Cancer Biology

Fall 2018

Dr. Dawang Zhou

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课程内容与成绩要求

主要内容：

1.癌症学说及癌症分类
2.癌症的分类：内因和外因
3.癌症的发生发展
4.原癌基因的发现：肿瘤病毒的研究
5.原癌症基因的发现：家族遗传的研究
6.抑癌基因的发现
7. 期中测试（30%）大约 11月06日
8.器官生长调控与肿瘤
9. 肿瘤代谢
10.基因组稳定性与肿瘤
11.肿瘤与微环境
12.肿瘤免疫
13.肿瘤干细胞
15. 学生演讲（25%）
16. 期末考试（25%）

总成绩： 出勤20%+期中30%+演讲25%+期末25%

课后作业：阅读5篇论文

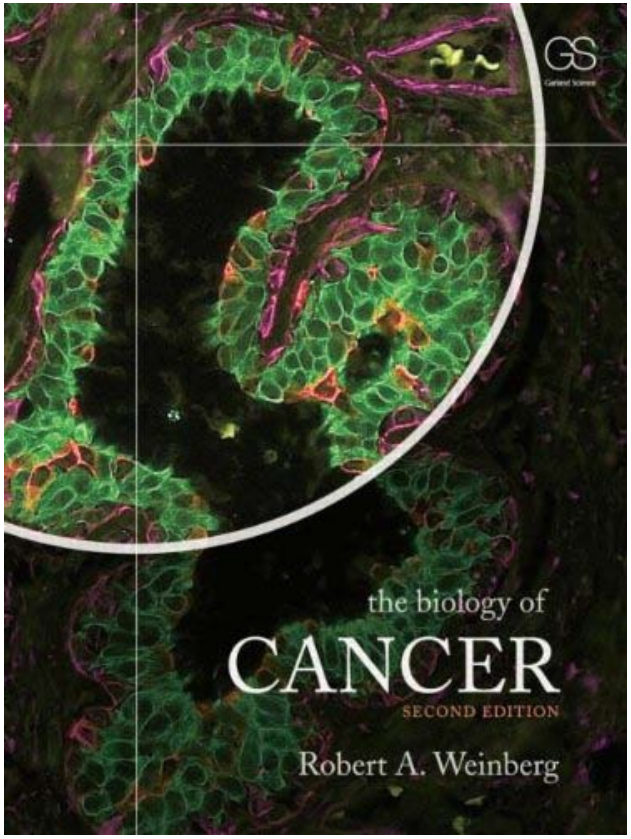
周	时间：周一3，4节	章节（A班， E207）	授课人	章节（B班，E407）	授课人
1	9月17日	癌症学说与分类	周大旺	癌症学说与分类	俞春东
2	10月8日	癌症发生发展-正常细胞的恶性转化	周大旺	癌症发生发展-正常细胞的恶性转化	俞春东
3	10月15日	癌症诱因-病毒/环境	周大旺	癌症诱因-病毒/环境	张永有
4	10月22日	病毒诱发癌症发生的机制	周大旺	病毒诱发癌症发生的机制	张永有
5	10月29日	癌基因	周大旺	抑癌基因	尤涵
6	11月5日	抑癌基因	尤涵	癌基因	周大旺
7	11月12日	期中考试		期中考试	
8	11月19日	基因组稳定性与肿瘤发生	协同中心	基因组稳定性与肿瘤发生	
9	11月26日	肿瘤代谢	协同中心	肿瘤代谢	
10	12月3日	肿瘤微环境	协同中心	肿瘤微环境	
11	12月10日	肿瘤免疫	协同中心	肿瘤免疫	
12	12月17日	肿瘤干细胞与异质性	莫玮	肿瘤干细胞与异质性	欧阳高亮
13	12月24日	学生专题汇报	周大旺	学生专题汇报	俞春东
14	12月31日	学生专题汇报	周大旺	学生专题汇报	俞春东

11月19-12月10日
E307

参考书和文献

Robert A. Weinberg

- 第一个抑癌基因Rb
- 人类的第一个原癌基因Kras



Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of

文献

1.Tumor supprssor（原癌基因）

Nature Reviews Cancer 9, 749-758 (October 2009) The first 30 years of p53: growing ever more complex

2. Oncogene （原癌基因）

Nature Reviews Cancer 3, 459-465. RAS oncogenes: the first 30 years

3.Tumor immunity （肿瘤免疫）

Cancer Cell, 2015, 27(4) Immune Checkpoint Blockade: A Common Denominator Approach to Cancer Therapy

4. Hippo and cancer （器官生长与肿瘤）

Br J Cancer. 2011;104(1):24-32. Mst1/2 signalling to Yap: gatekeeper for liver size and tumour development

5.Hallmarks of cancer （肿瘤综述）

Cell. 2011;144(5):646-74. Hallmarks of cancer: the next generation. Hanahan D(1), Weinberg RA.

课程目标

- 掌握肿瘤学的基本概念
- 了解肿瘤发病主要因素
- 了解肿瘤学研究的概况
- 文献阅读、总结、批判

周大旺教授

❖ 1997年	厦门大学	有机化学学士
❖ 2002年	美国纽约城市大学	生物化学硕士
❖ 2006年	美国爱因斯坦医学院	微生物与免疫学博士
❖ 2006-09年	美国哈佛大学医学院	医学系博士后
❖ 2009-11年	美国哈佛大学医学院	医学系讲师
❖ 2011-至今	厦门大学生科院	课题组长、教授、博导

周大旺教授简介

- ❖ 科技部重点研发计划项目首席科学家
- ❖ 国家基金委杰出青年基金项目获得者
- ❖ 教育部“长江学者奖励计划”特聘教授
- ❖ 国家科技部中青年科技创新领军人才
- ❖ 国家千人计划生物医药专委会副主任
- ❖ 荣获中国侨界贡献奖和普洛麦格创新奖

主要研究方向与成果

- ➢ Hippo信号通路在器官再生重塑调控与疾病发生中机制与功能
- ➢ 近五年以通讯作者在以下等刊物上发表研究论文11篇，其中CNS子刊6篇（3篇为封面文章）
- ➢ 靶向Hippo激酶促进肝脏损伤修复抑制剂专利以“里程碑1000万付款加销售提成”成功转让

