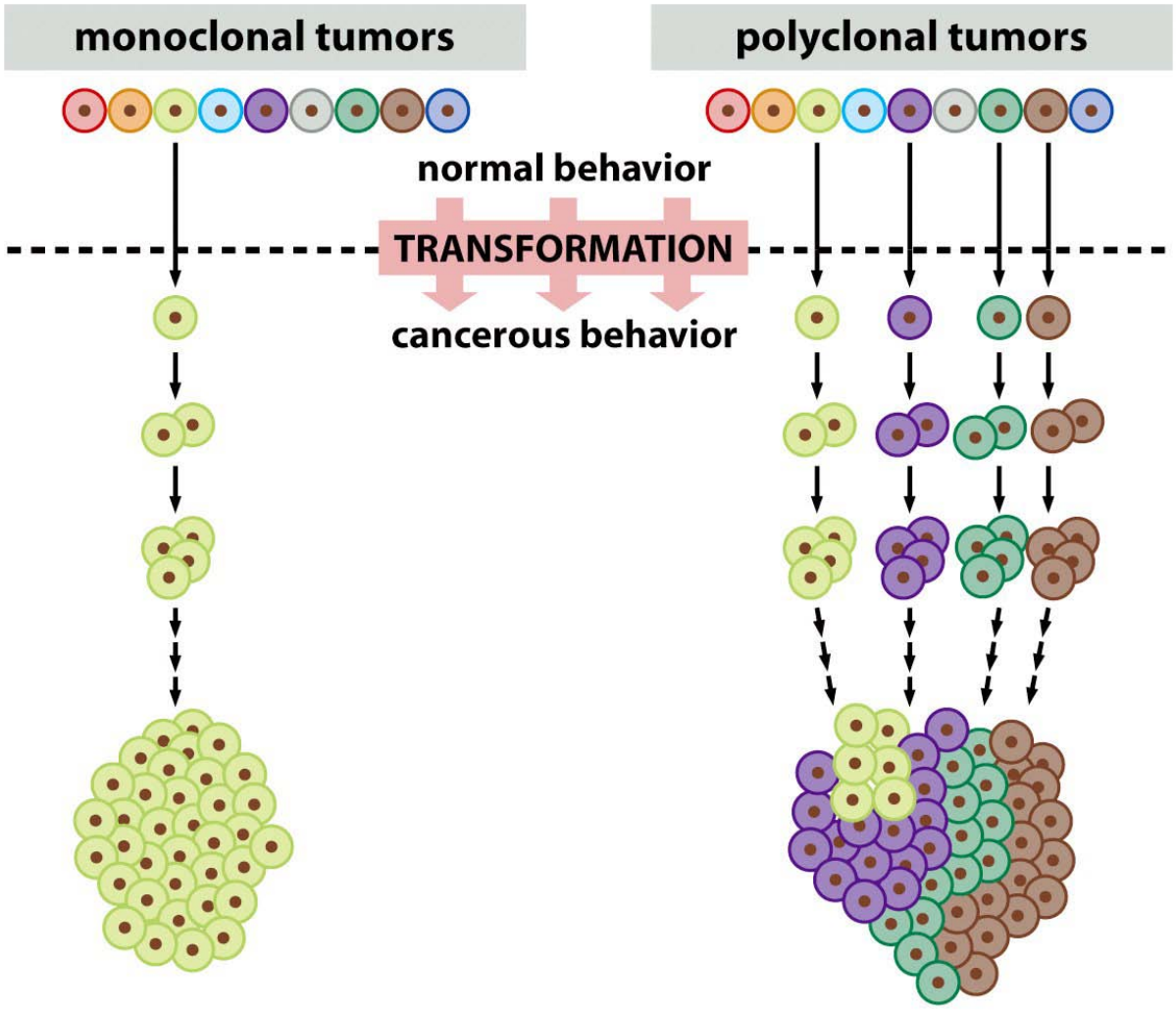
FRom JNCI, 1994

AgeKill.pcx

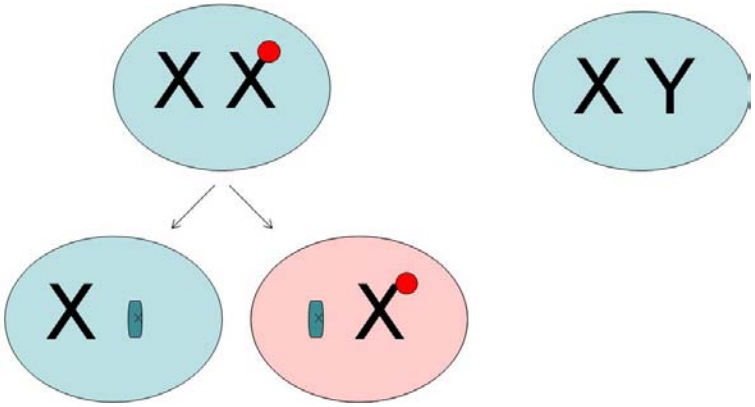
Learning objectives

- Cancer origin: Monoclonal
- Multistep carcinogenesis

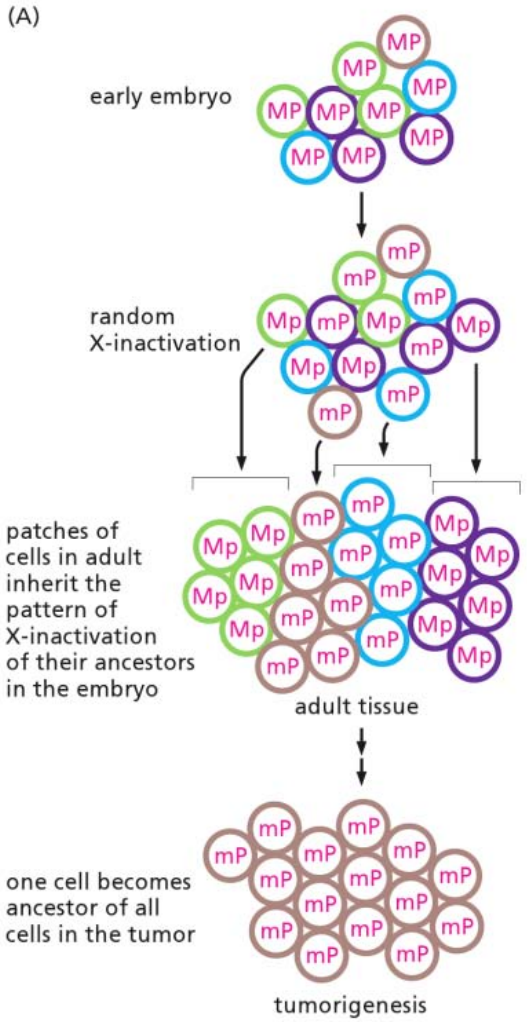
Origin of tumor cell

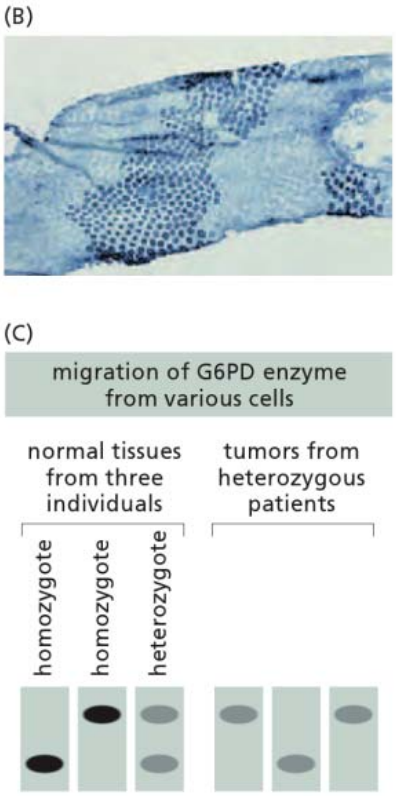


G6PD

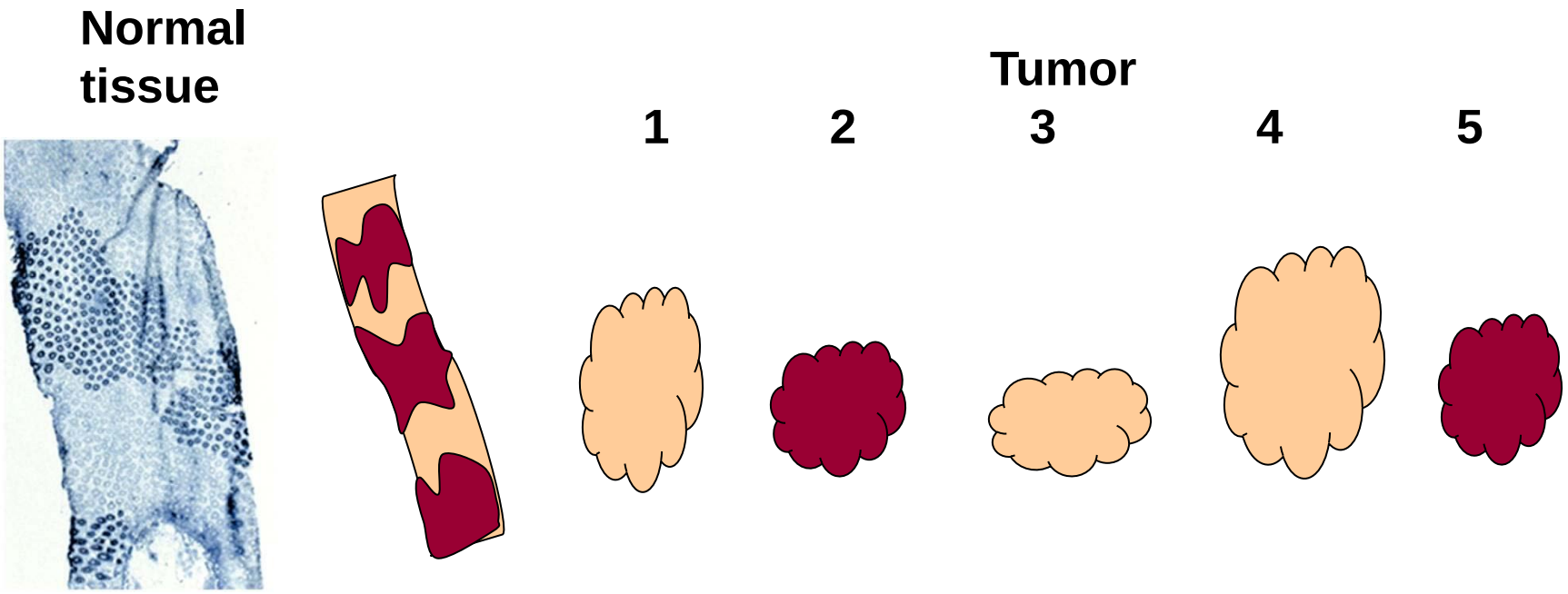


1965
Glucose-6-phosphate dehydrogenase G6PD
30% African American women are heterozygous with a thermal stable form.





Tumors are monoclonal



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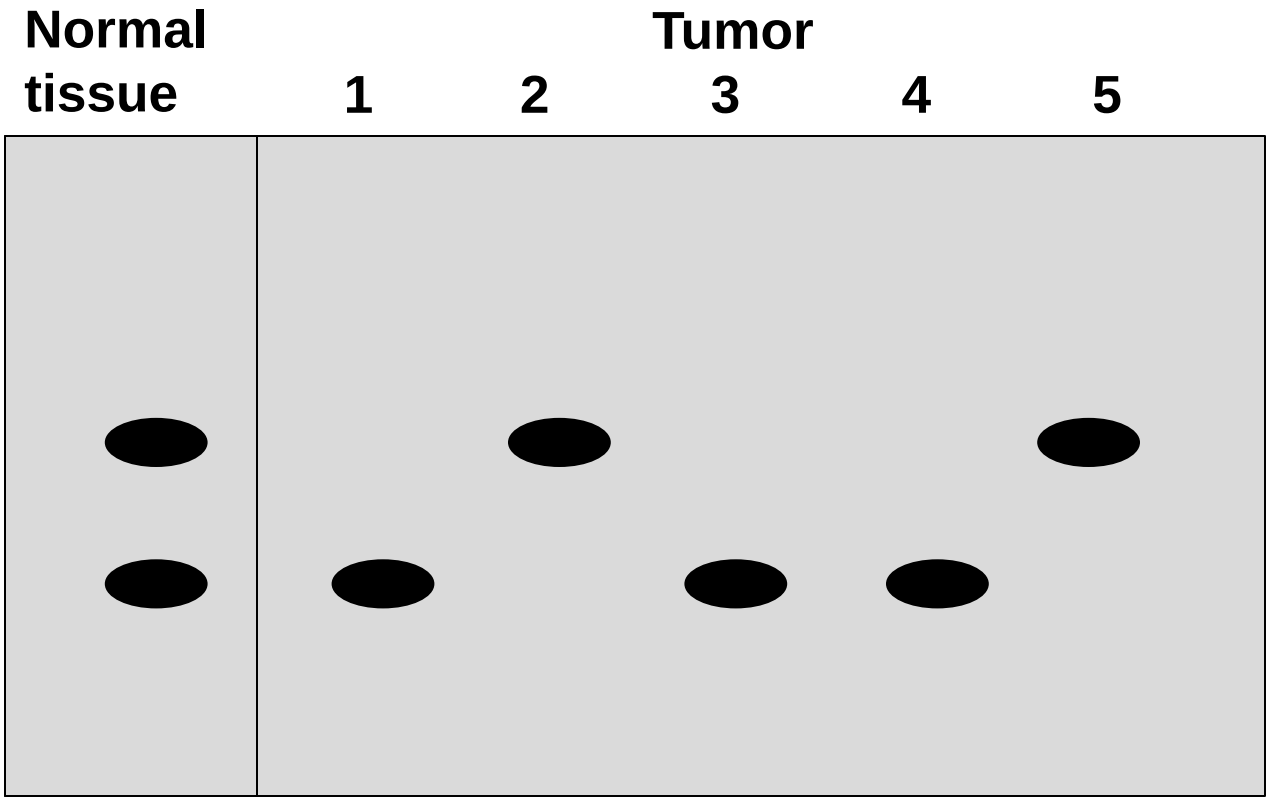
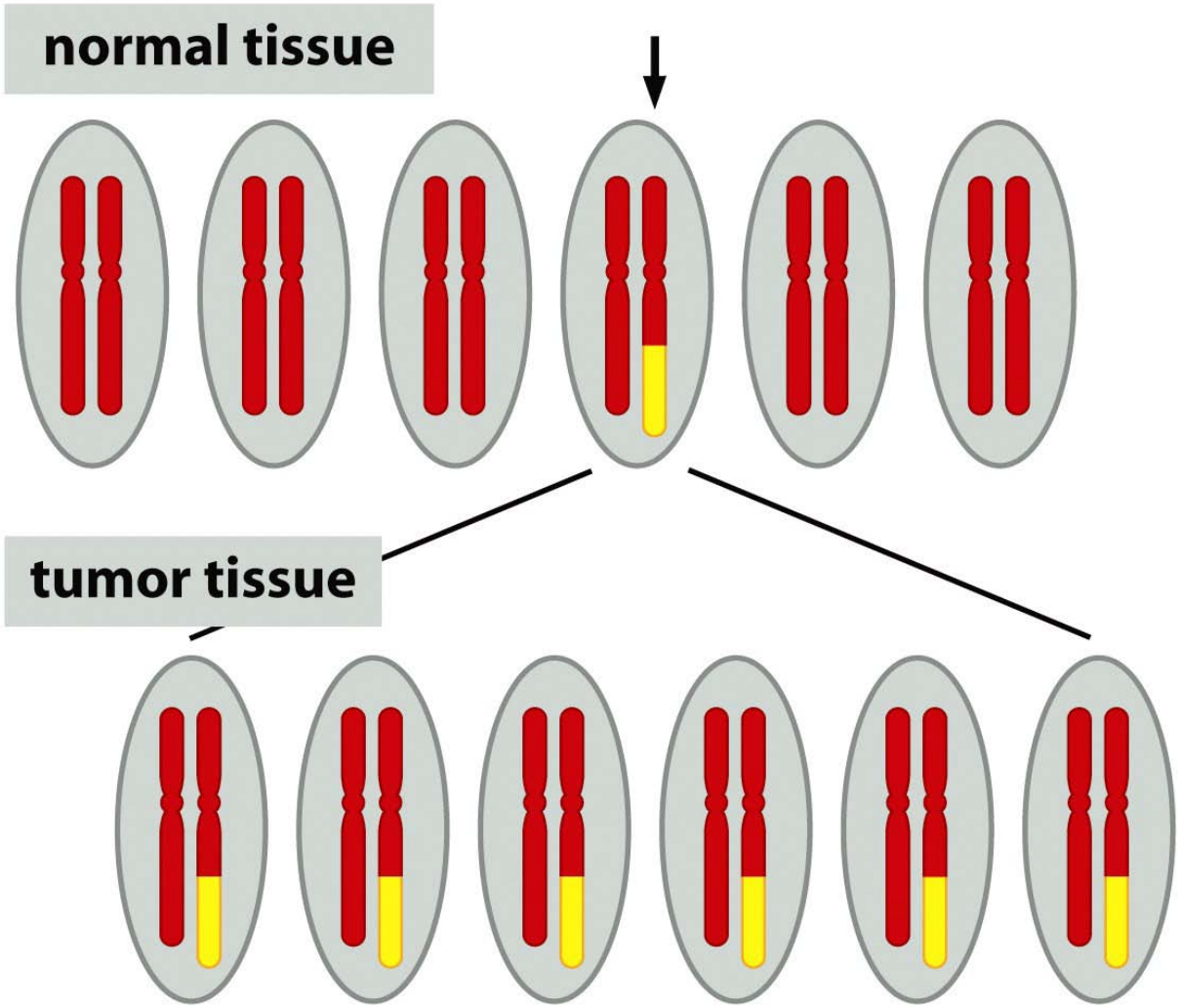


Electrophoresis: Migration of G6PD on starch gel. 1974

2. Chromosomal aberration

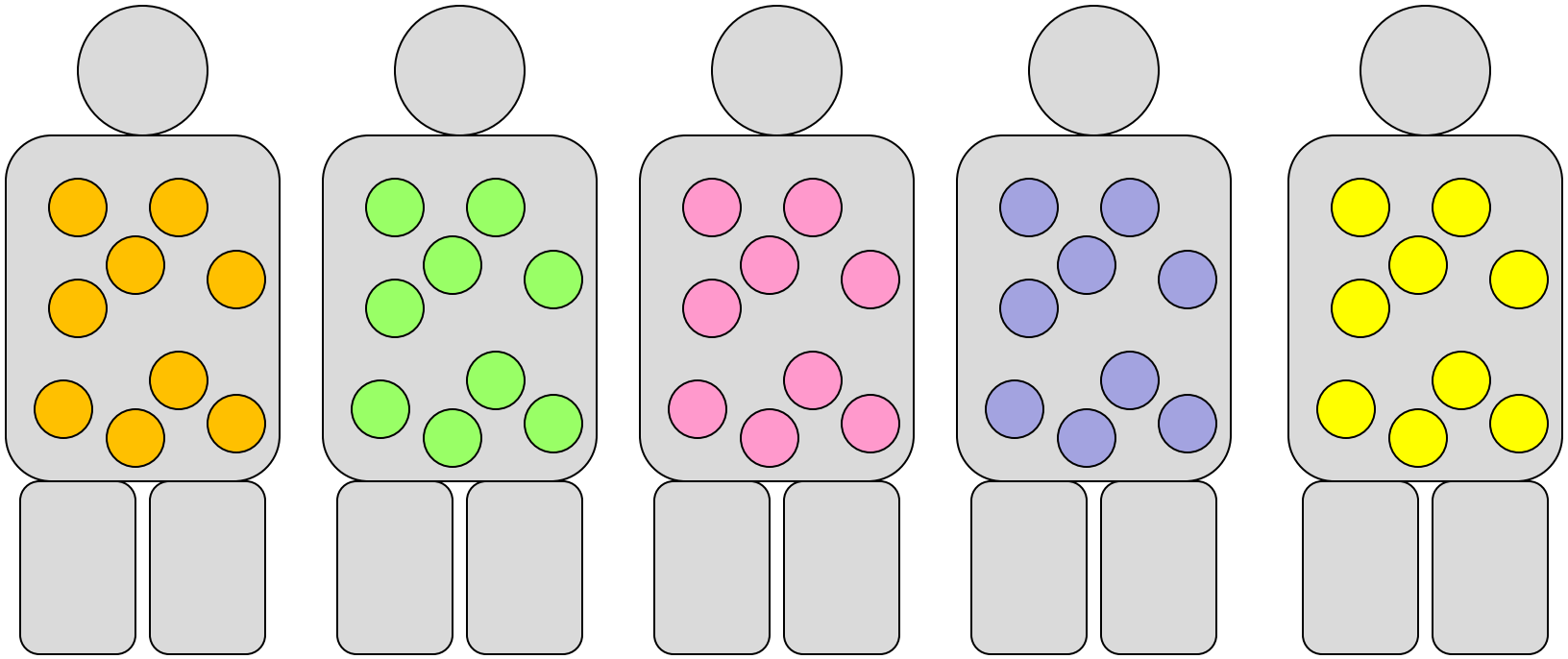


3. Leukemia – Myelomas（骨髓瘤）

- Precursors of plasma cells （浆细胞）
- Secrete antibody, $10^{9\text{-}11}$ different kinds of Abs
  - Polyclonal origin → Many Abs
  - Monoclonal origin → 1 Ab