封面文章　封面文章　封面文章

Cancer Biology

第一讲：癌症学说及癌症分类

癌症概况

世界范围

根据《世界癌症报告》，2012年癌症新发病例达1409万，死亡820万，现有癌症患者3254.5万，分别比2000年的1000万、620万、2240万增加40.9%、32.3%、45.3%。世界卫生组织预测2025年全球人口83亿，癌症新发病例将达到2000万，死亡病例达到1140万。

中国

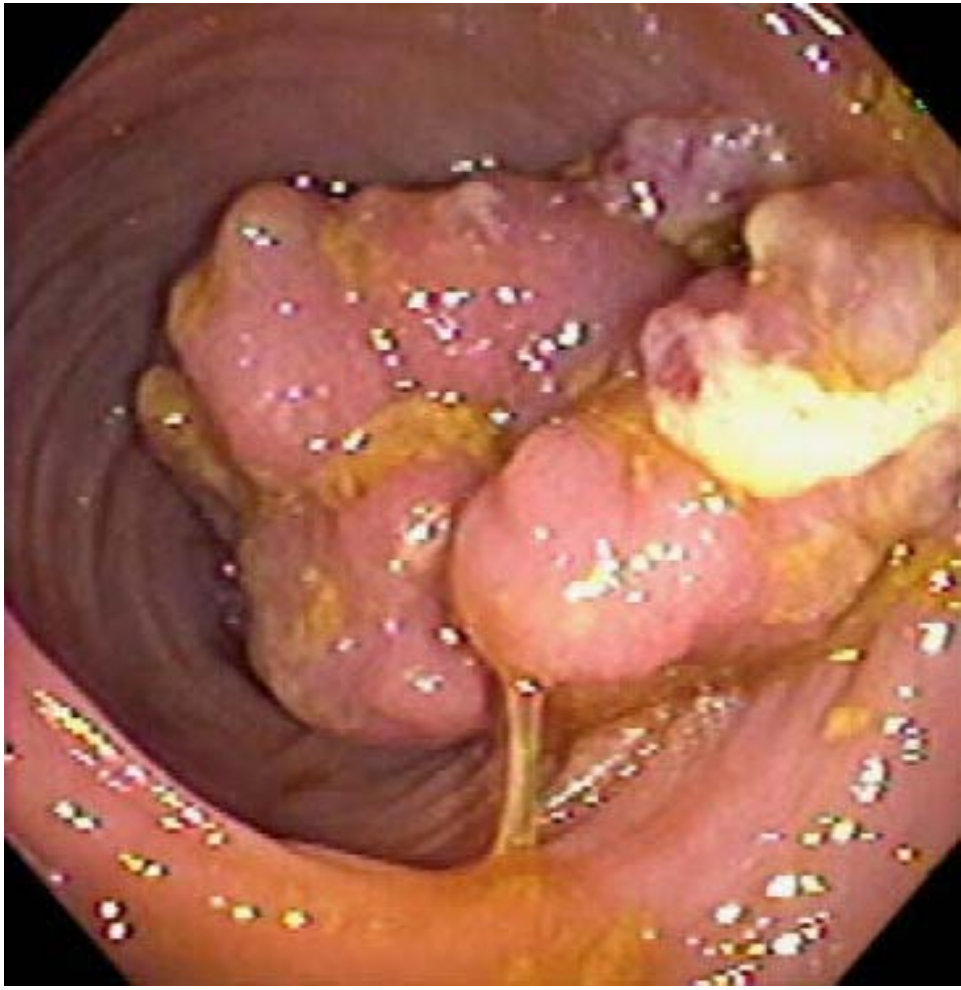
我国流行情况亦如此，根据1990—1992年和2004—2008年次全国死亡原因调查，15年间癌症死亡率上升25.5%，占总死因构成比由17.94%上升至22.32%。2012年中国癌症新病例达312万，每分钟就有6人患上癌症；癌症死亡220万，占全球癌症死亡26.9%。到2020年将达276万。

由此可见，癌症是本世纪人类的第一杀手，并成为全世界的公共卫生问题。

Introduction

- What **is** cancer?
- What **causes** cancer?
- How do we **prevent** cancer?
- How do we **treat** cancer?

Colon Cancer



What is cancer?

- **A foreign body?**
- **A parasite?**
- **Produced by “evil” force?**

Neoplasma:

“Neo”=New
“Plasma”= formation;

Tumor:

Solid mass,
tumor means a neoplasm that has formed a lump

History of Cancer

- Hippocrates（希波克拉底）: Greek physician (460-370 B.C) “father of medicine”
- body was composed of four fluids:
  - blood, phlegm（痰）, yellow bile and black bile.

Humour	Season	Element	Organ	Qualities	Ancient name	Modern	MBTI	Ancient characteristics
Blood	spring	air	liver	warm & moist	sanguine	artisan	SP	courageous, hopeful, amorous
Yellow bile	summer	fire	spleen	warm & dry	choleric	idealist	NF	easily angered, bad tempered
Black bile	autumn	earth	gall bladder	cold & dry	melancholic	guardian	SJ	despondent, sleepless, irritable
Phlegm	winter	water	brain/lungs	cold & moist	phlegmatic	rational	NT	calm, unemotional

What is cancer?

- **Hippocrates: Greek physician (460-370 B.C) “father of medicine”**

- **body was composed of four fluids:**

Blood（血）, phlegm（痰）, yellow bile （黄胆汁） and black bile （黑胆汁）.

- **excess of black bile → cancer.**

- **for the next 1400 years.**

New Technology： Microscope

- **1590**：Dutch（荷兰） eye glass makers, *Zaccharias Janssen* and son *Hans Janssen*： multiple lenses placed in a tube:
  - forerunner of the compound microscope and telescope.

- **1665**, *Robert Hooke* (1635-1703), English microscopist
- --empty small compartments (隔舱）
  The “cell” was discovered!
  Latin, *cellula* ; i.e., small compartment

1665, *Robert Hooke* (1635-1703)

New Technology： Microscope

- **1676, *Anton van Leeuwenhoek*, using a simple microscope, was the first to observe microorganisms**
- **1700, first description of the nucleus by *Leeuwenhoek.***

New Theory： Cell

- 1838 *Matthias Schleiden* (1804-1881)

  German botanist（植物学家）

  Thousands of **plant** specimens

  → all the vegetables are made of cells.

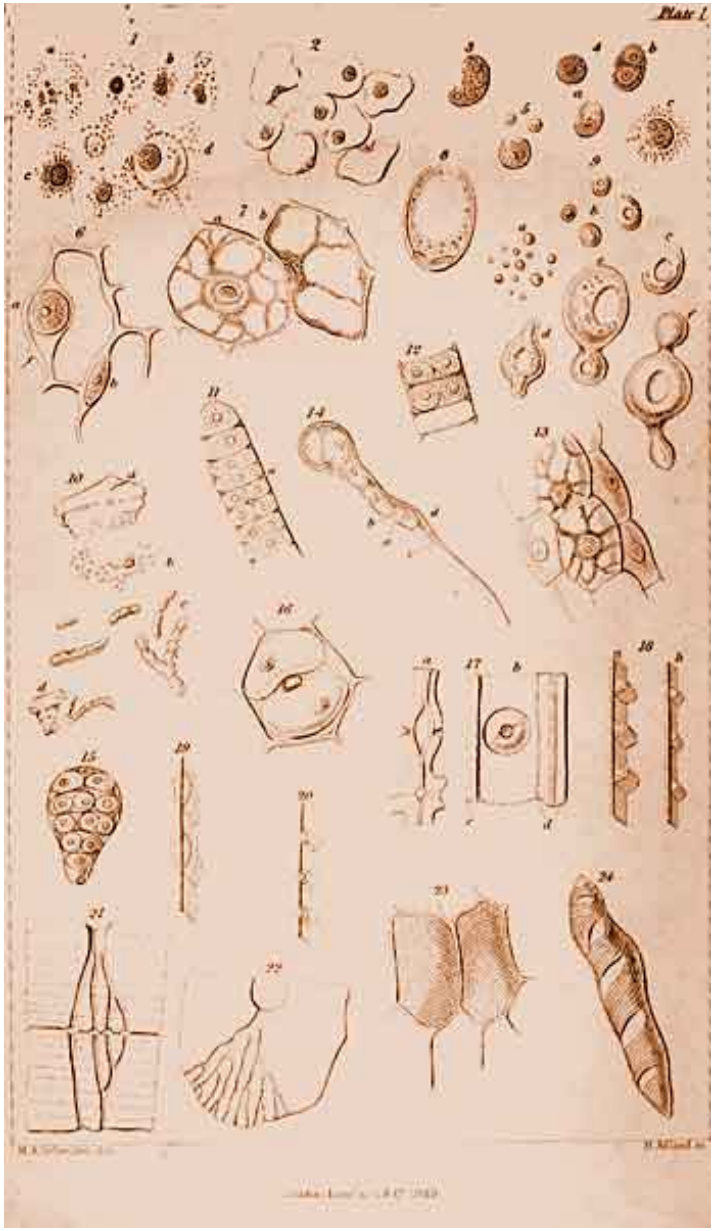
- 1839, *Theodor Schwann* (1810-1882)

  German zoologist and physiologist (生理学家）

  → all living beings were composed of cells.

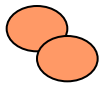
施莱登

1838 *Matthias Schleiden*

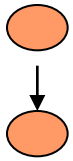


Cell theory

1. All living beings are composed of cells.



2. The living beings may grow and reproduce themselves because the cells may in turn multiply.



3. The new cells are formed from other pre-existing ones.

Histology 组织学

- *Marie François Bichat*, French pathologist (1771-1802)
  A texture was a “tissue” by its macroscopic （宏观） physical properties.
  tissu = to weave (编织式样)

- in 1819, *A. Mayer* -Histology.
  histos = tissue
  logos = study

1852: first textbook of Histology：
Rudolph von Kölliker (1817-1905)
Swiss professor of Anatomy

<<*Handbuch der Gewebelehre*>>
(i.e., The book for teaching tissues)

Histology of Tumor

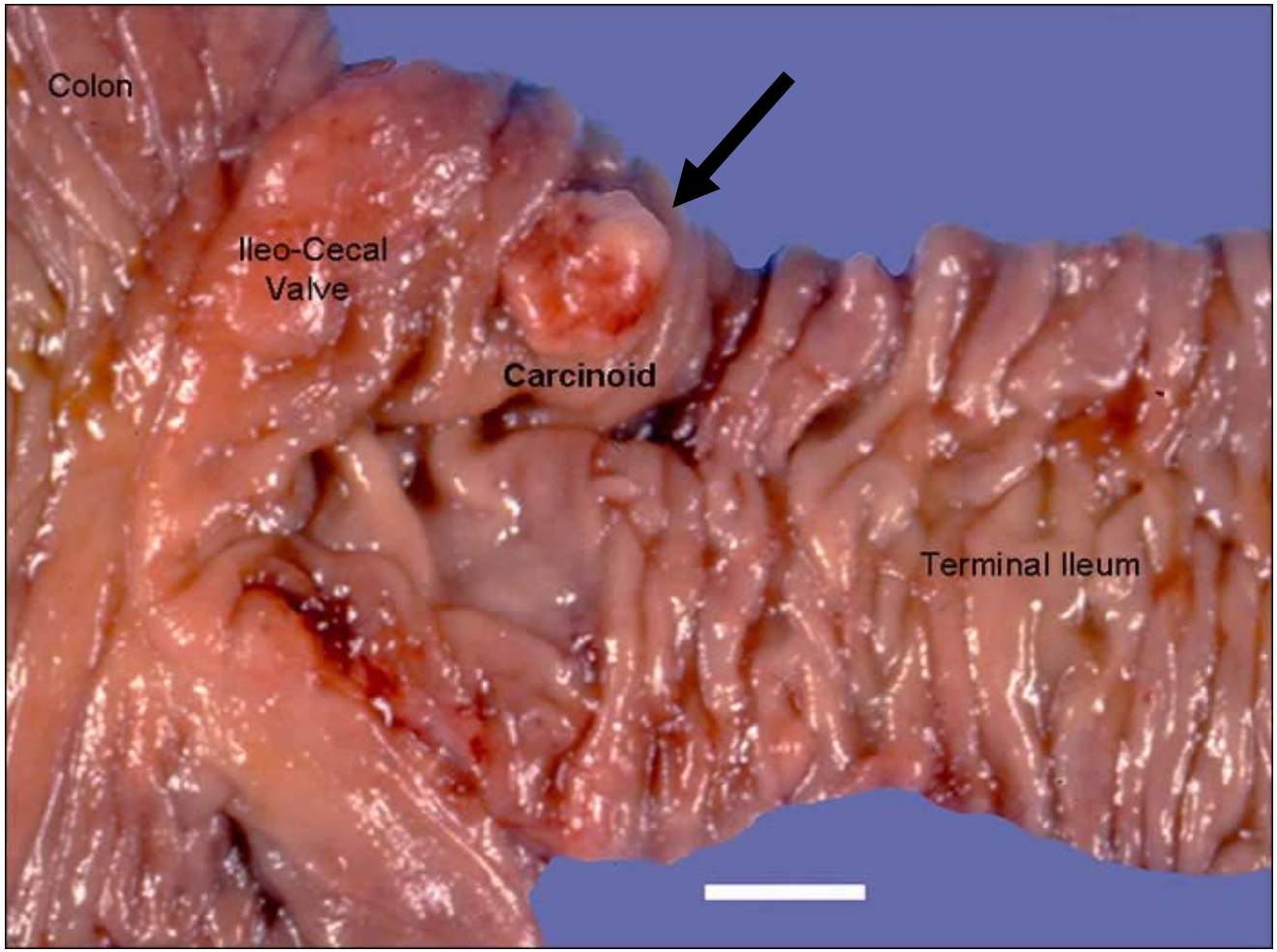
- A foreign body?
- A parasite?
- Produced by “evil” force?