Origin of tumor cell: monoclonal

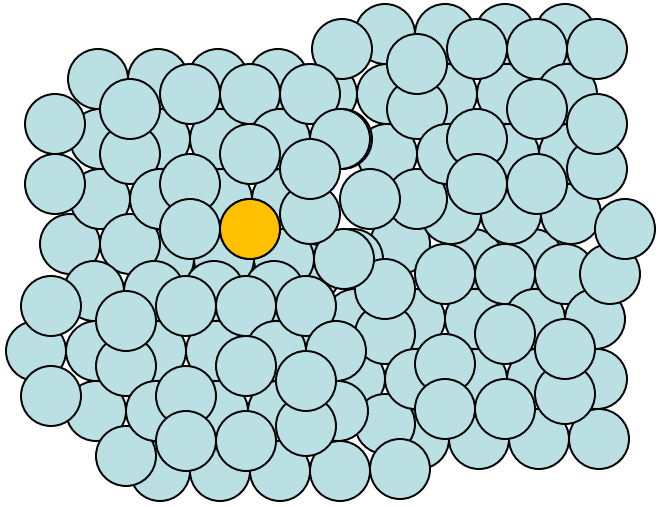
Ab producing cells **$10^{9\text{-}11}$ different kinds**

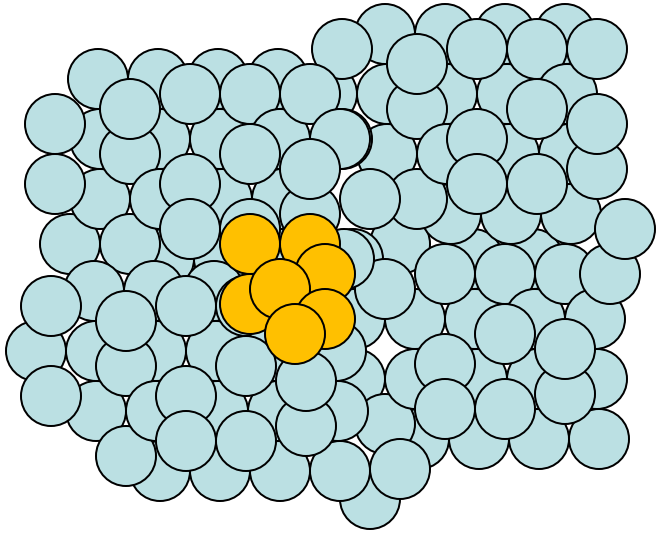


Significance of monoclonal origin

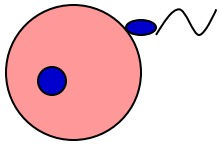
Human body: $>10^{13}$ cells

Life time: $>10^{16}$ cells (renewal and repair)





Accuracy of replication



1 cell → more than 10^{16} cells

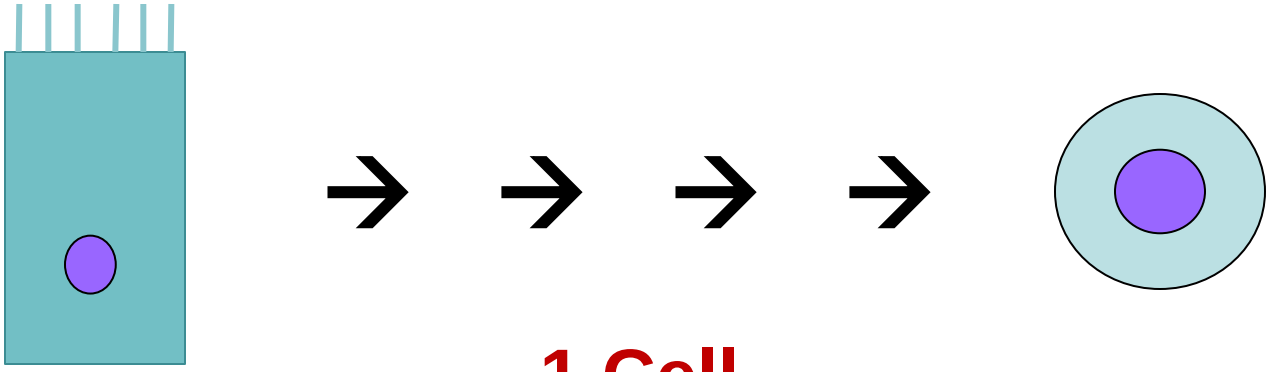
Human genome

= 3×10^9 nucleotides (letters) haploid

6×10^9 diploid

Need to copy ~ 10^{26} letters

Origin of cancer cell

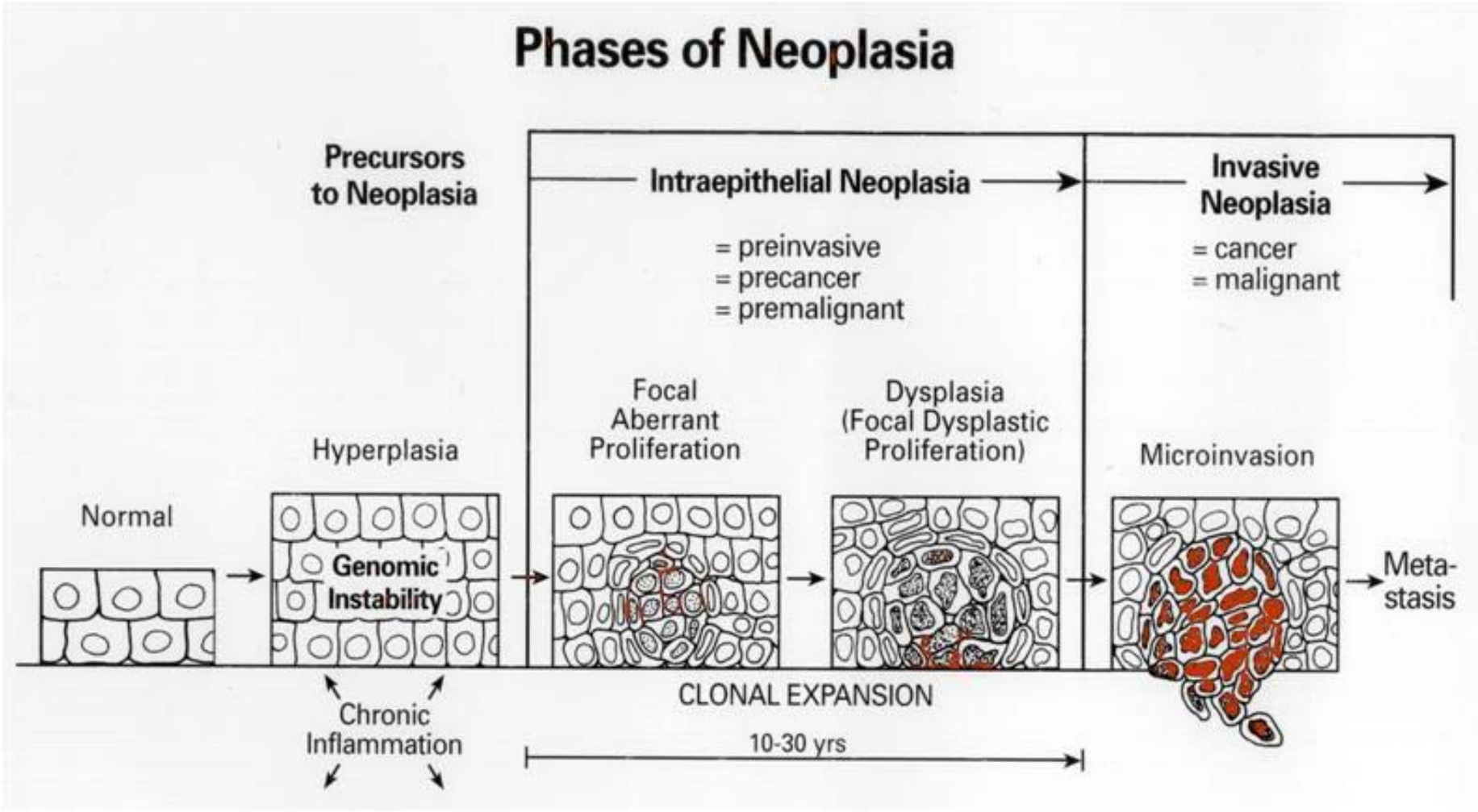


1 Cell

Gene

Environment

Sources of error/damage



jamesbacus.com/ Images/WS_Photo_4.JPG

Development of cancer

- **Normal cells**

  → → → → cancer cells?

  the concept of “multistep carcinogenesis”