- Tumor under microscope:
  - Mass of cells
  - Similarity to surrounding tissue
  - Less organized

  → Tumors arise from self

Carcinoid Tumor（大肠类癌）of the Ileum

大肠



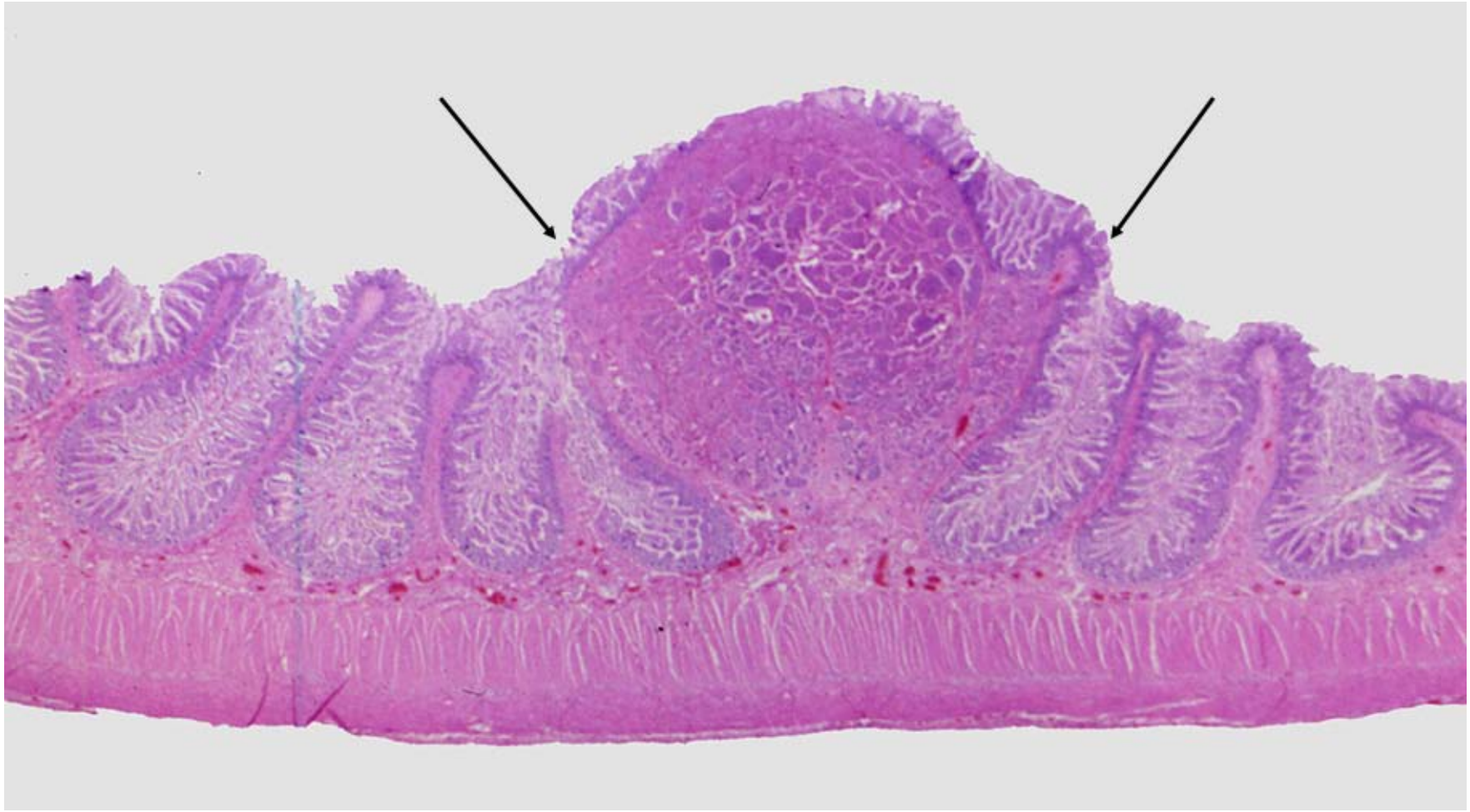
小肠

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

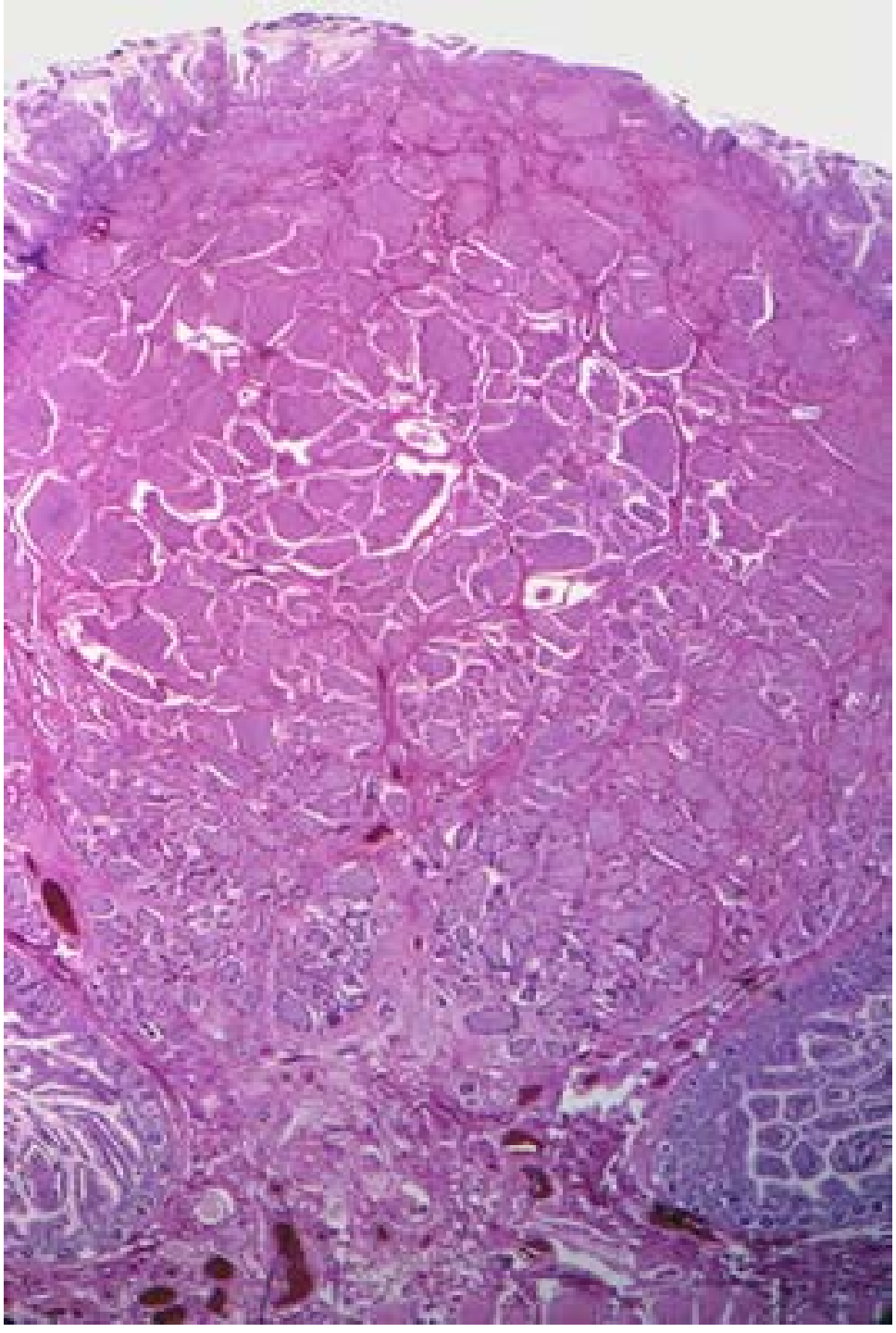
a slow-growing type of neuroendocrine tumor

小肠： 十二指肠**(Duodenum),** 空肠**(Jejunum),** 回肠**(***Ileum***).**

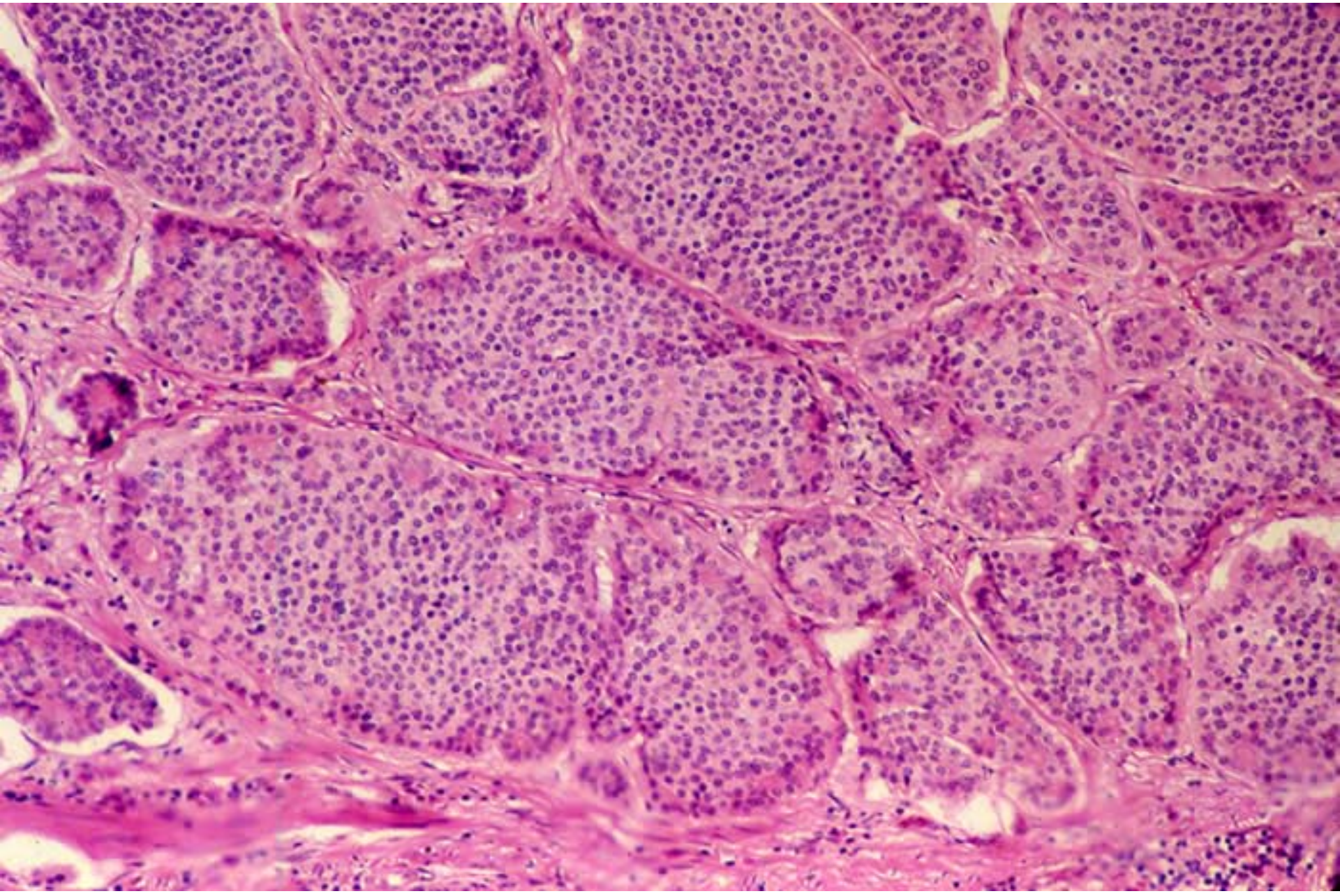
Submucosal（黏膜层下） carcinoid tumor of illeum