- Histological observation

  Microscopic features of tumor cells

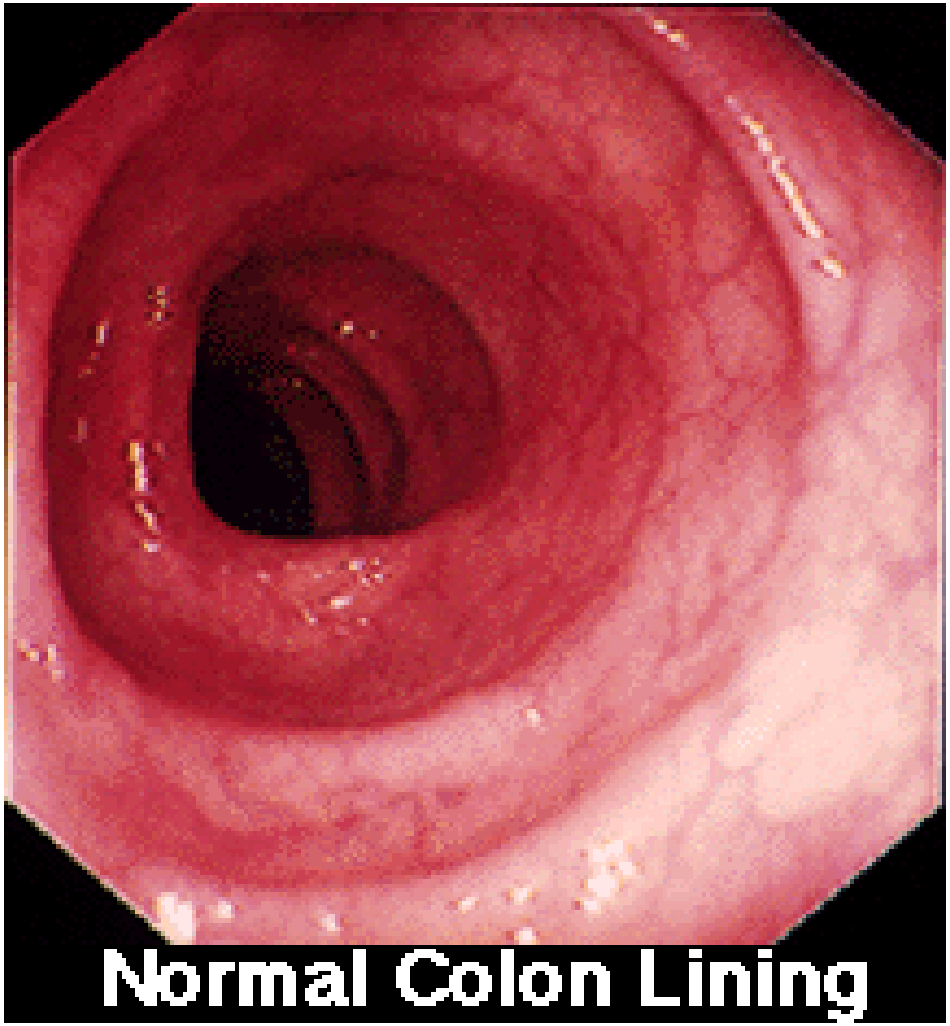
  ⇕

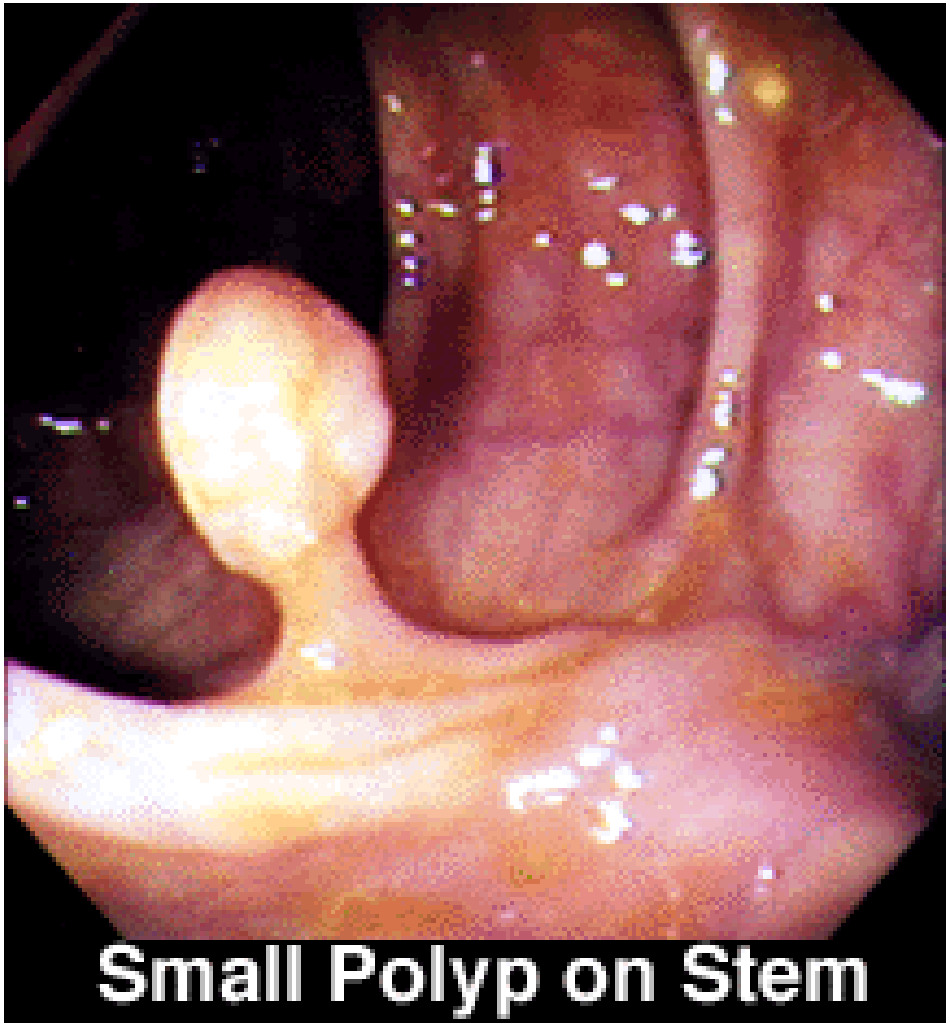
  Molecular mechanism

  ⇕

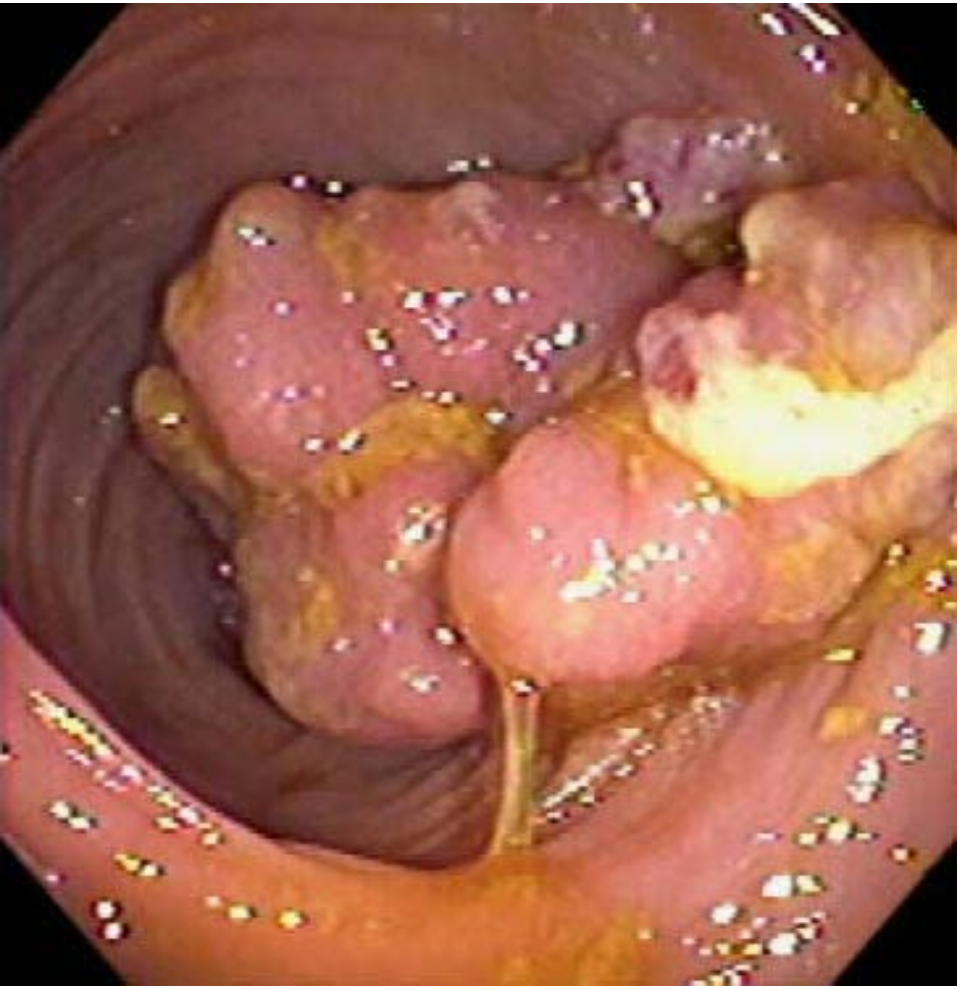
  Therapy

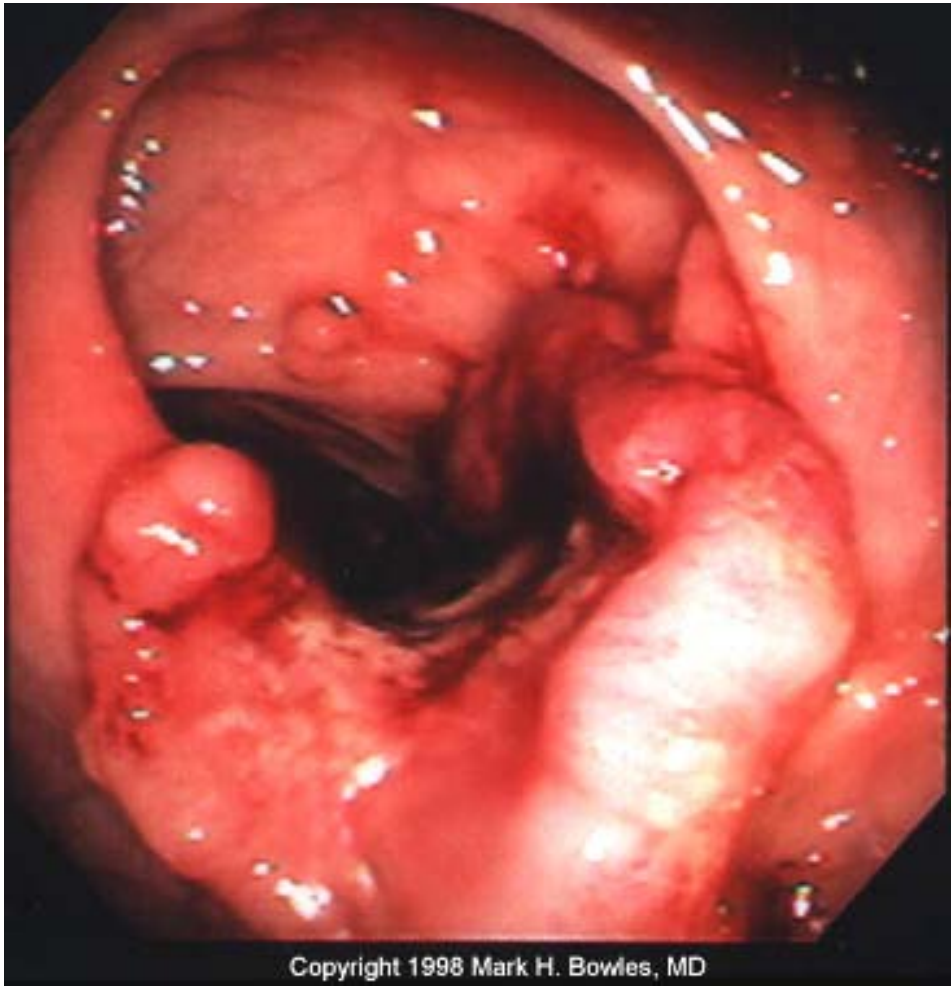
Colon cancer



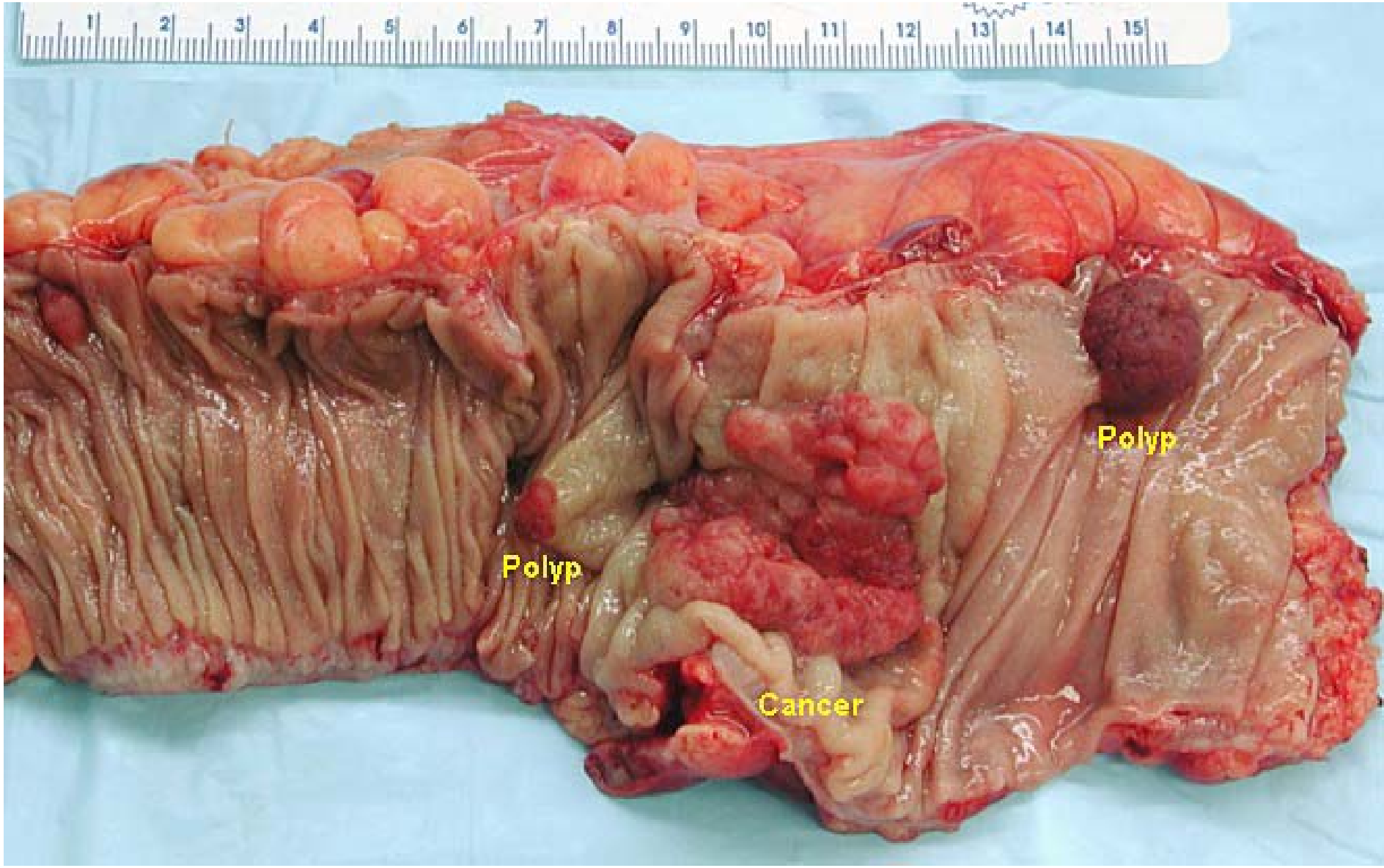


Colon Cancer



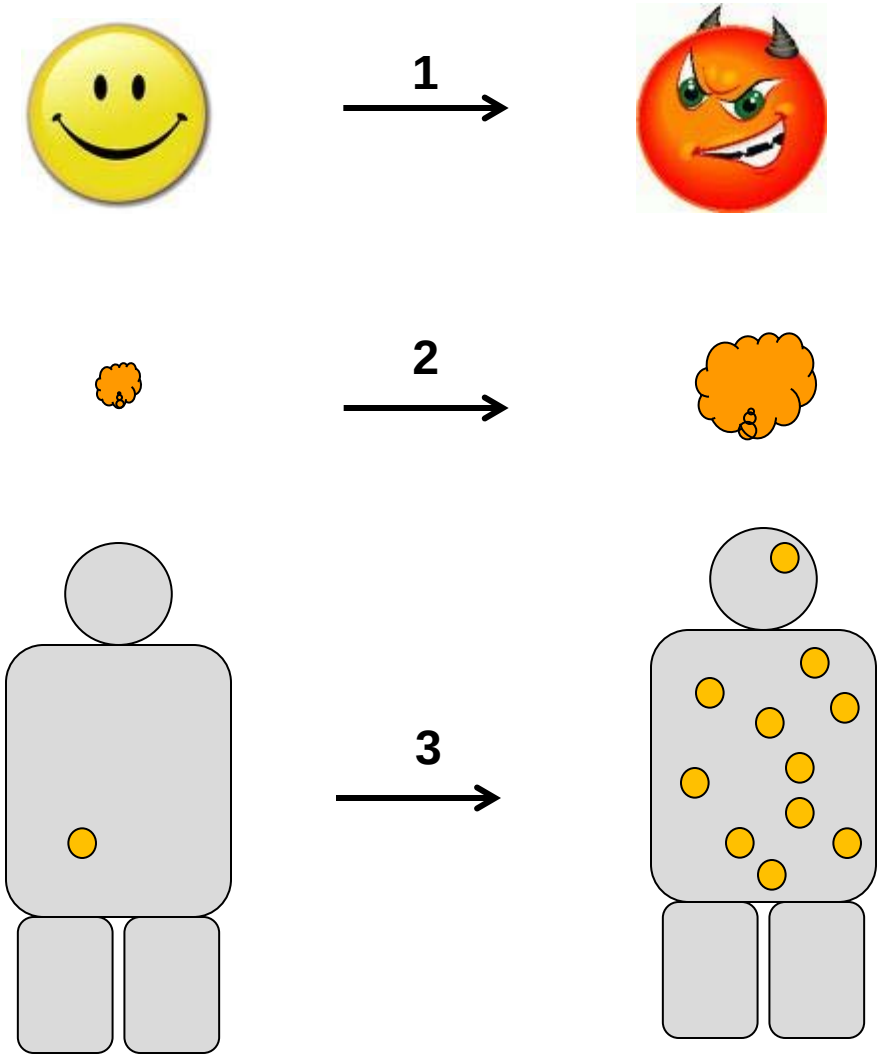


Colon cancer



http://www.nitisurgical.com/colon_cancer_pictures.htm

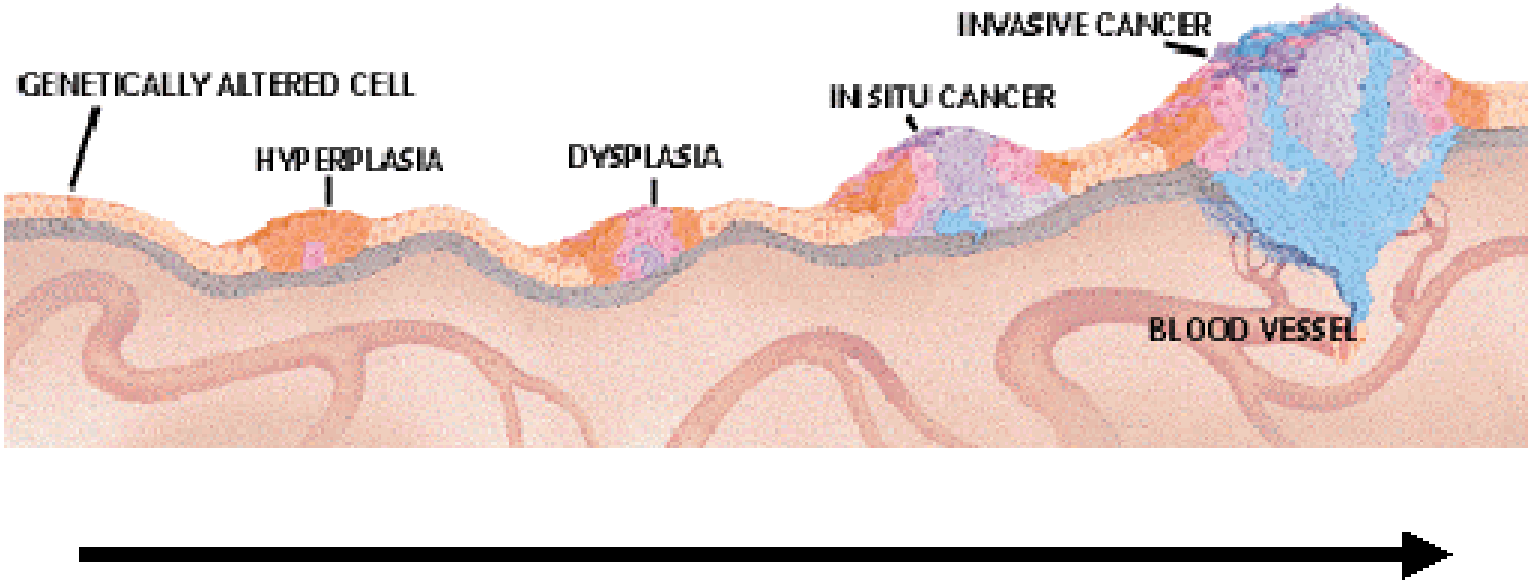
Cancer development



Cancer development

Multistep Carcinogenesis

How cells become cancerous:



the concept of “multistep carcinogenesis”

How cells become cancerous

- Normal cell
- Immortalized cell
- Transformed cell
- Metastatic cells

Cell growth homeostatis in a multicellular animal. What's normal?

To exist in an orderly, developmentally regulated tissue, cells generally have some common characteristics:

- **Limited proliferation capacity:** somatic cells are subject to the Hayflick limit (Hayflick, *Exp. Cell Res.* **37** 614 (1965) and are limited to 40-50 divisions before undergoing senescence and death.
- **Anchorage dependence:** proliferation requires binding via integrins to extracellular matrix **(ECM)** components. Specific integrins recognize specific ECM molecules.
- **Contact inhibition:** contact with **like** cell types inhibits cell movement and proliferation, quiescent G0 cells, monolayers in cell culture. Contact with **unlike** cells allows motility and hence spontaneous cell sorting.
- **Growth factor dependence:** proliferation depends on availability of tissue-type specific growth factors. In many cases factor withdrawal leads to apoptosis. Growth in serum-rich or conditioned media (autocrine factors, plating density dependence of growth).

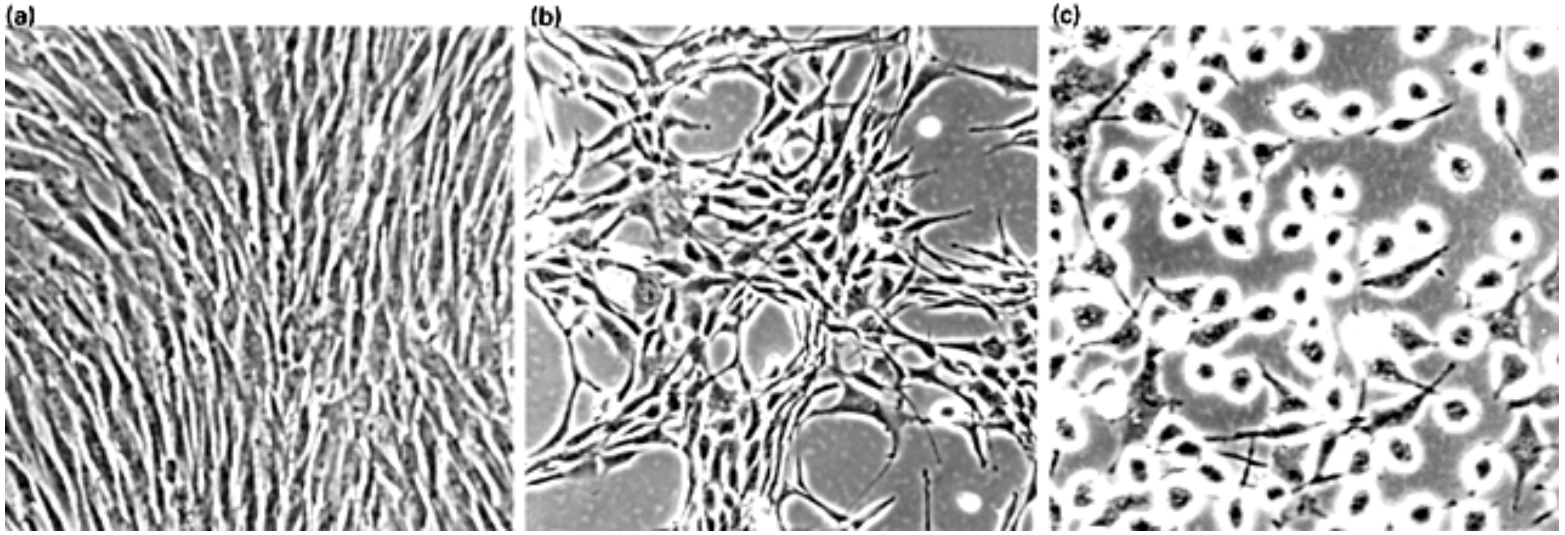
Transformation

- **Immortalization and aneuploidy:** survival and continuous growth beyond normal limits involves changes at the telomere that frequently result in major chromosomal rearrangements.
- **Partial or complete loss of growth factor dependence:** growth on less rich serum, or at lower initial cell density.
- **Loss of contact inhibition:** overgrowth of monolayers.
- **Loss of anchorage requirement:** growth on soft agar or in suspension.

Tumorigenicity is not solely loss of proliferation control; loss of contact and anchorage dependence leads to the motility and invasiveness of malignant tumor cells.

Normal

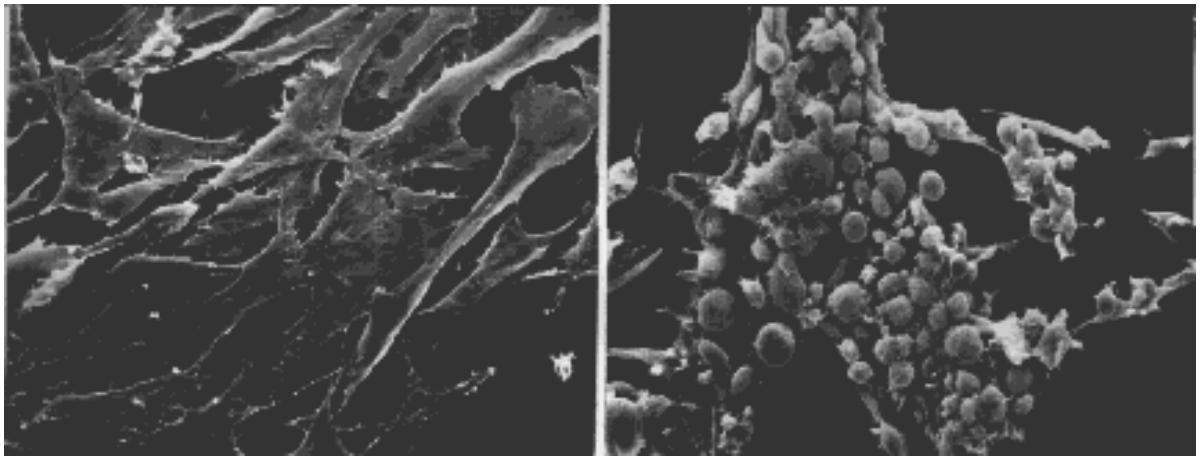
Transformed



contact-inhibited

pile up, rounded

Transformed 3T3 cells

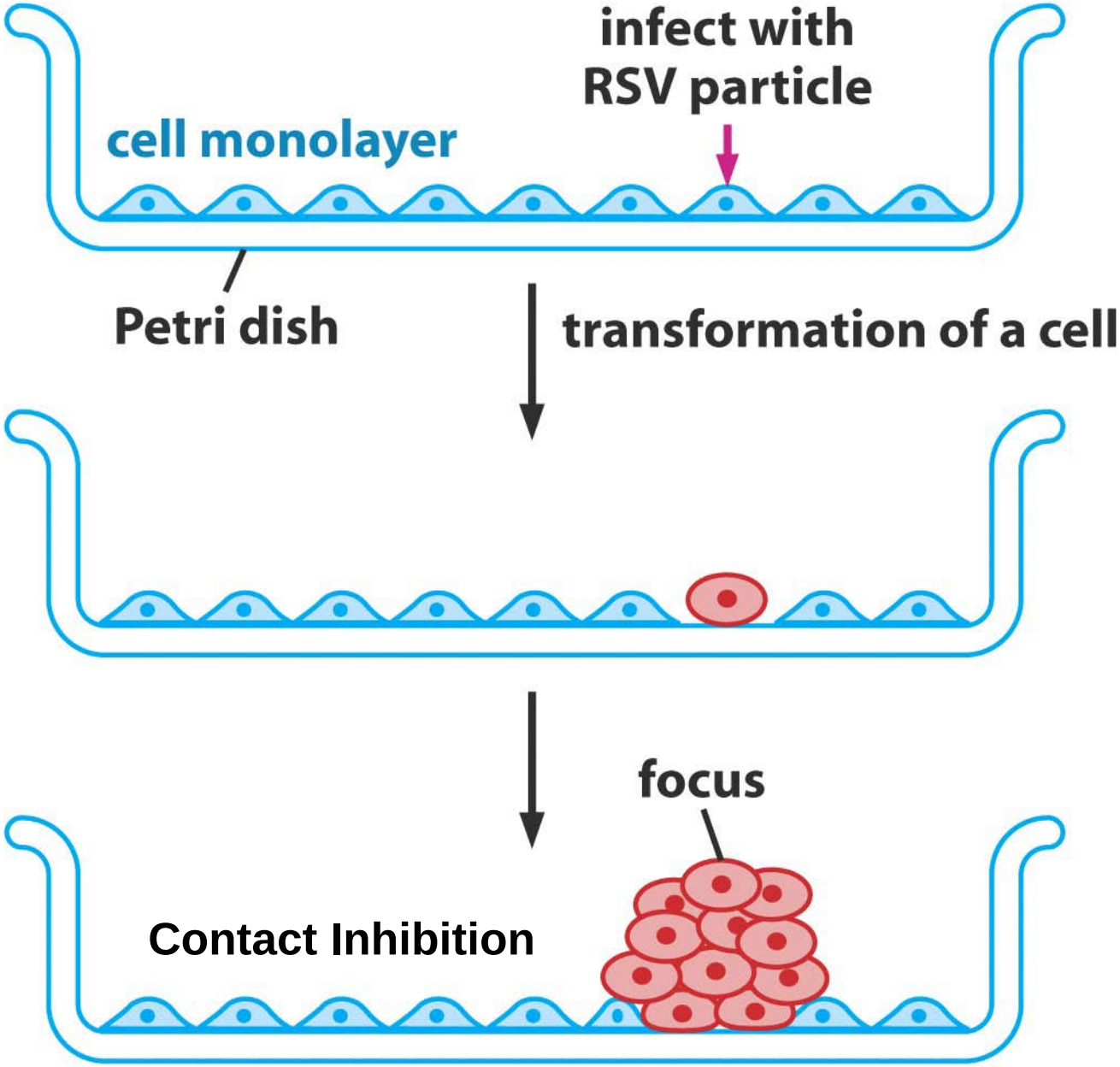


Growth characteristics of cells in culture (parallels what happens in vivo)