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



closely packed, uniform round cells with small, central nuclei



Classification of tumors

1. Based on clinical effect on patients
2. Based on location/tissue of origin
3. Based on microscopic features
4. Stages of tumor

Based on clinical effect on patients

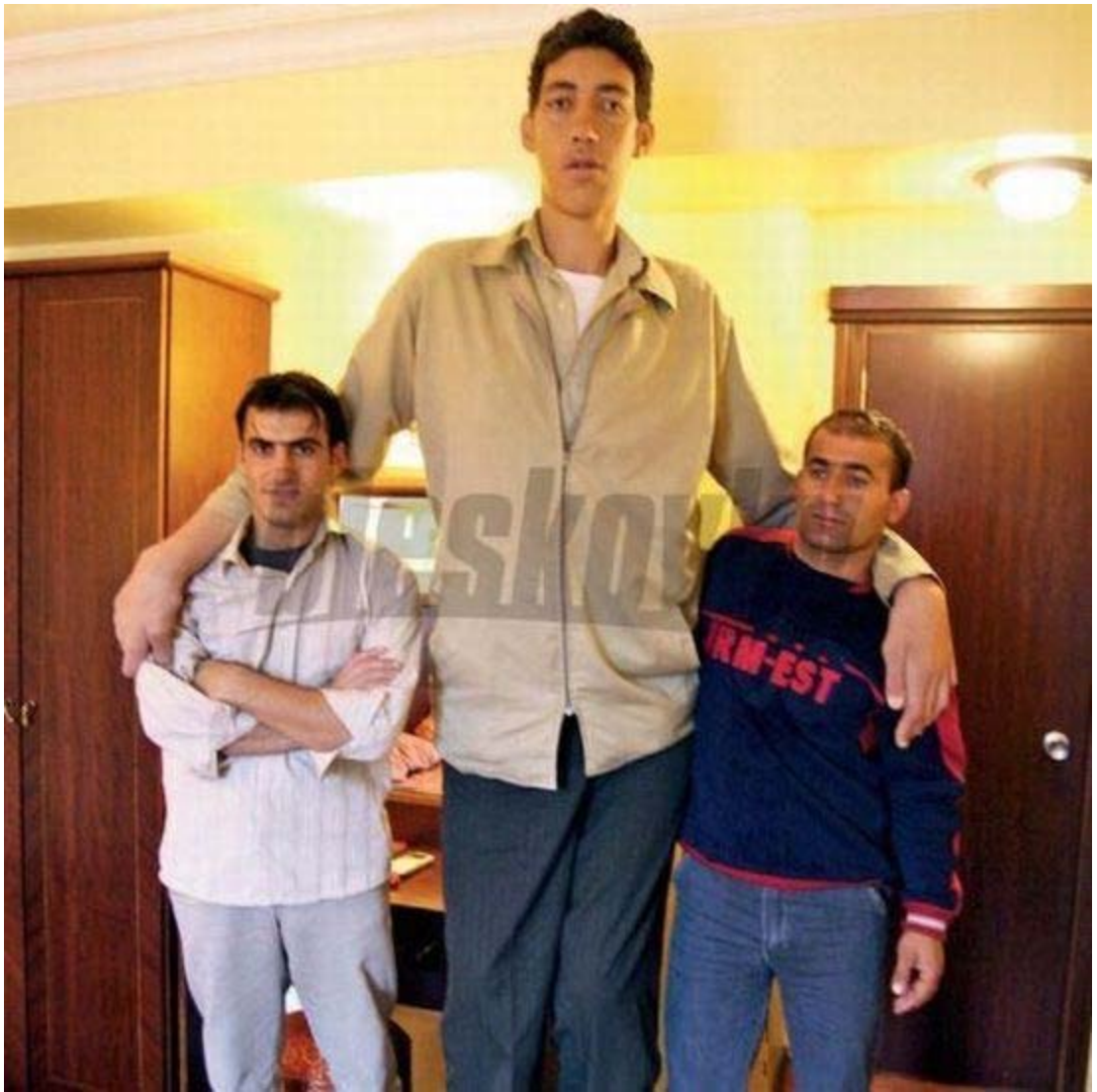
- Benign:
  - Grows locally
  - Without invading of adjacent tissues
- Malignant
  - Invade nearby tissues
  - Spawned metastasis

Clinical effect of Benign tumor

- Secrete high levels of hormones
- Grow only in one place, cannot spread or invade other parts
- Be dangerous if they press on vital organs

Guinness World Records

2.47 m Sultan Kosen, from Turkey



2009 World’s tallest man

pituitary gigantism
（垂体性巨人症）

World’s tallest woman

Pituitary tumor （Benign)

Because she is illiterate, since 1992 Yao Defen has been forced to earn a living by traveling with her father and performing.