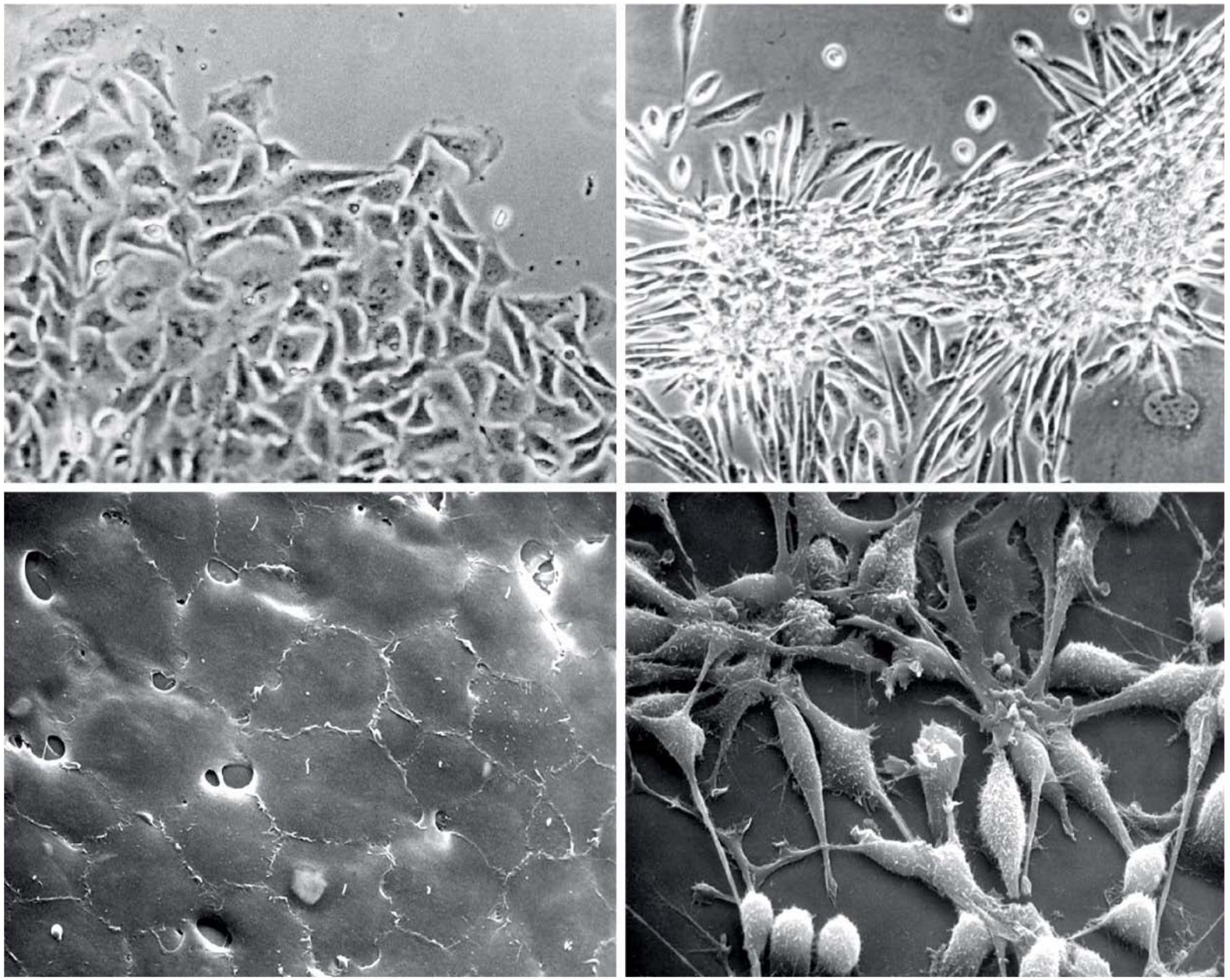
- **Normal primary cells:**
  survive only a relatively short time in culture (days to weeks)
- **Immortalized (established) cells:**
  - **unlimited replicative potential**
  - **anchorage dependence (prefer to adhere to culture plate)**
  - **serum dependence (require growth factors)**
  - **contact inhibited (stop growing when cells are confluent)**
- **Transformed cells:**
  - **less dependent on substratum**
  - **less dependent on growth factors**
  - **not contact inhibited**
  - **form tumors (tumorigenic) when injected into a host, but will not necessarily kill the host**
- **Metastatic cells:**
- **fully transformed cells that have the ability to migrate and invade tissues;**
  will establish new colonies and kill the host

What is cancer?
at cellular level…

- **Properties of transformed cells**


infect with
RSV particle
cell monolayer
Petri dish
transformation of a cell
focus
Contact Inhibition

+RSV



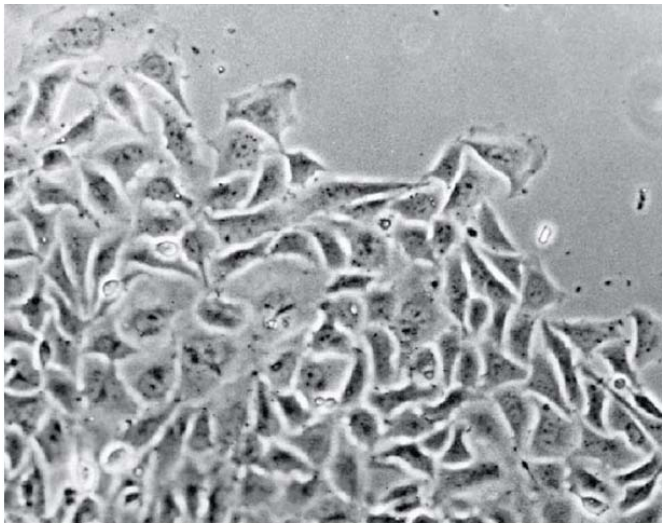
Transformed cells

- Change in cell shape
- Loss of contact inhibition
- Proliferate indefinitely

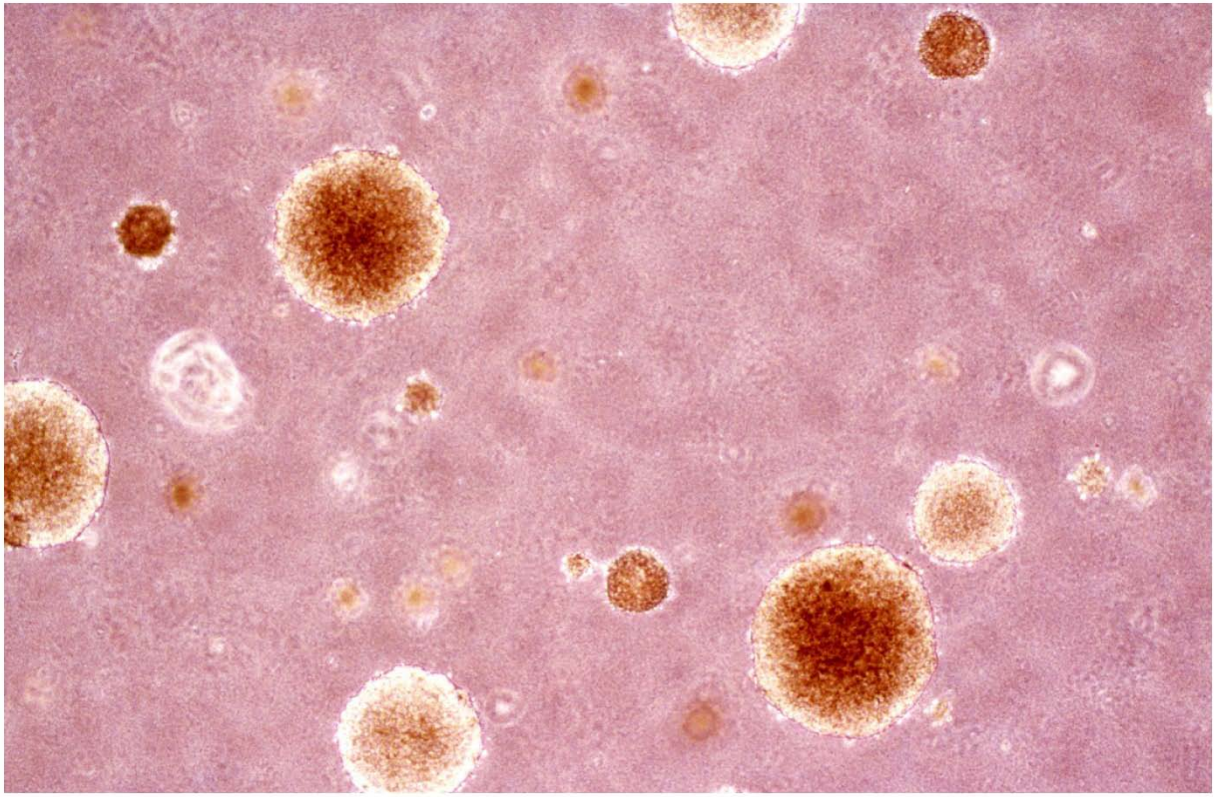
- → Your evaluation of the transformed cells:
  - Neoplasia
  - Metastatic tumor

Assay 1 for Transformed cells

- Ability to grow without attachment



Foci formation on soft agar dish



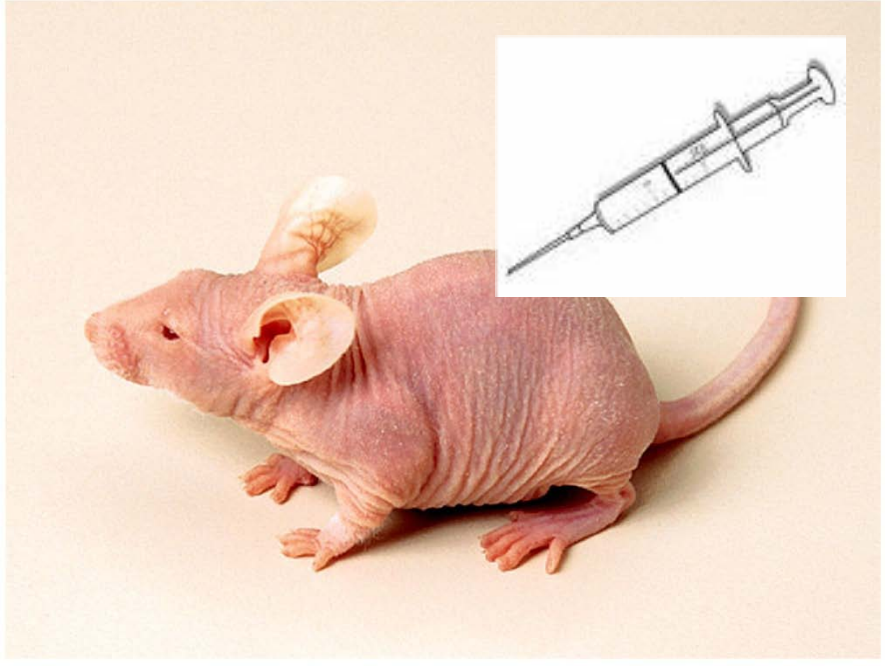
Assay 2 for Transformed cells

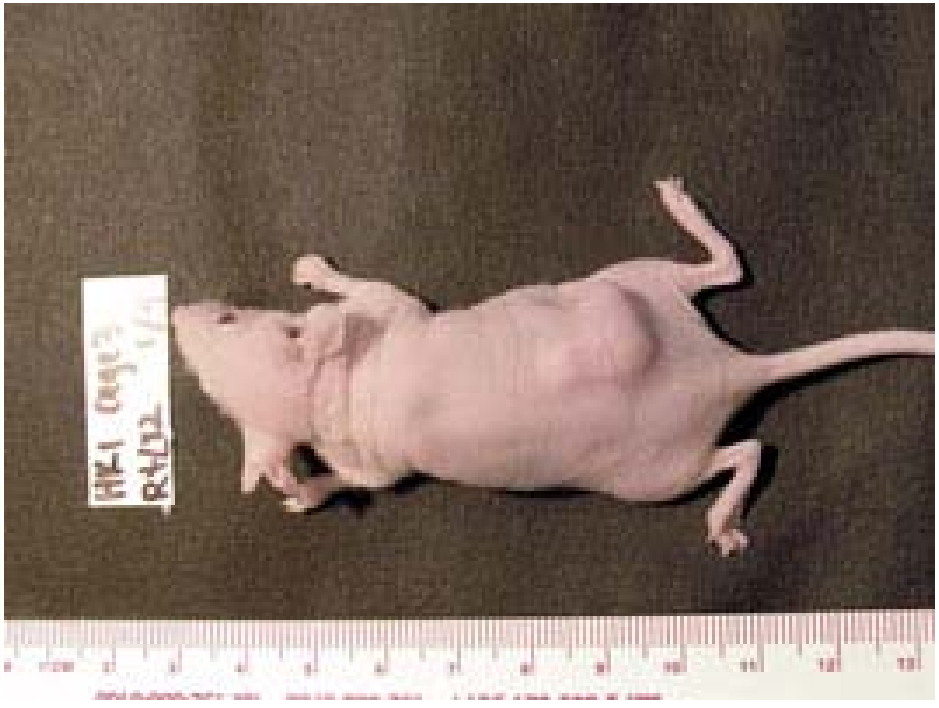
Nude mice

1. Lacks thymus

- **Immuno-compromised**
- **Accept grafts from unrelated sources, such as human c**

2. No hair: Easy to see tumors



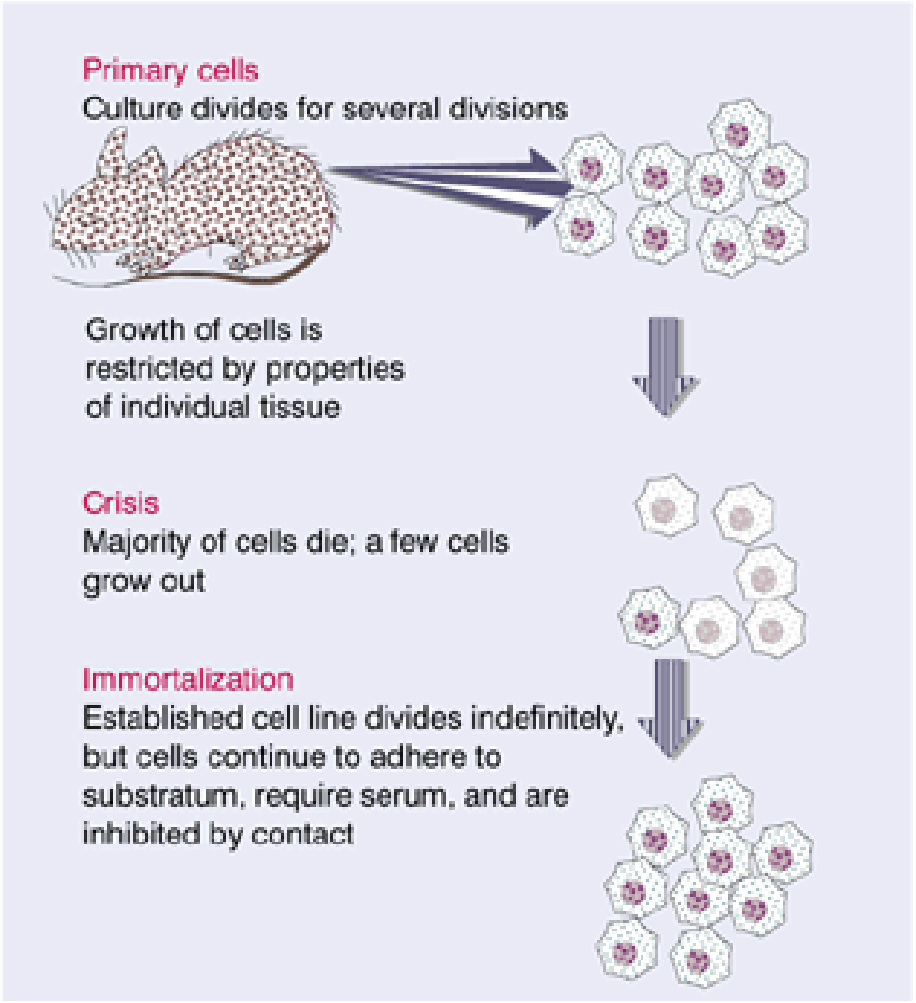


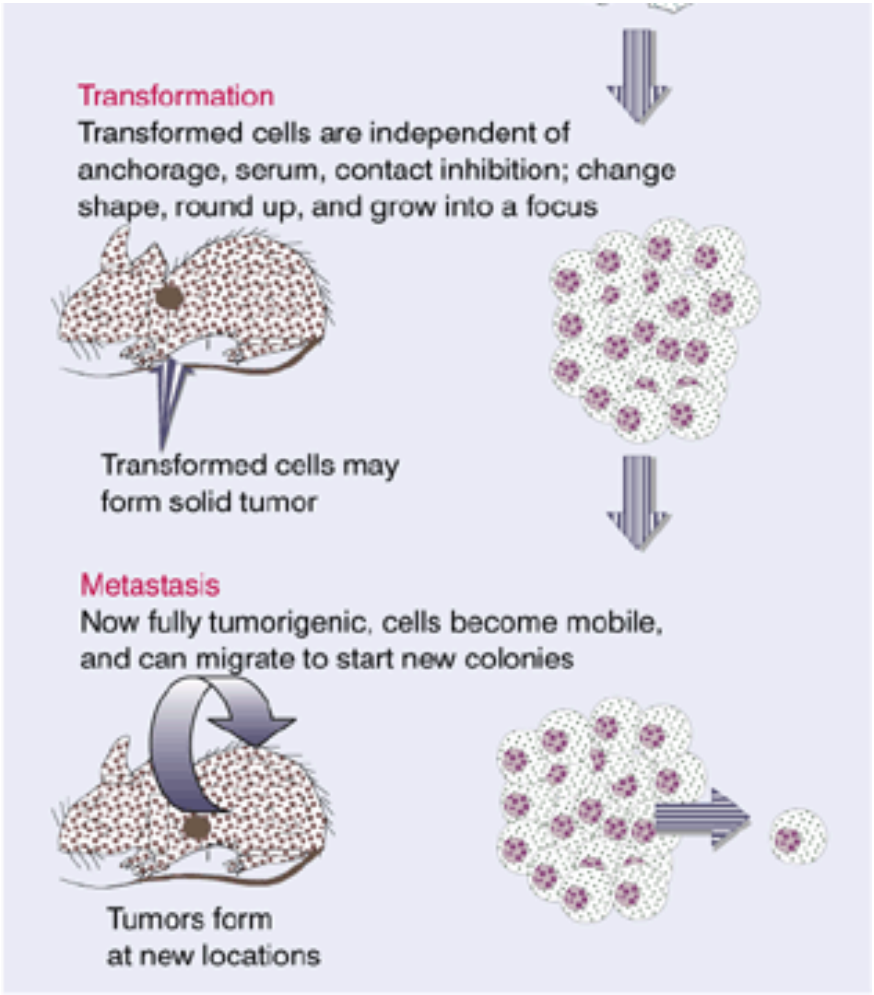
How bad are the cells?
2 functional assays

1. Foci formation on soft agar

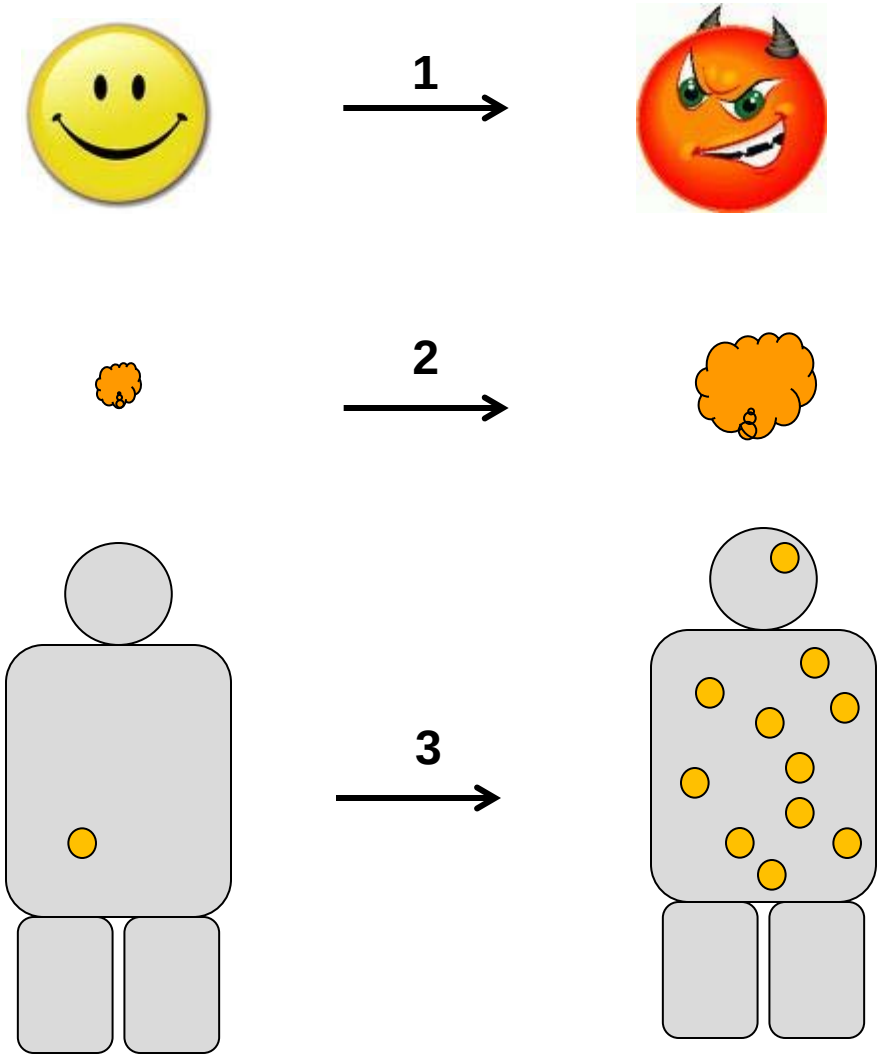
2. Tumor formation in Nude mice

How to distinguish a cancer cell from a normal cell





Cancer development



cancer progression

Normal cells

↓

Hyperplasia

↓

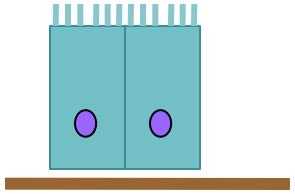
Dysplasia (Metaplasia)

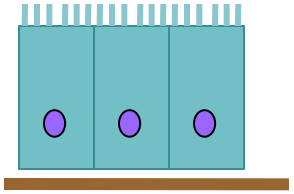
↓

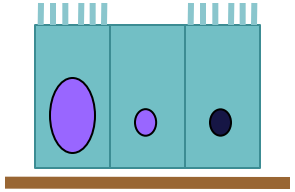
Neoplasia

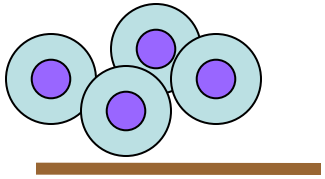
↓

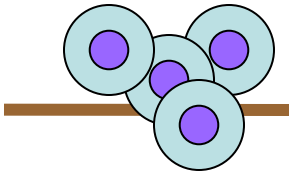
Metastasis







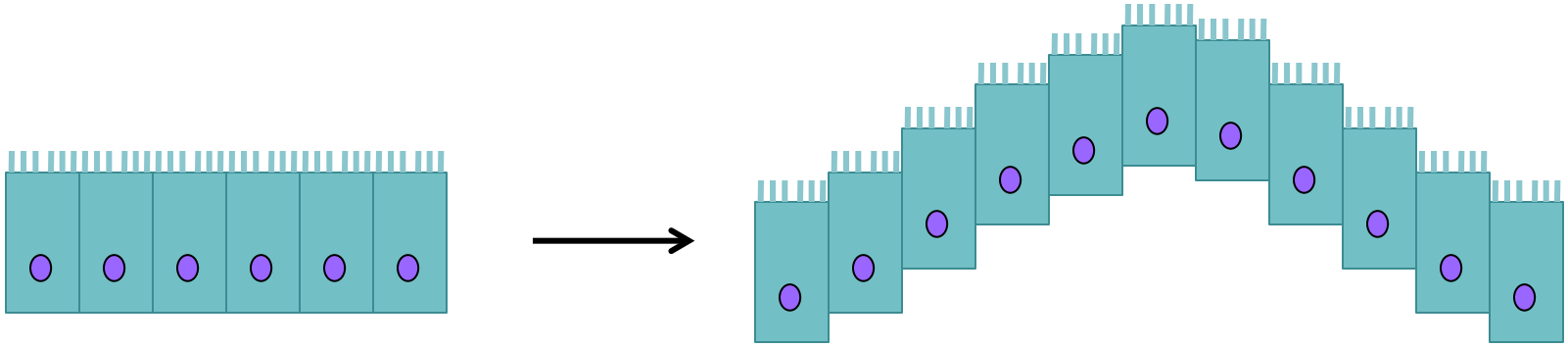




1. Hyperplasia

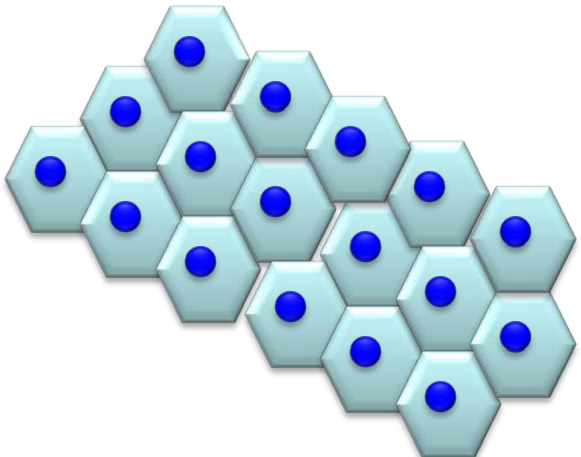
Hyper-: more; Hypo-: Less

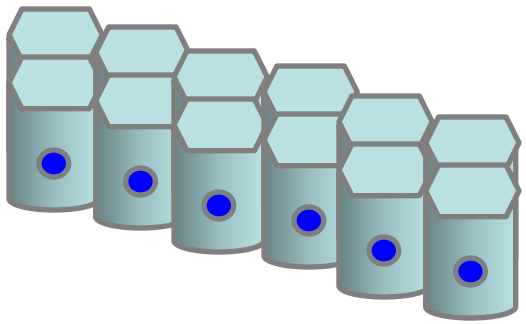
- Increased cell number
- Apparently normal cellular morphology



2. Metaplasia

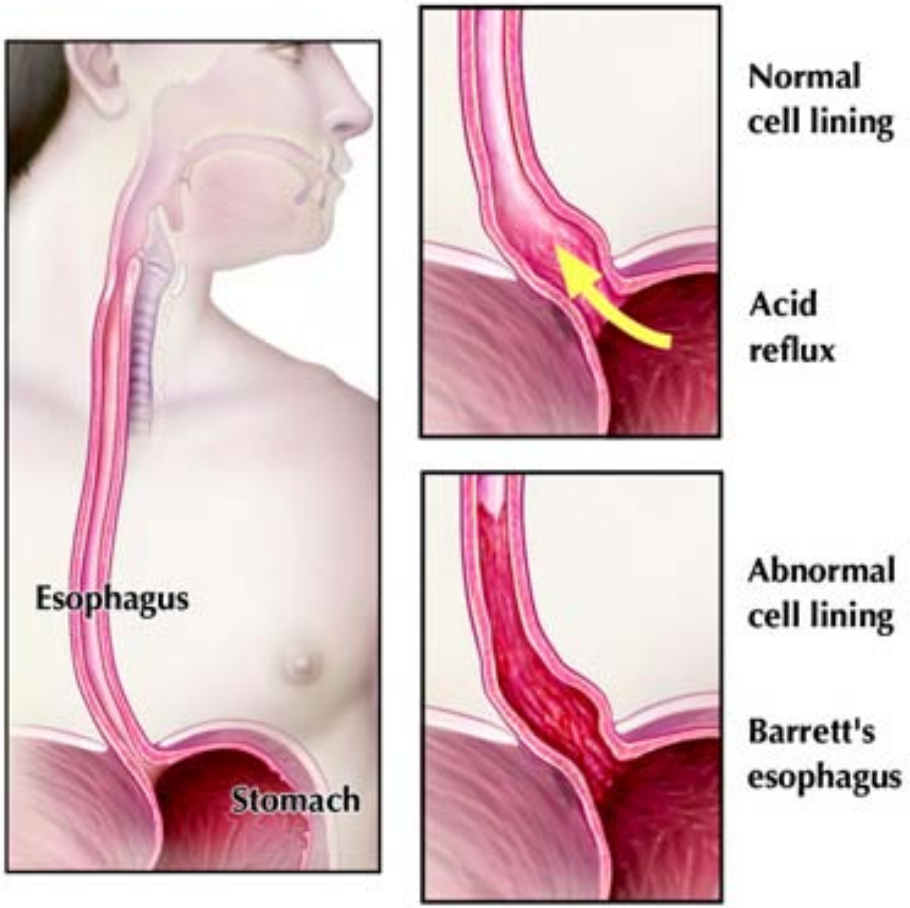
- Cells adopt the feature of another lineage
- Barrett's esophagus:
  - squamous cell → secretory cell
  - 30x risk for highly malignant cancer



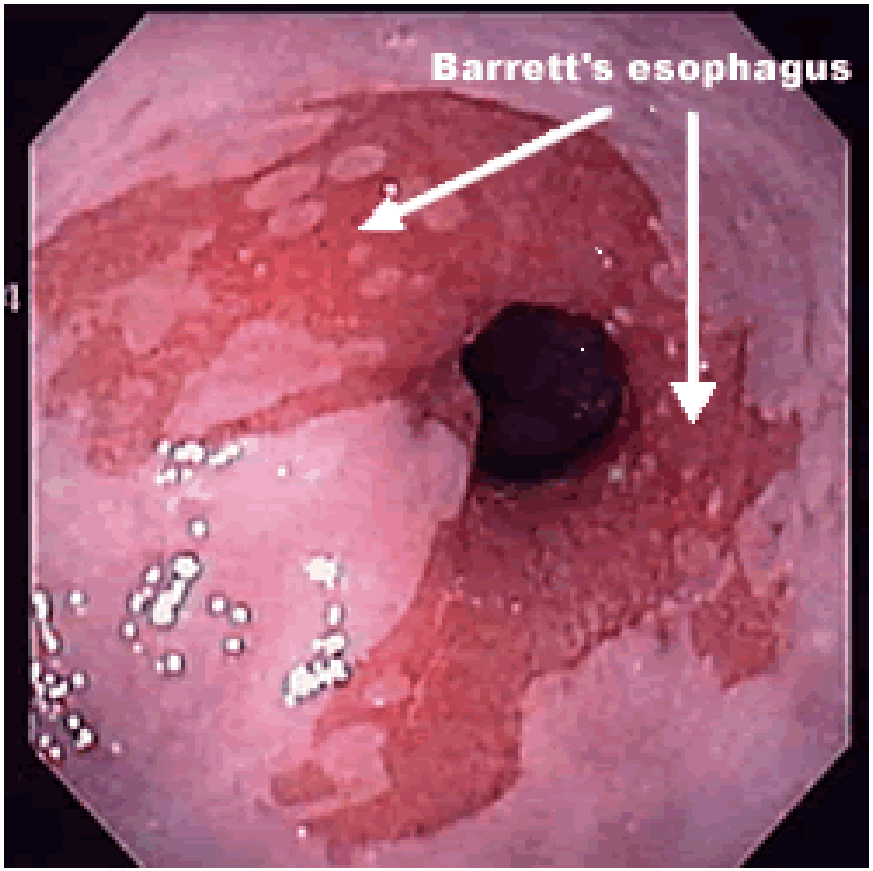


Metaplasia

1950: Barrett first described the columnar metaplasia



Barrett's esophagus



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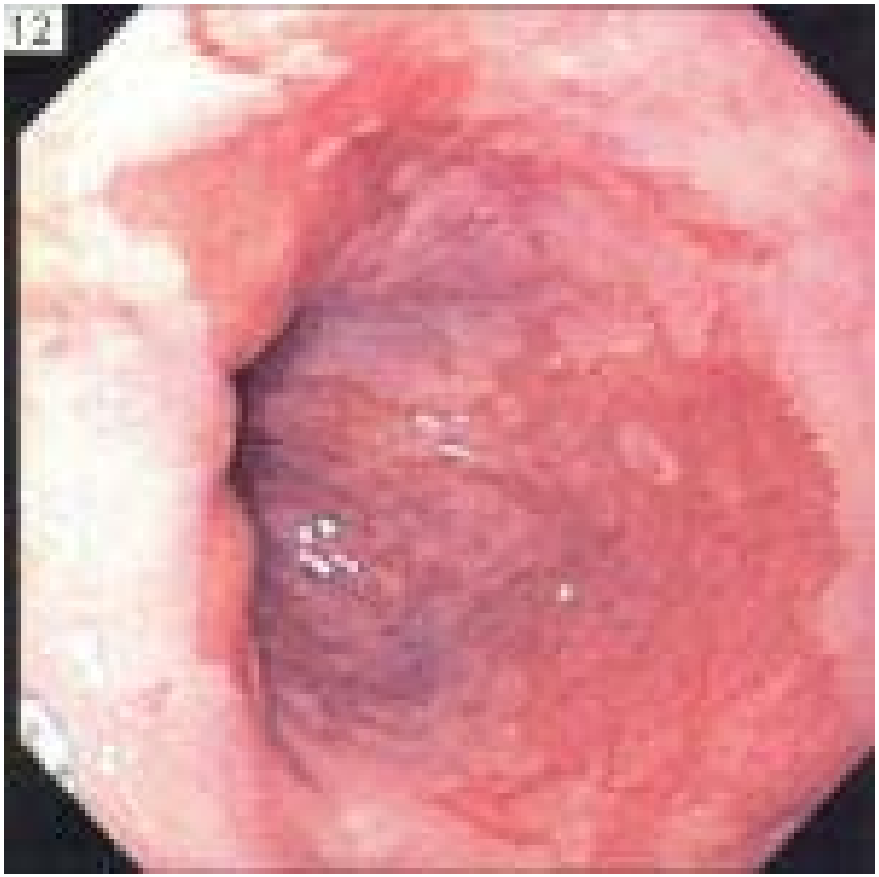
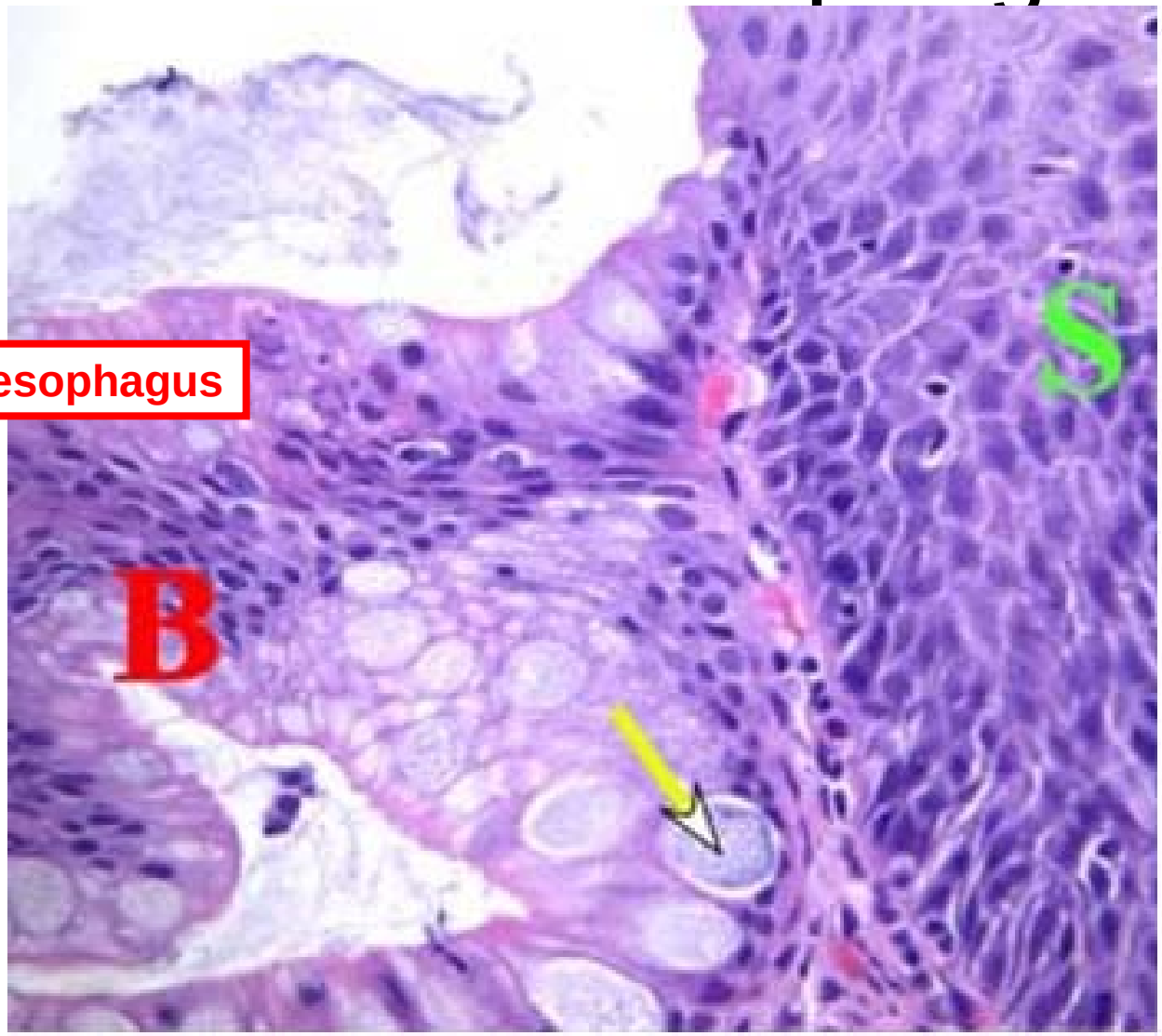


http://www.atillaertan.com/Barretts-esophagus/index-barretts.php

Barrett’s esophagus



Barrett’s esophagus

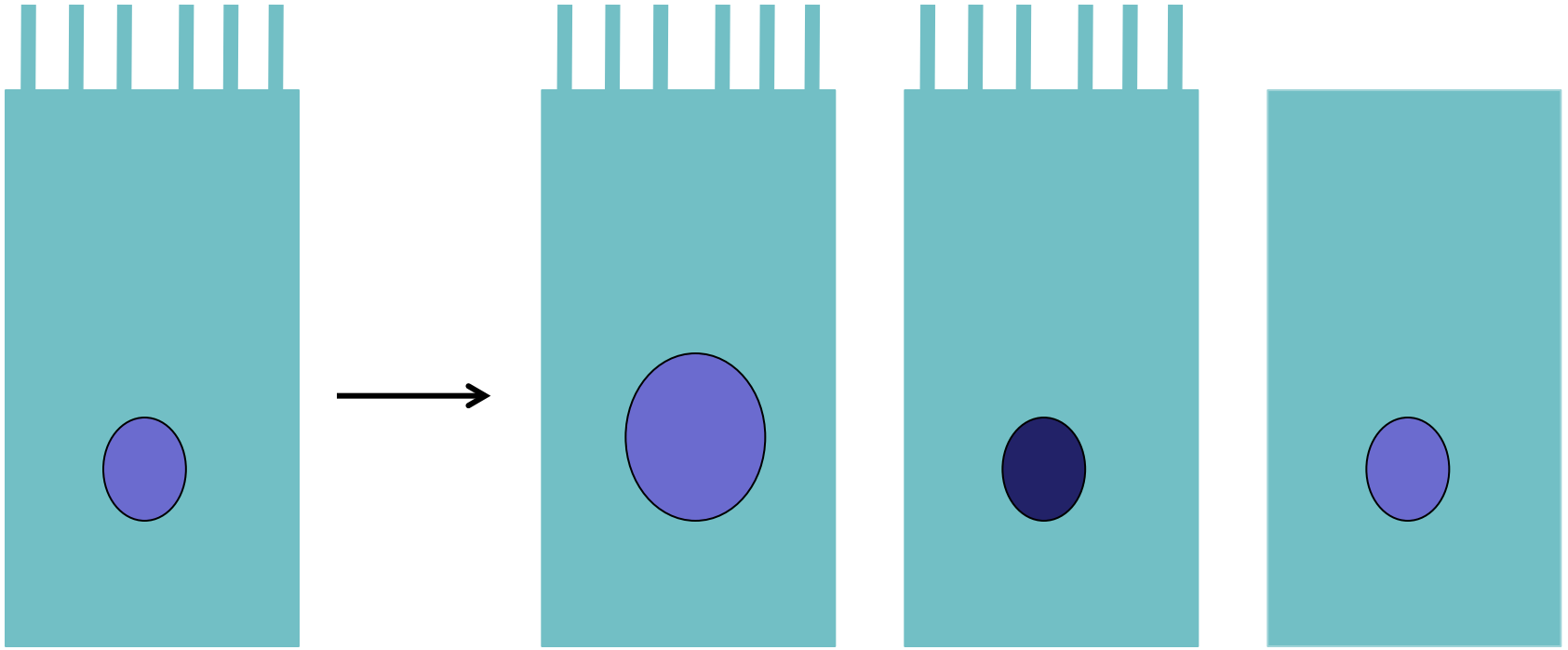
Squamous epithelial cells

Goblet cells

Barrett's metaplasia under the microscope

http://www.bcm.edu/medicine/barretts/index.cfm?pmid=9314

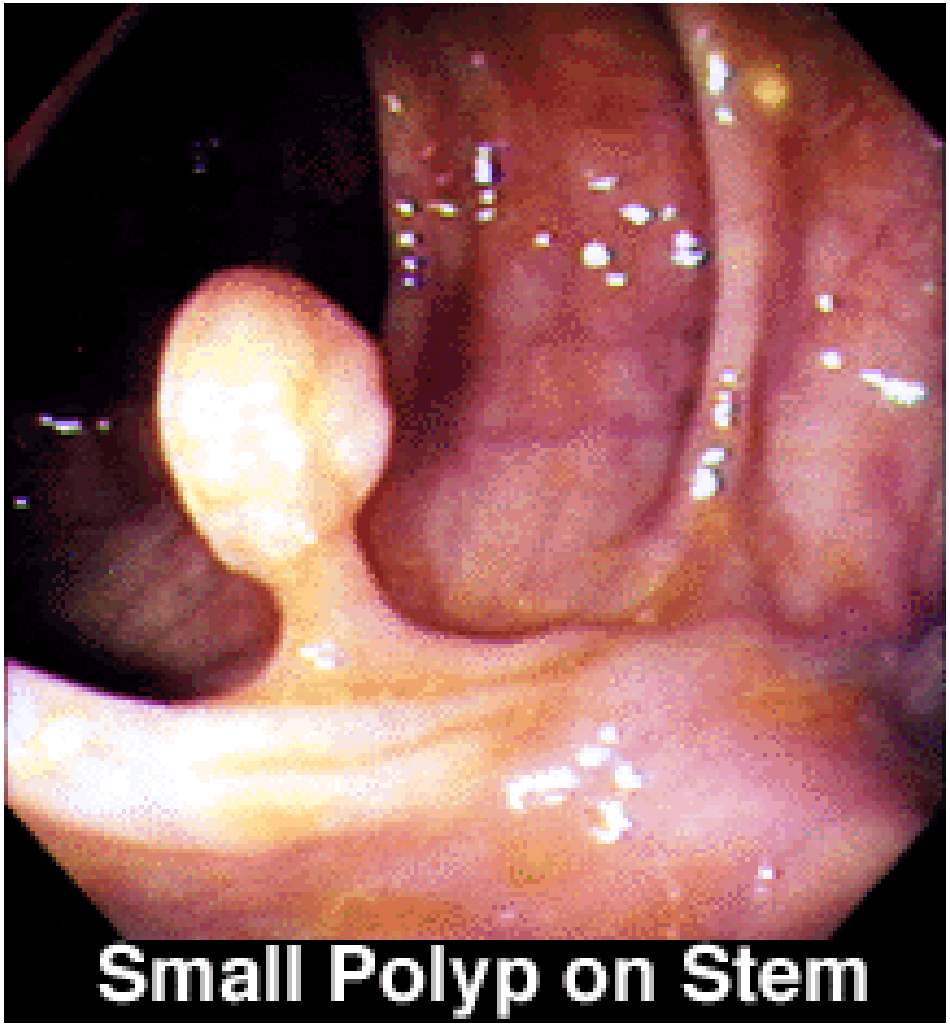
3. Dysplasia



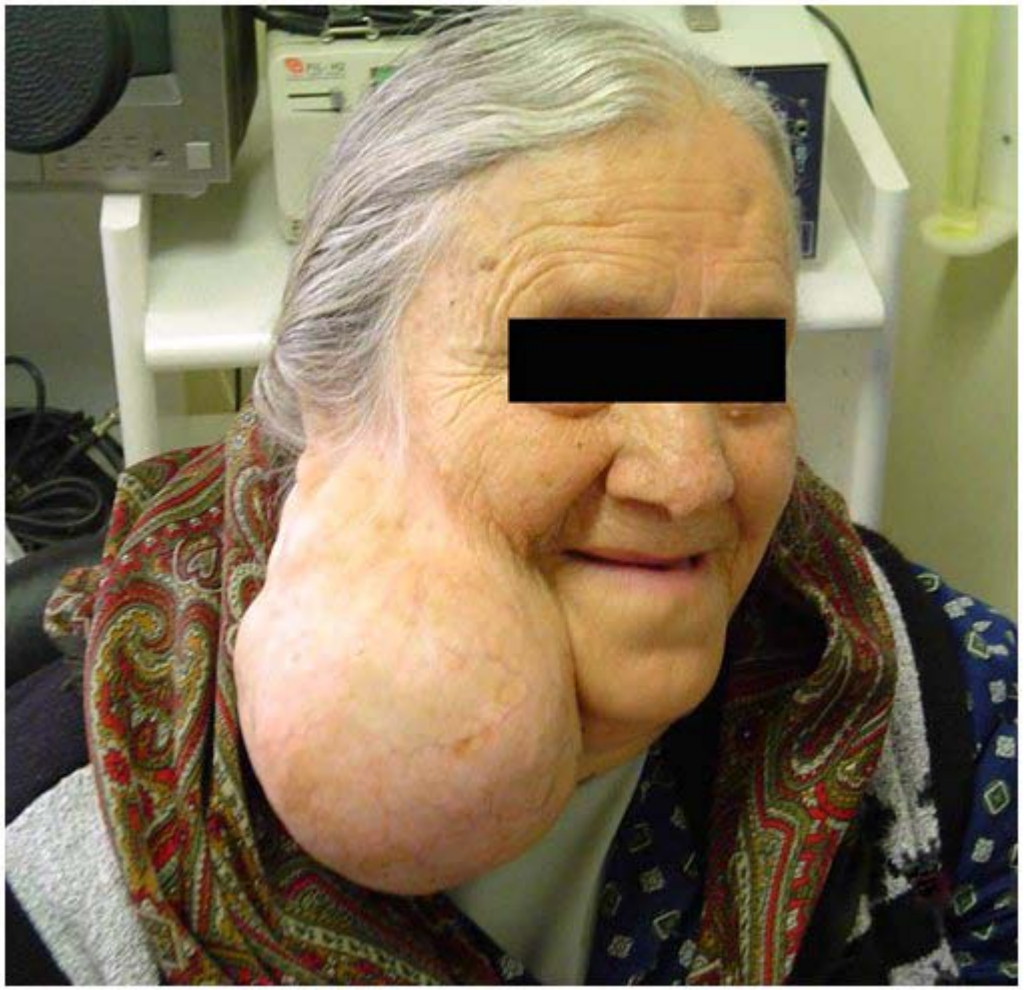
3. Dysplasia

- Abnormal cytologically,
- but still resemble the normal tissue
  - Variability in the sizes of nuclei
  - Increased staining for nuclei
  - Increased nuclear/cytoplasmic ratio
  - Increased mitotic activity
  - Decreased cytoplastic features of the normal differentiated tissue
  - Pre-malignant

Polyps



Warts, Adenoma



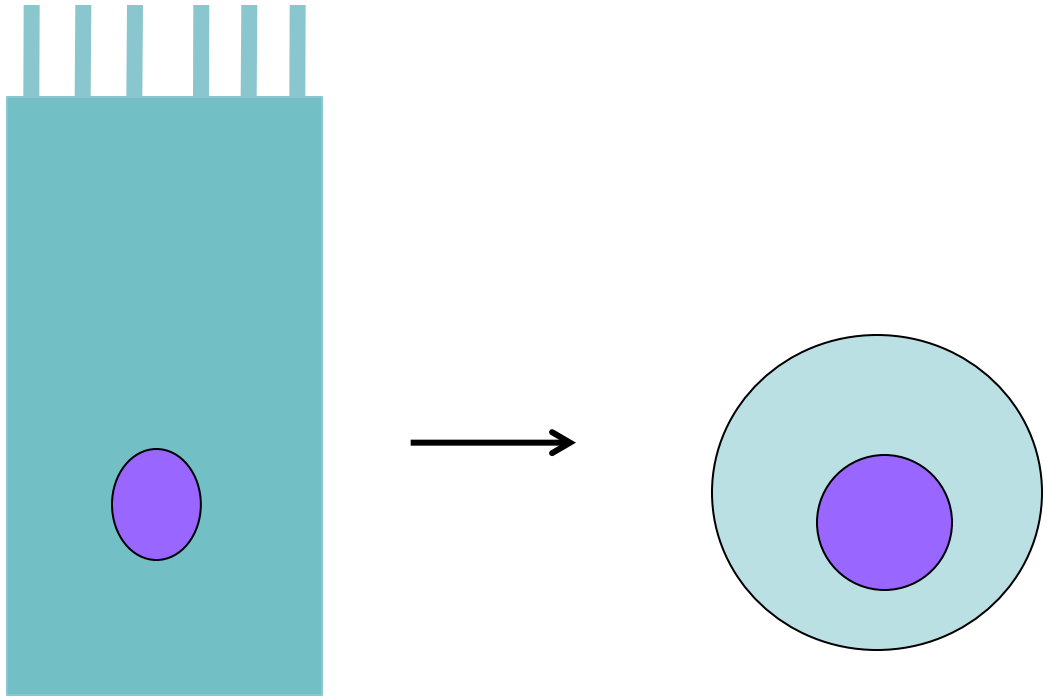
Adenomas, polyps, warts

- Dysplastic cytologically
- Grow to a certain size, then stop
- Respect the boundary of basement membrane

- Benign tumor, but could be pre-malignant

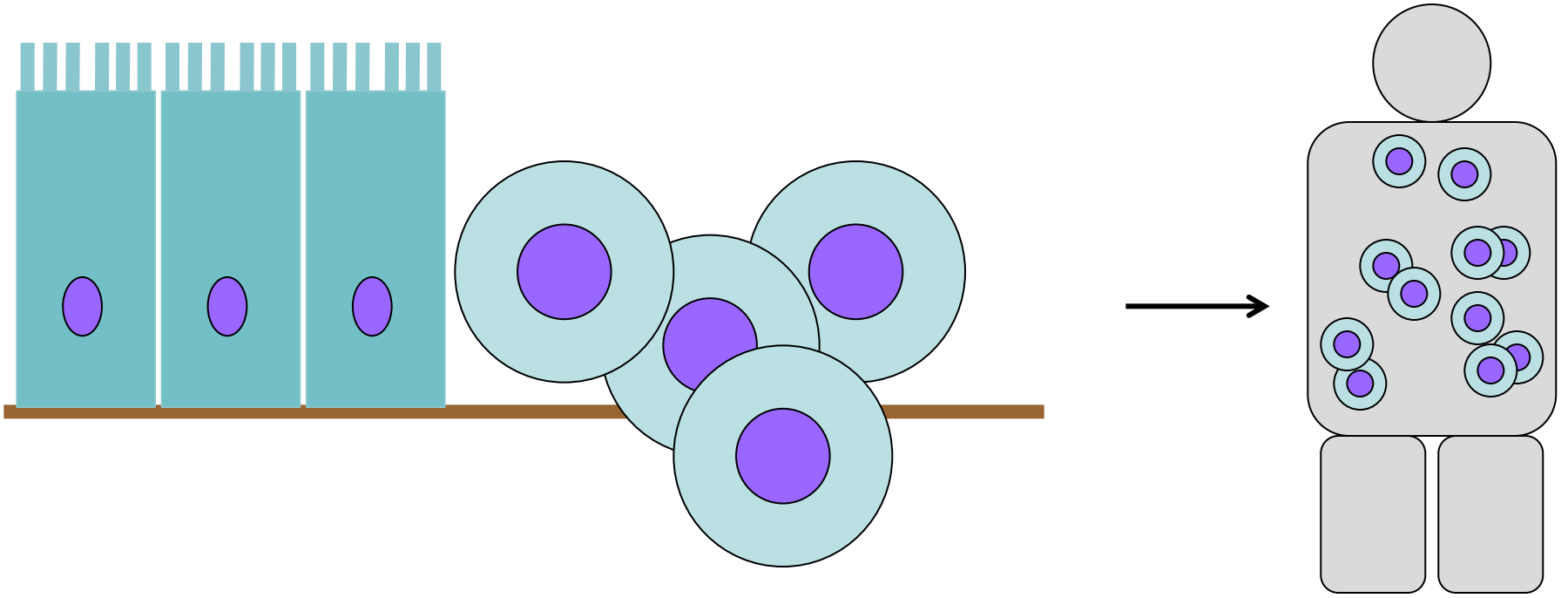
4. Neoplasia

- New tissue, very different from the surrounding normal tissue



5. Metastatic cancer

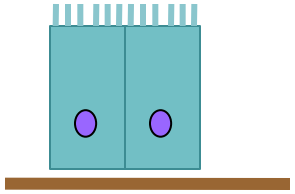
- Invade basement membrane/ other tissues



Invasion **Metastasis**

Summary: cancer progression

Normal cells



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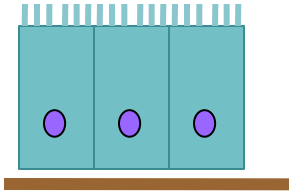
Hyperplasia



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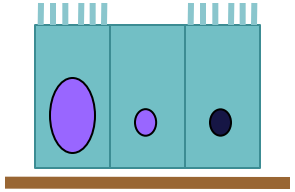
Dysplasia (Metaplasia)



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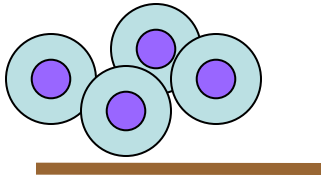
Neoplasia



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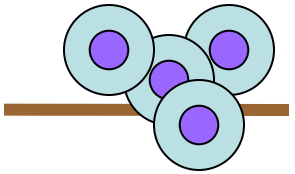
Metastasis



Case study: Barrett's esophagus

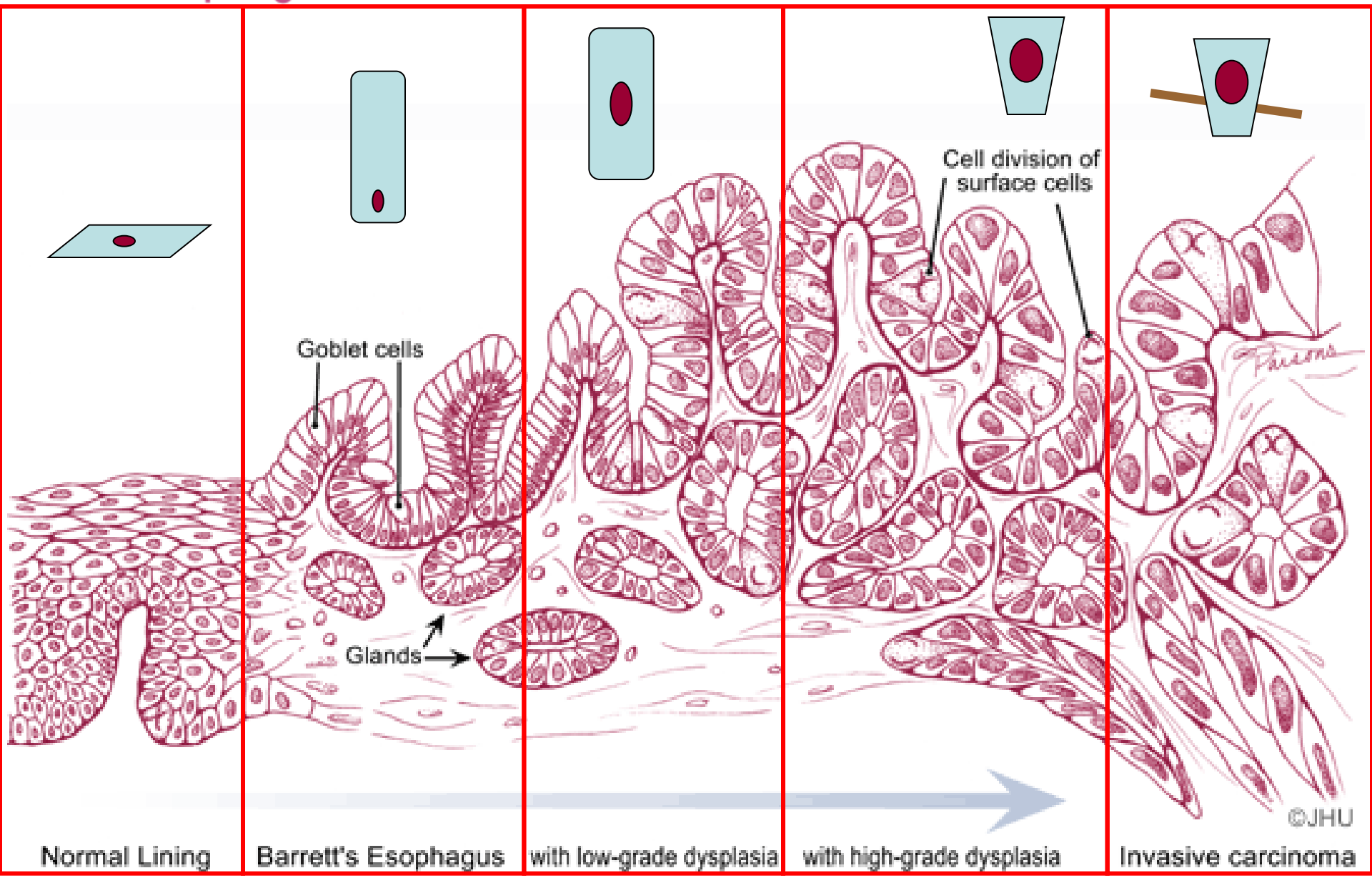
The American Gastroenterologic Association advises:

Reflux symptoms (usually heartburn) for several years

Upper endoscopy examination

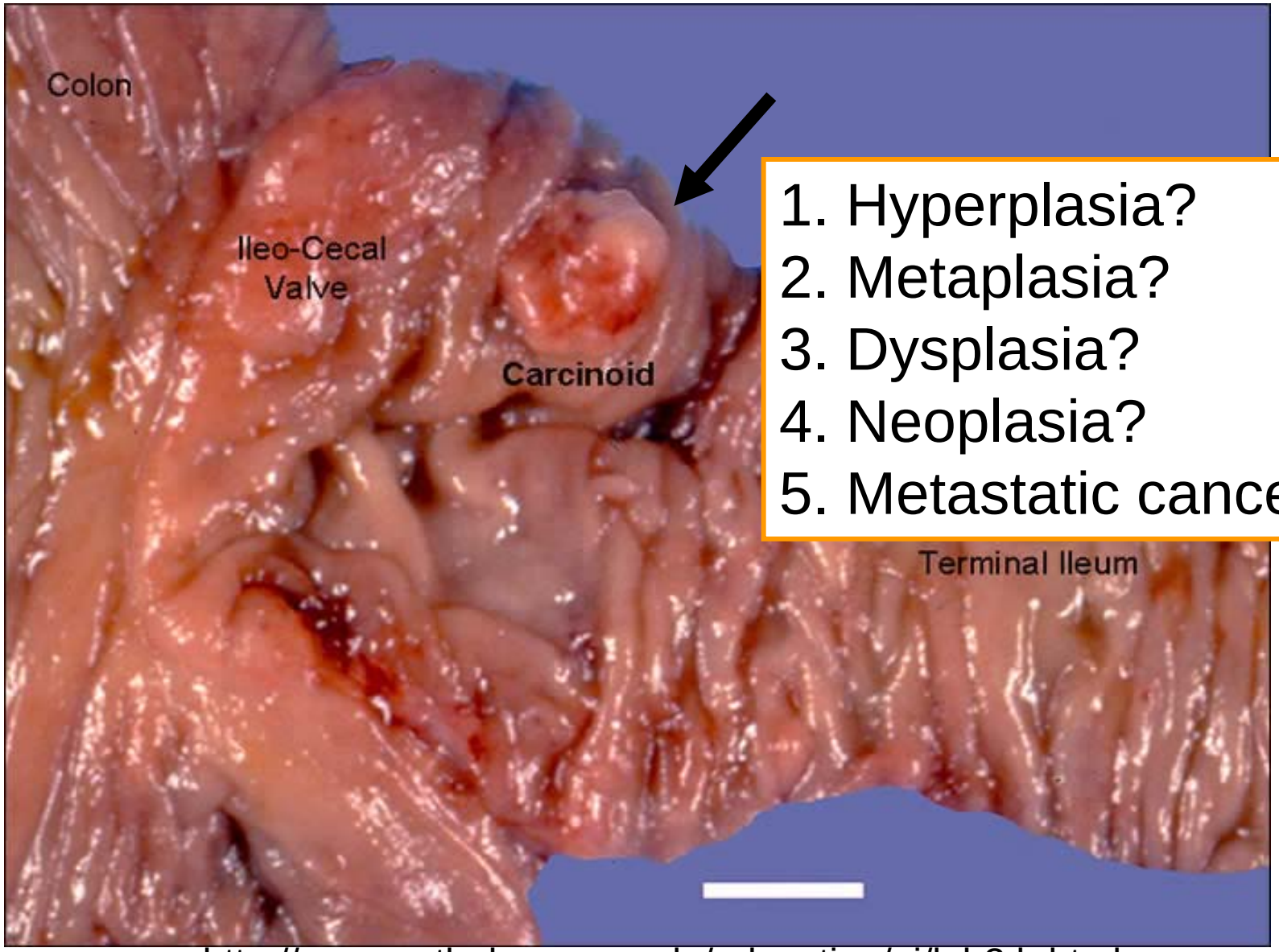
→Barrett's esophagus?
→Premalignant features?

Barrett's Esophagus:



pathology2.jhu.edu/ beWeb/images/beprog.gif

Carcinoid Tumor of the Ileum

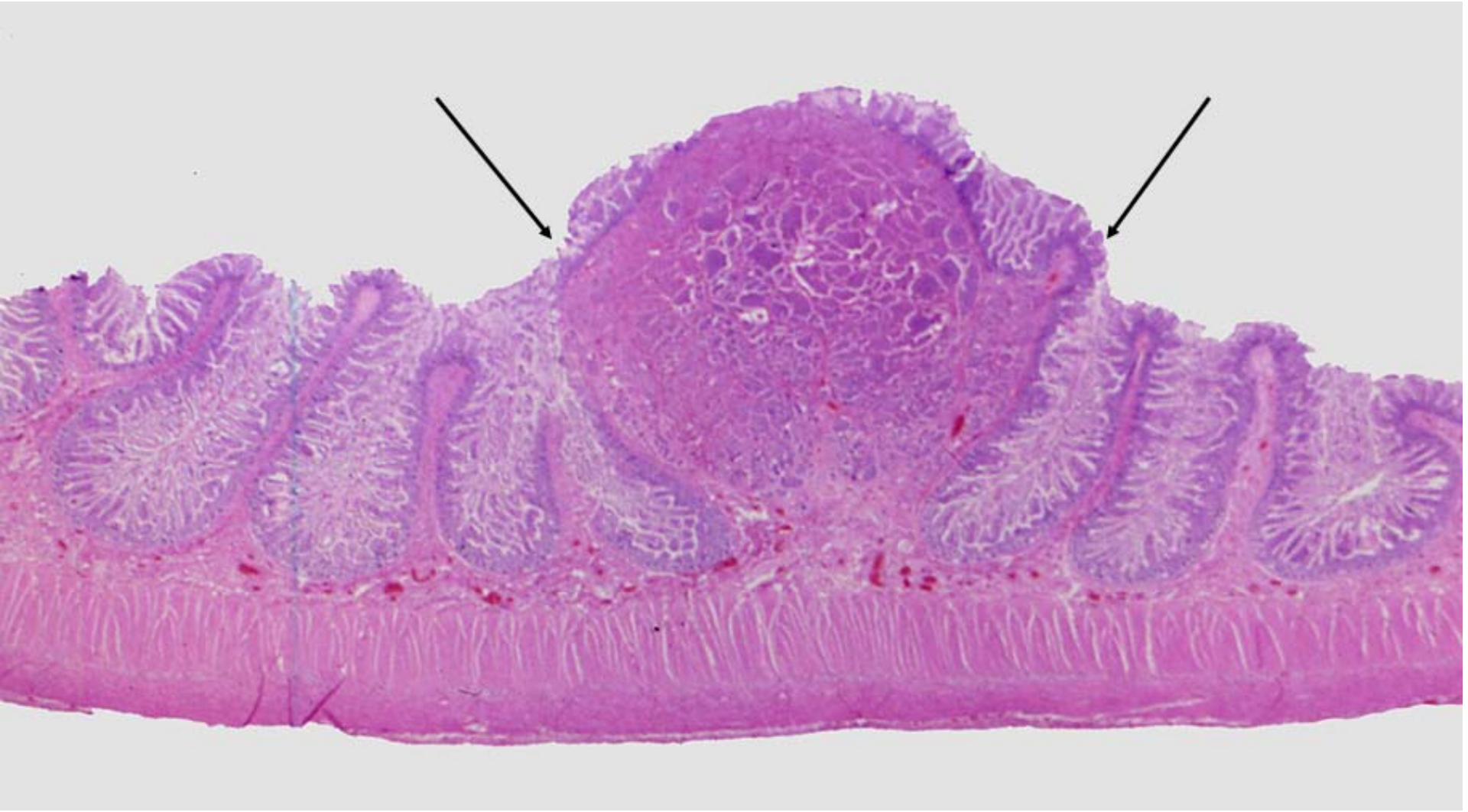


1. Hyperplasia?
2. Metaplasia?
3. Dysplasia?
4. Neoplasia?
5. Metastatic cancer?

大肠

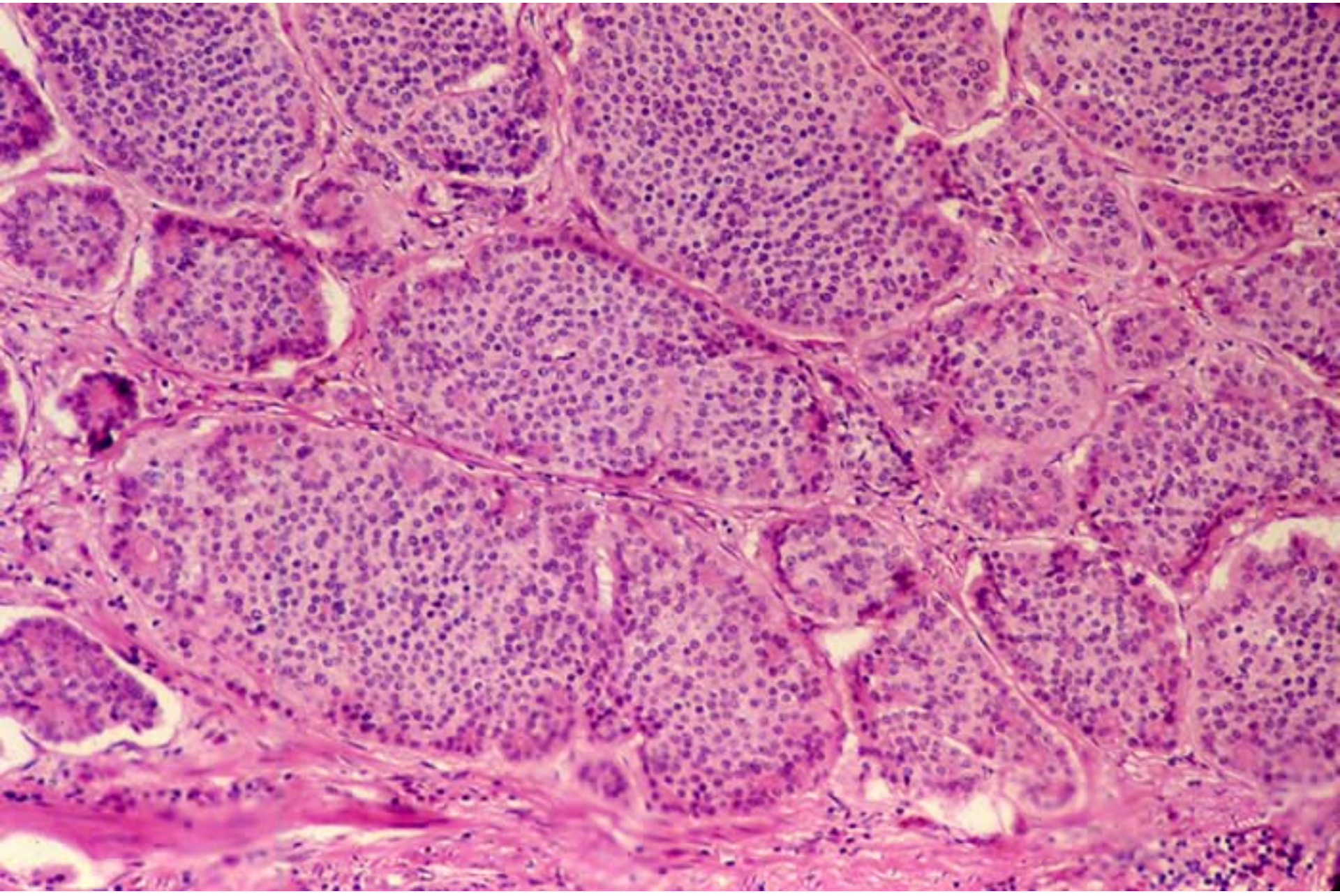
http://www.pathology.vcu.edu/education/gi/lab2.h.html

submucosal carcinoid tumor of illeum

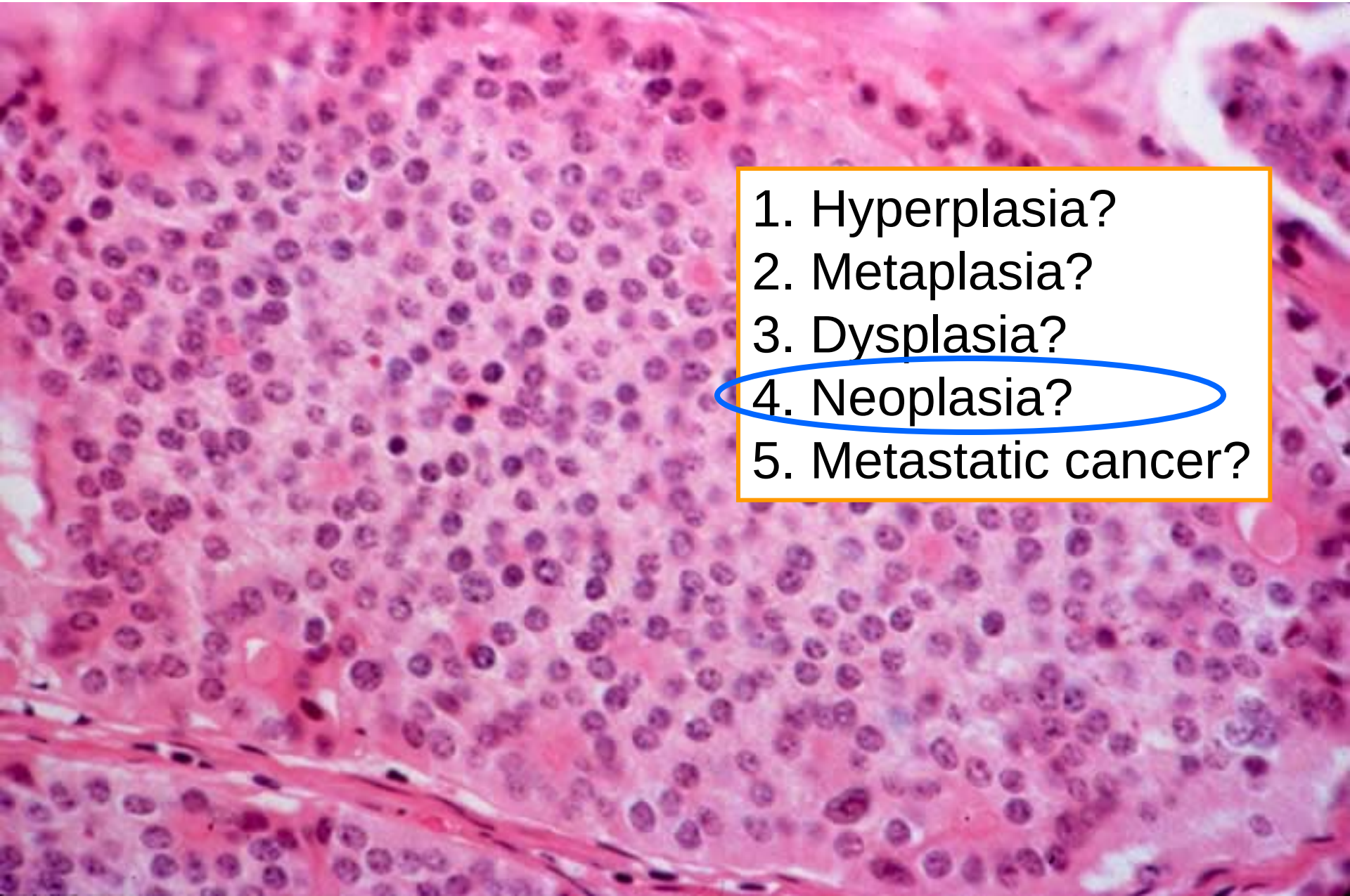


http://www.pathology.vcu.edu/education/gi/lab2.h.html

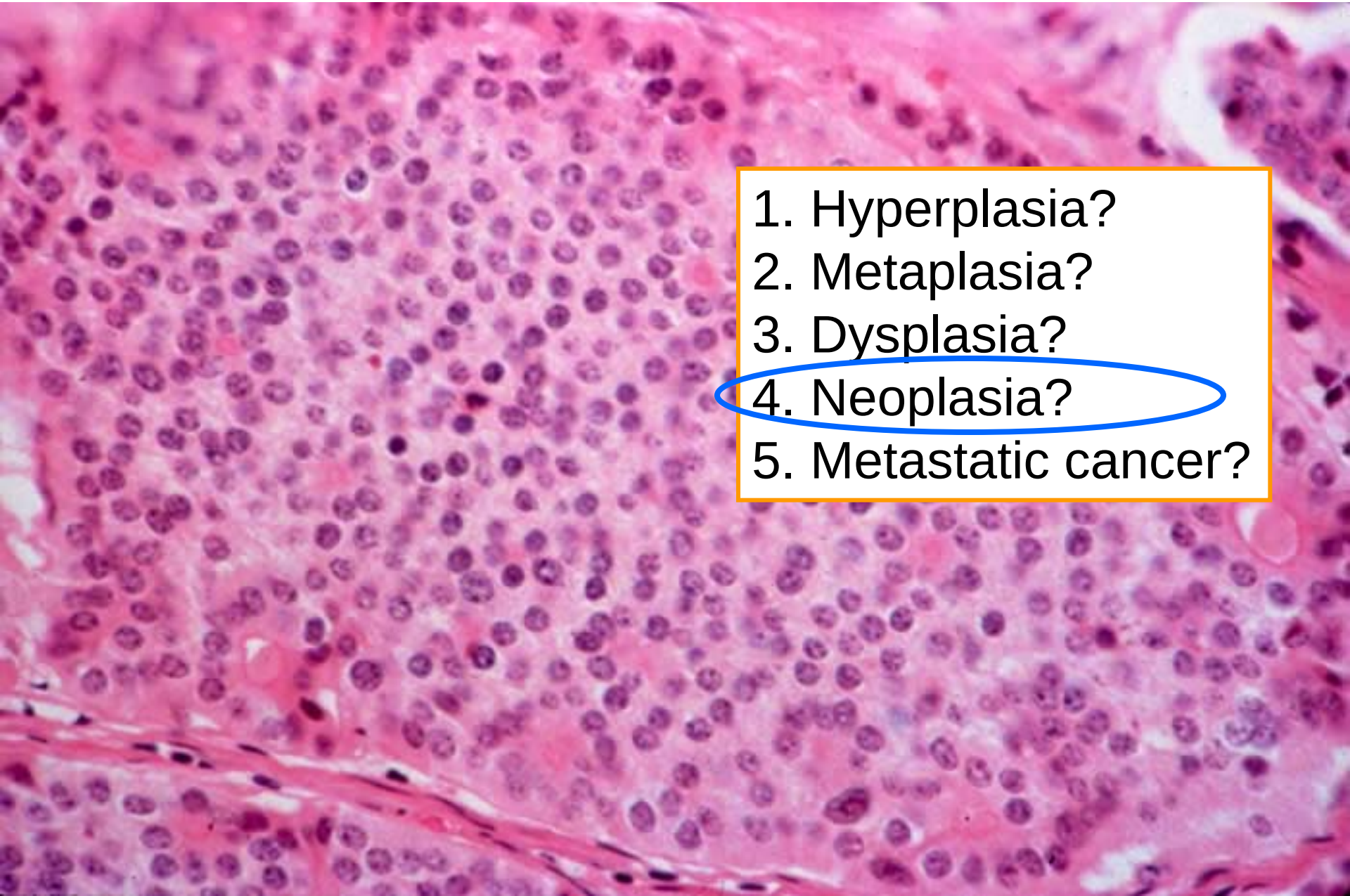
closely packed, uniform round cells with small, central nuclei



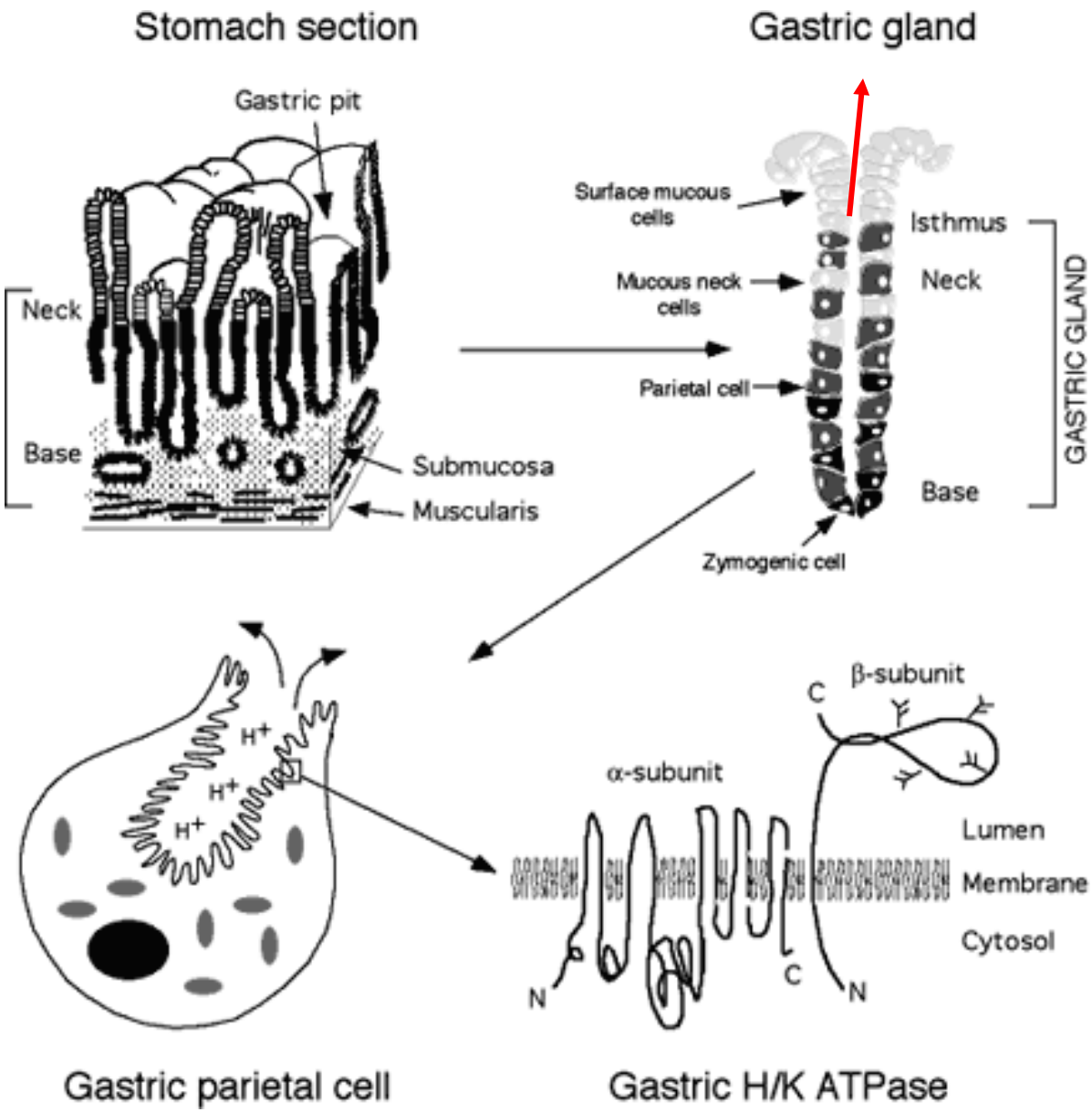
Little mitotic activity



Little mitotic activity

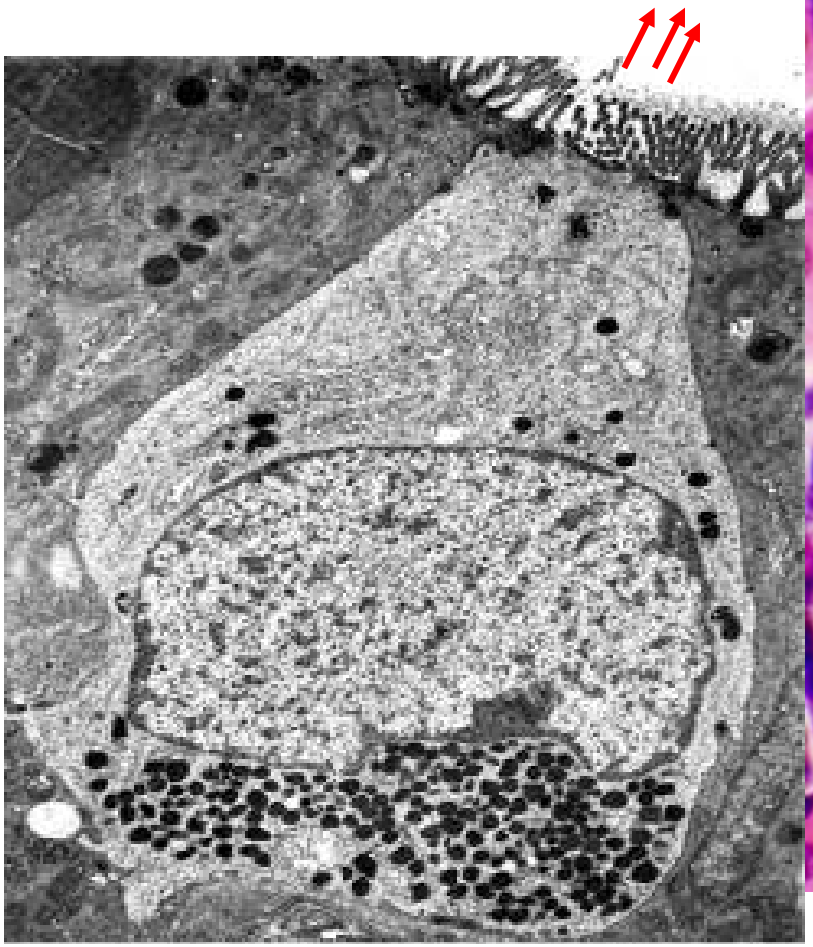


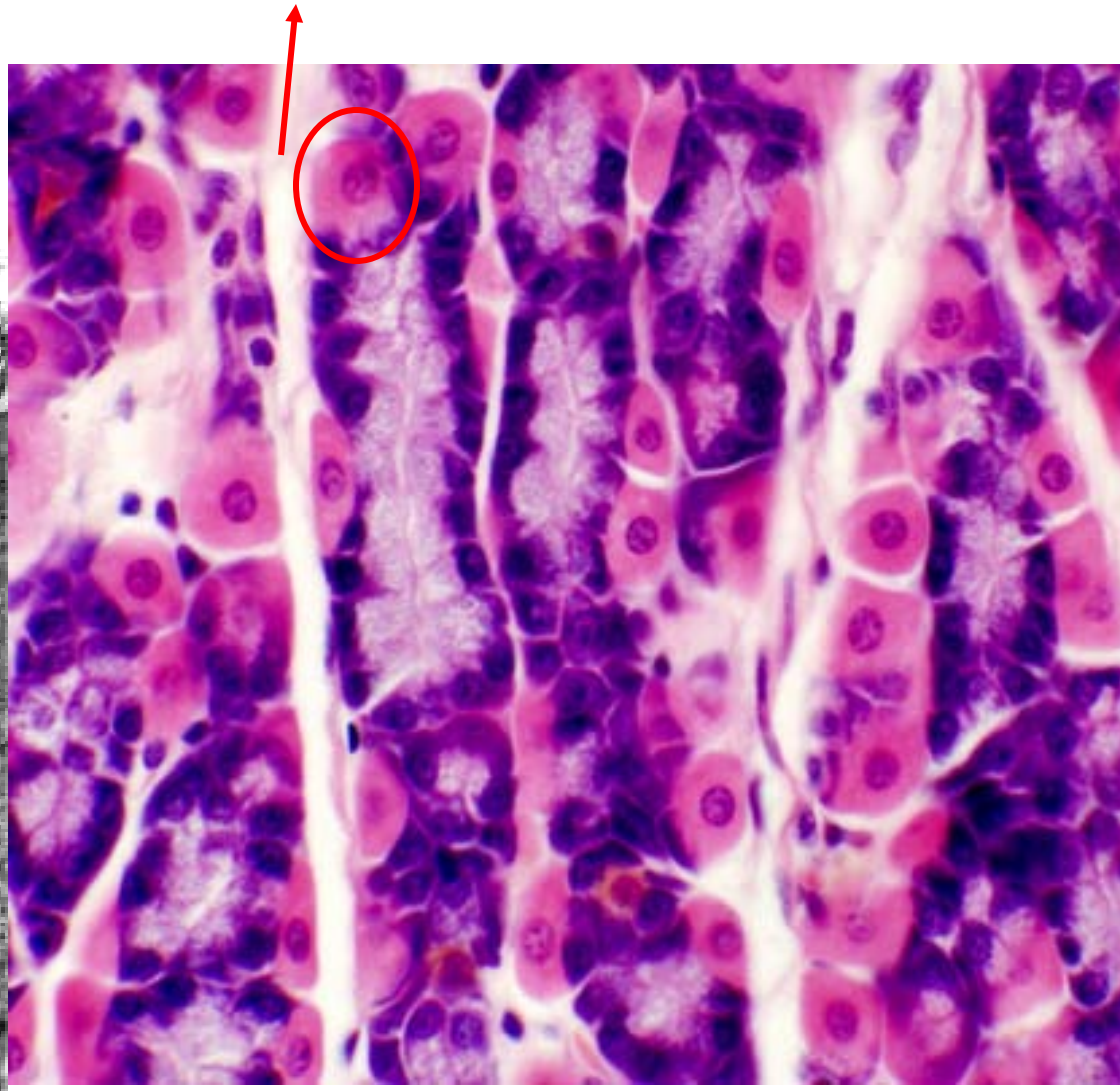
Stomach atrophy and cancer



Parietal cells:

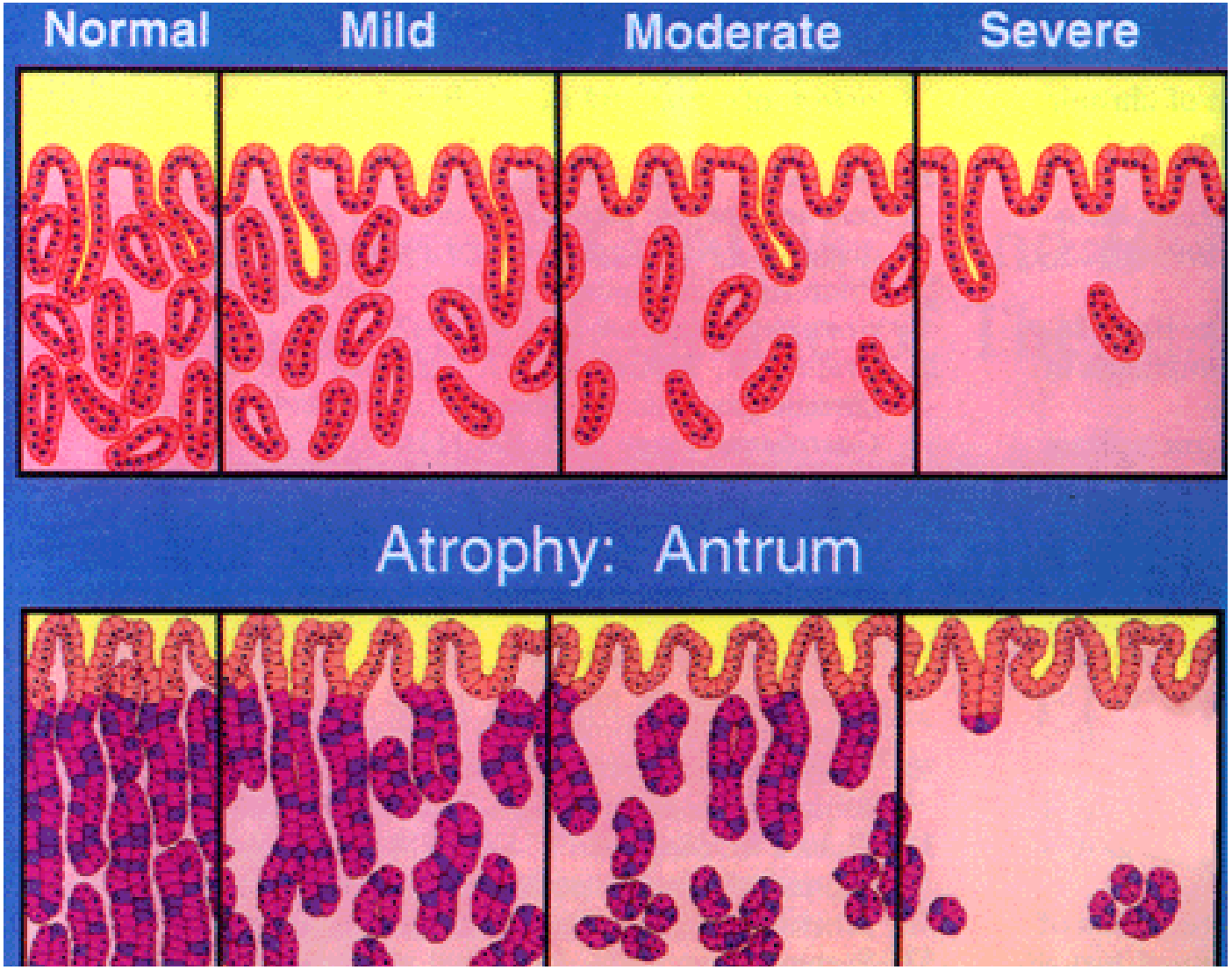
- HCl
- Intrinsic Factor

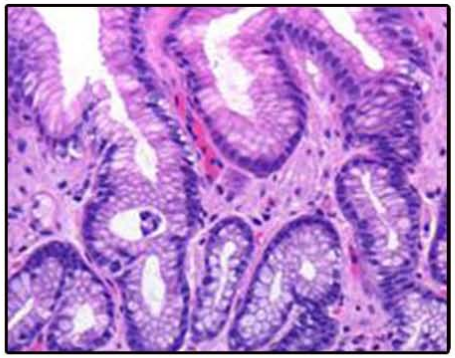


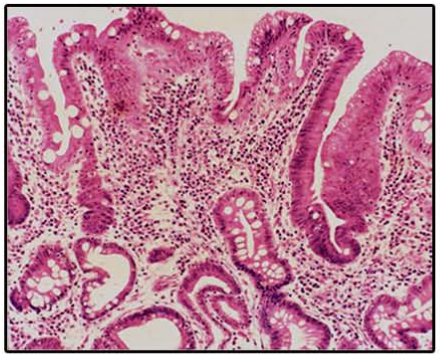


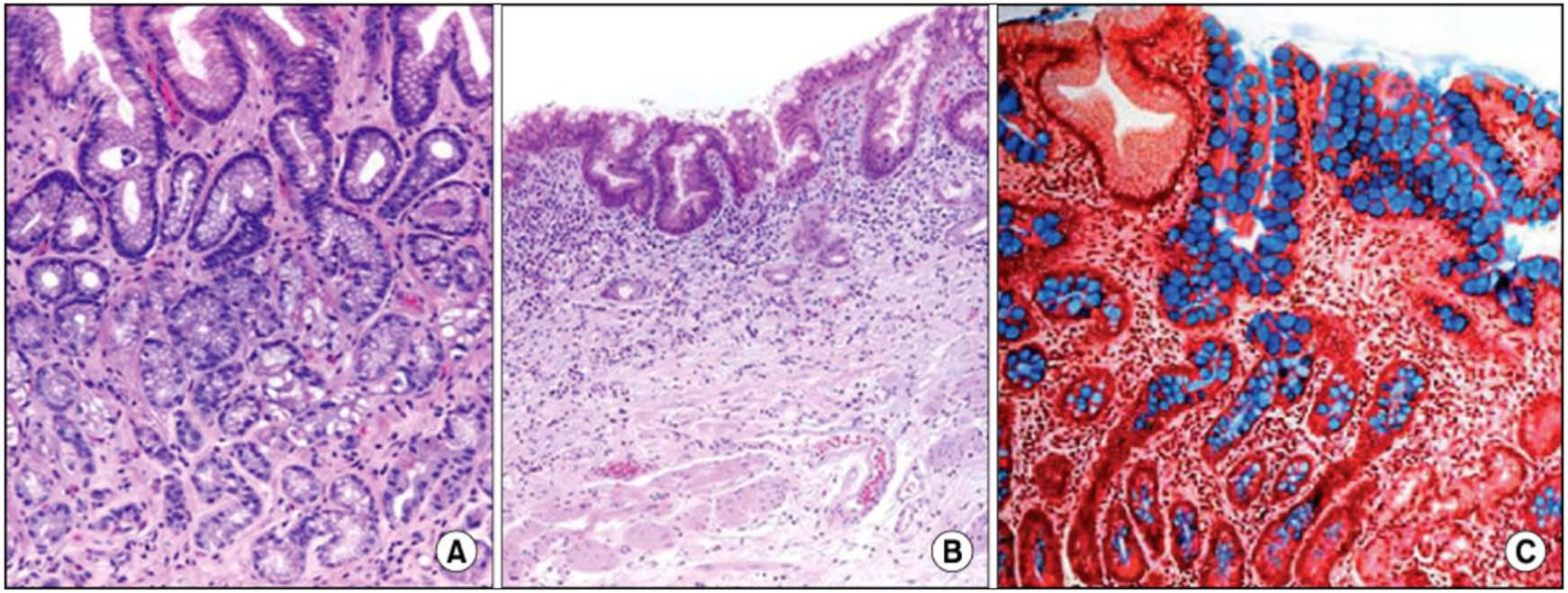
http://www.mc.vanderbilt.edu/histology/labmanual2002/labsection3/EsophagusandStomach03.htm

Stomach atrophy

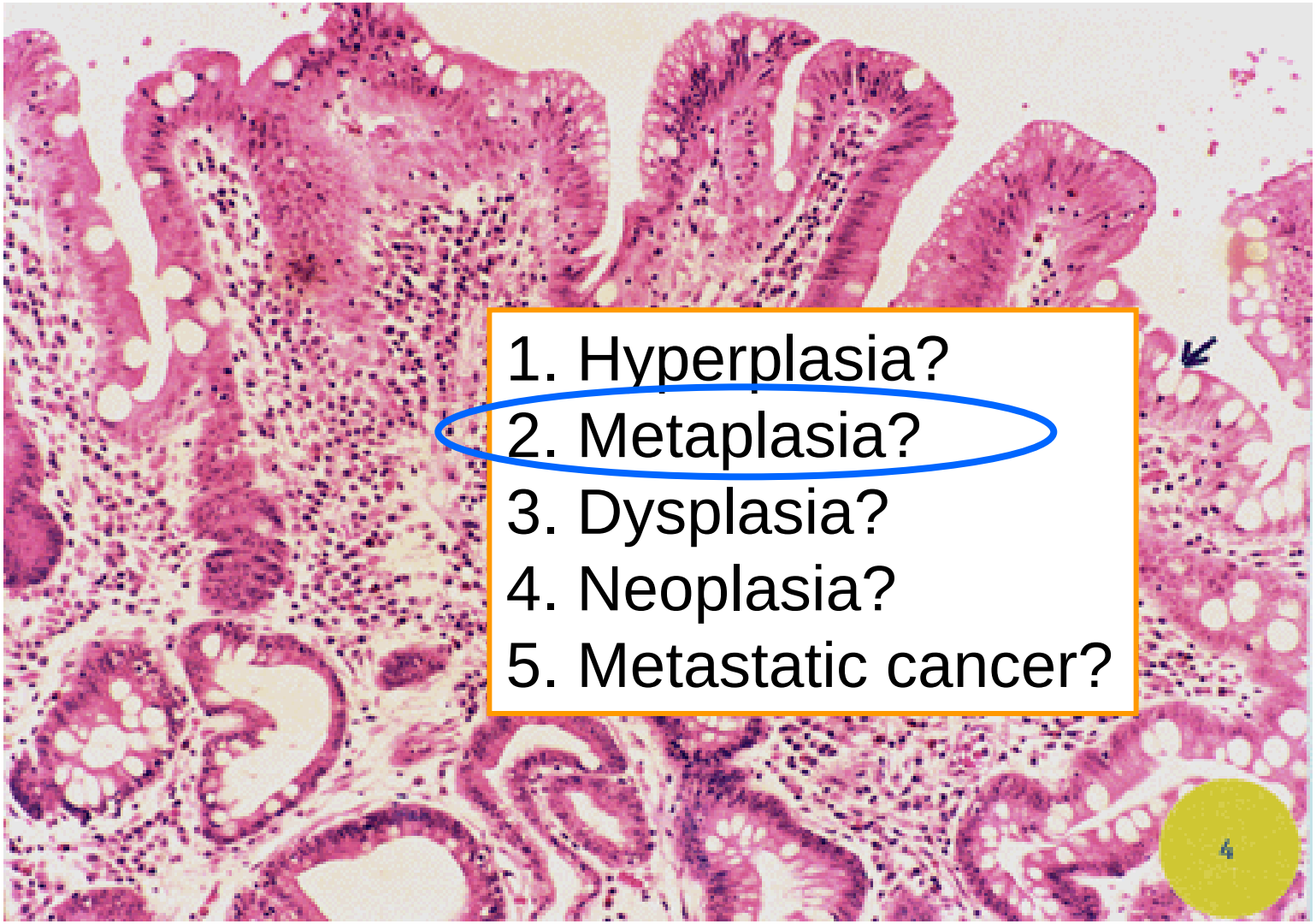






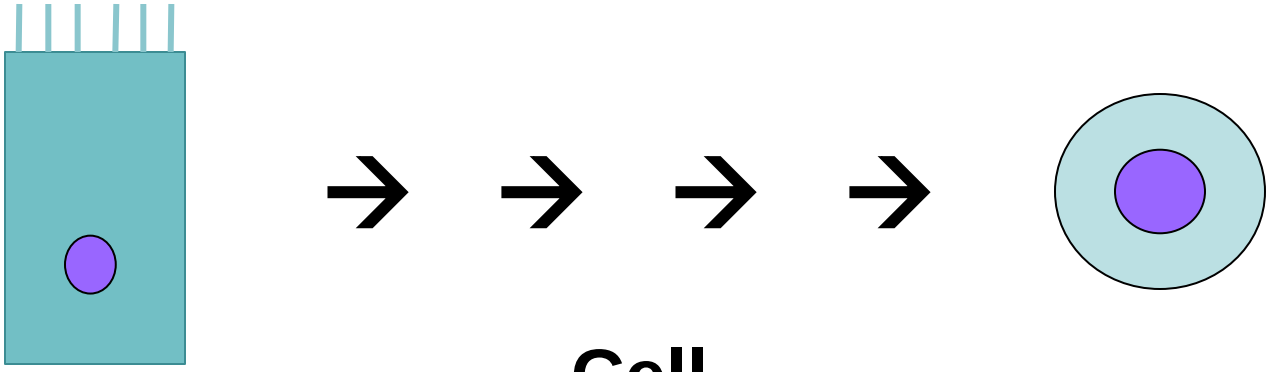

A
B
C

Stomach atrophy



http://pathsrvr.rockford.uic.edu/inet/GI/GI%20Station%207.htm

Origin of cancer cell



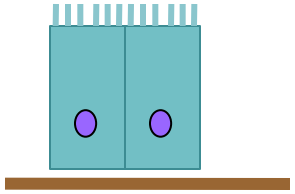
Cell

Gene

Environment

Summary: cancer progression

Normal cells



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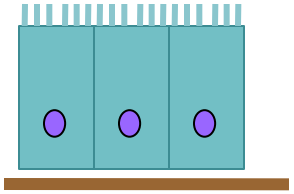
Hyperplasia



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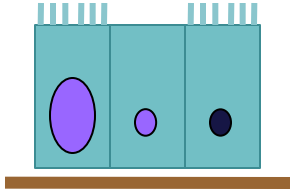
Dysplasia (Metaplasia)



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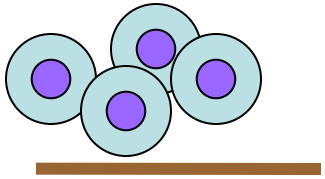
Neoplasia



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Metastasis