Acromegaly（肢端肥大症）

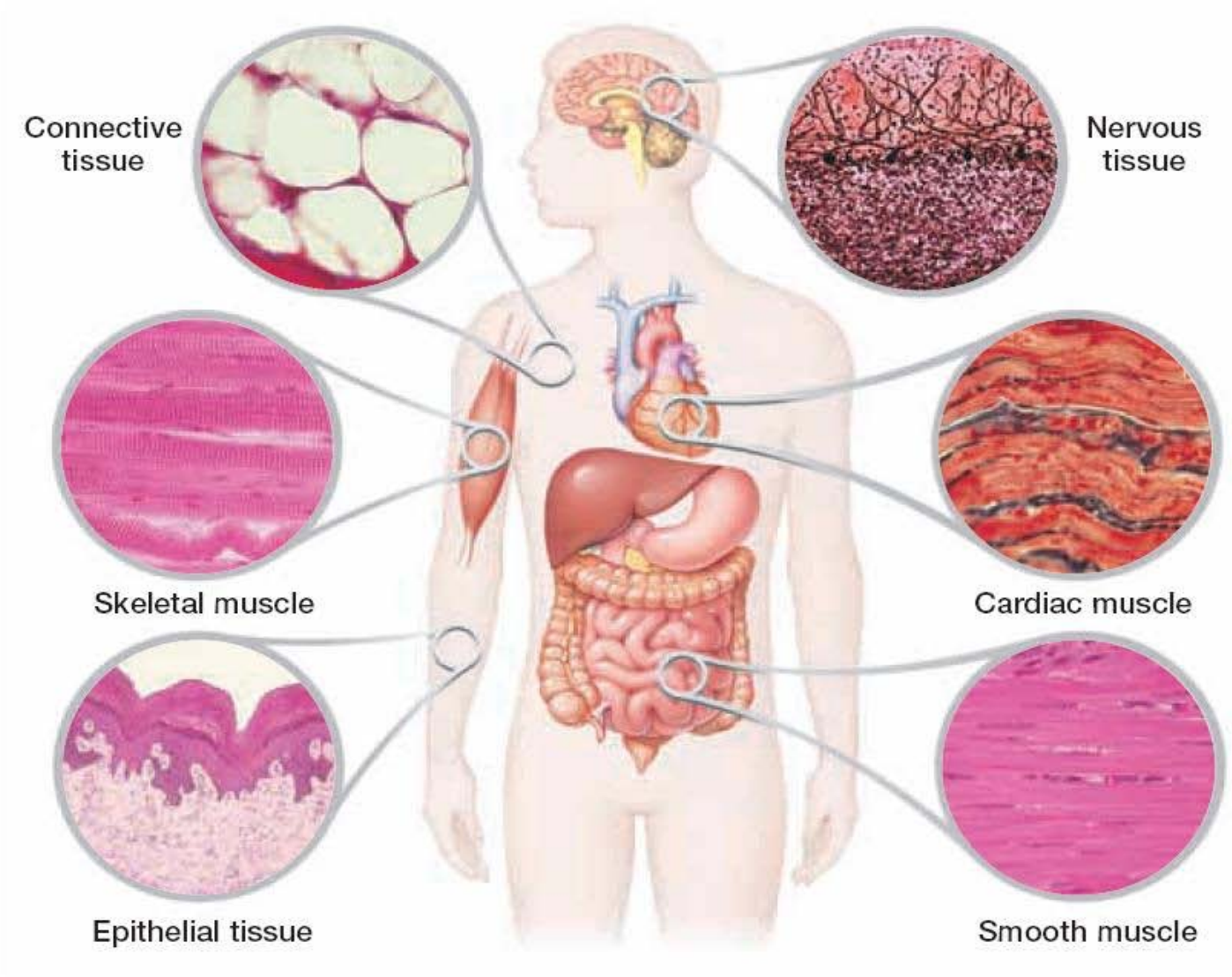
Clinical effect of Malignant tumor

- 90% cancer deaths are due to metastasis

Classification based on tissues

Human Body Tissues

asweknowit.net/images_edu/ dwa5%20tissues.jpg



Knowing Cancer Origin Informs Therapy

Prostate	33%
Lung & bronchus	13%
Colon & rectum	11%
Urinary bladder	6%
Melanoma of skin	4%
Non-Hodgkin lymphoma	4%
Kidney	3%
Oral Cavity	3%
Leukemia	3%
Pancreas	2%
All Other Sites	18%

Total Men: 689,560

Target-specific Drugs:

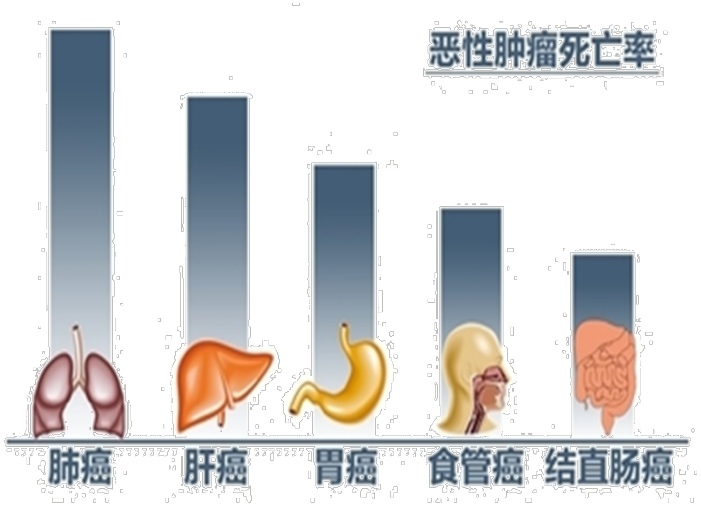
- HERCEPTIN
- TARCEVA
- AVASTIN, ERBITUX
- RITUXAN
- SUTENT
- GLEEVEC
- TARCEVA

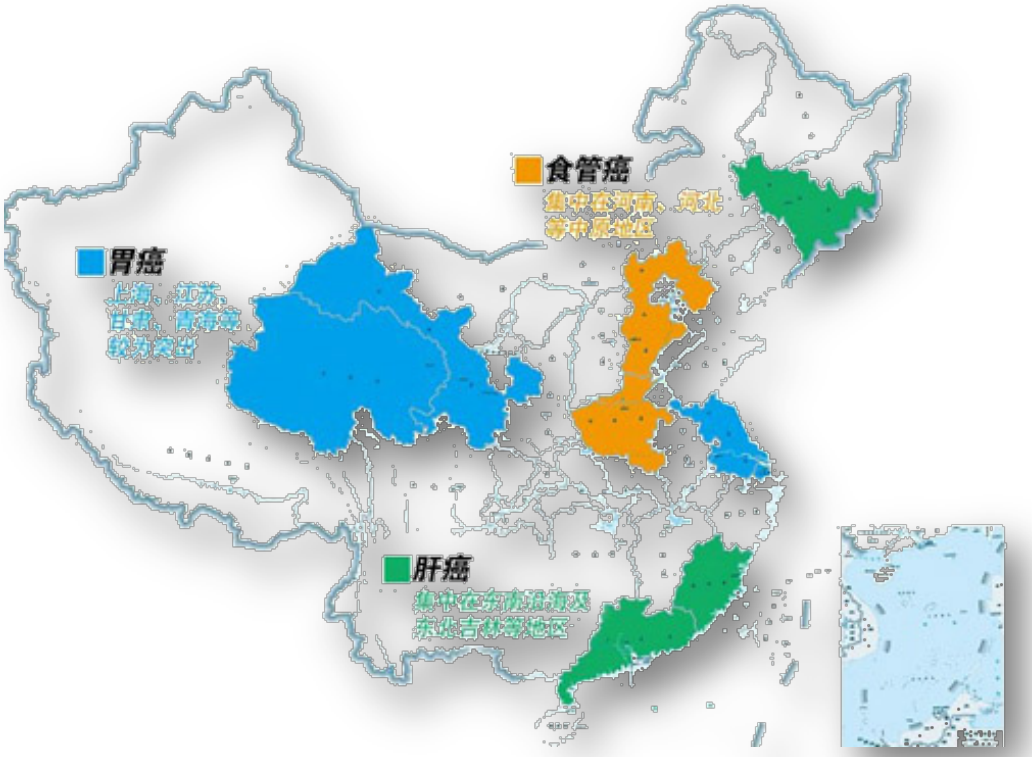
32%	Breast
12%	Lung & bronchus
11%	Colon & rectum
6%	Uterine corpus
4%	Ovary
4%	Non-Hodgkin lymphoma
4%	Melanoma of skin
3%	Thyroid
2%	Urinary bladder
2%	Pancreas
20%	All Other Sites

Total Women: 668,470

Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2004.

更令人关注的是，2012年中国新增癌症病例高居世界第一位，肝癌和食管癌患者约占全球一半，死亡分别占全球的51%和49%；胃癌症例和死亡均占全球40%；鼻咽癌80%发生在中国。

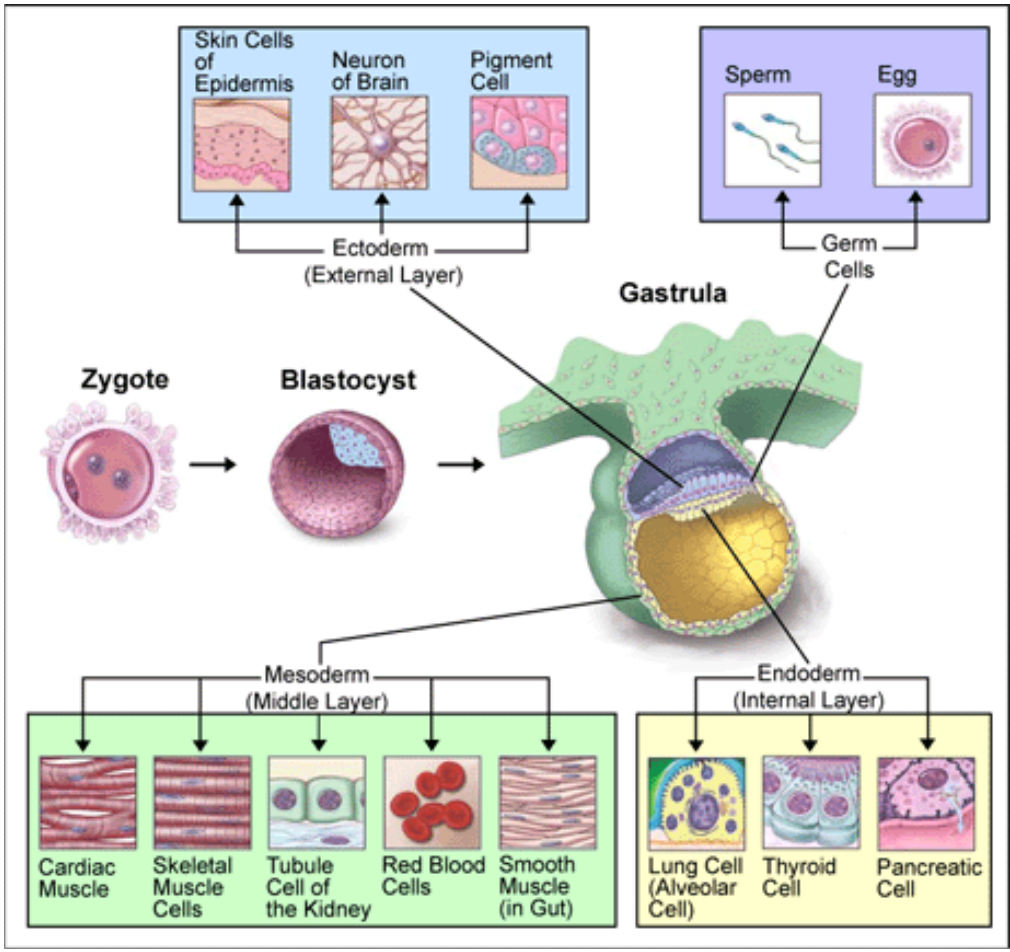




全国肿瘤登记中心发布的《2012中国肿瘤登记年报》

Cancer Cell types

- **Most adult cancers are carcinomas**
  - **Epithelial origin**
- **In contrast, most childhood cancers are:**
  - **Leukemias/lymphomas**
  - **Blastomas → Embryonal cells**
  - **Sarcomas → Mesenchymal origin**



Source:http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html

Normal Proliferative Human Cells & Tissues

Epithelial Linings

- **Respiratory epithelium**
- **Gastro-intestinal linings**
- **Genito-urinary tract**

Glandular Linings

- **Mammary gland**

Skin

Ovary and Testis

Bone Marrow

Myoblasts

Fetal Tissues

Organ Hypertrophy

Wound Healing

Neurogenesis

Based on tissue/cell of origin

I. **Carcinomas** = epithelia derived

   >80% of all human cancer-related deaths

1. **Adeno**carcinoma ← gland epithelia
2. **Squamous cell** carcinoma ← Seal, protective layers
3. Other

Classification of Epithelium

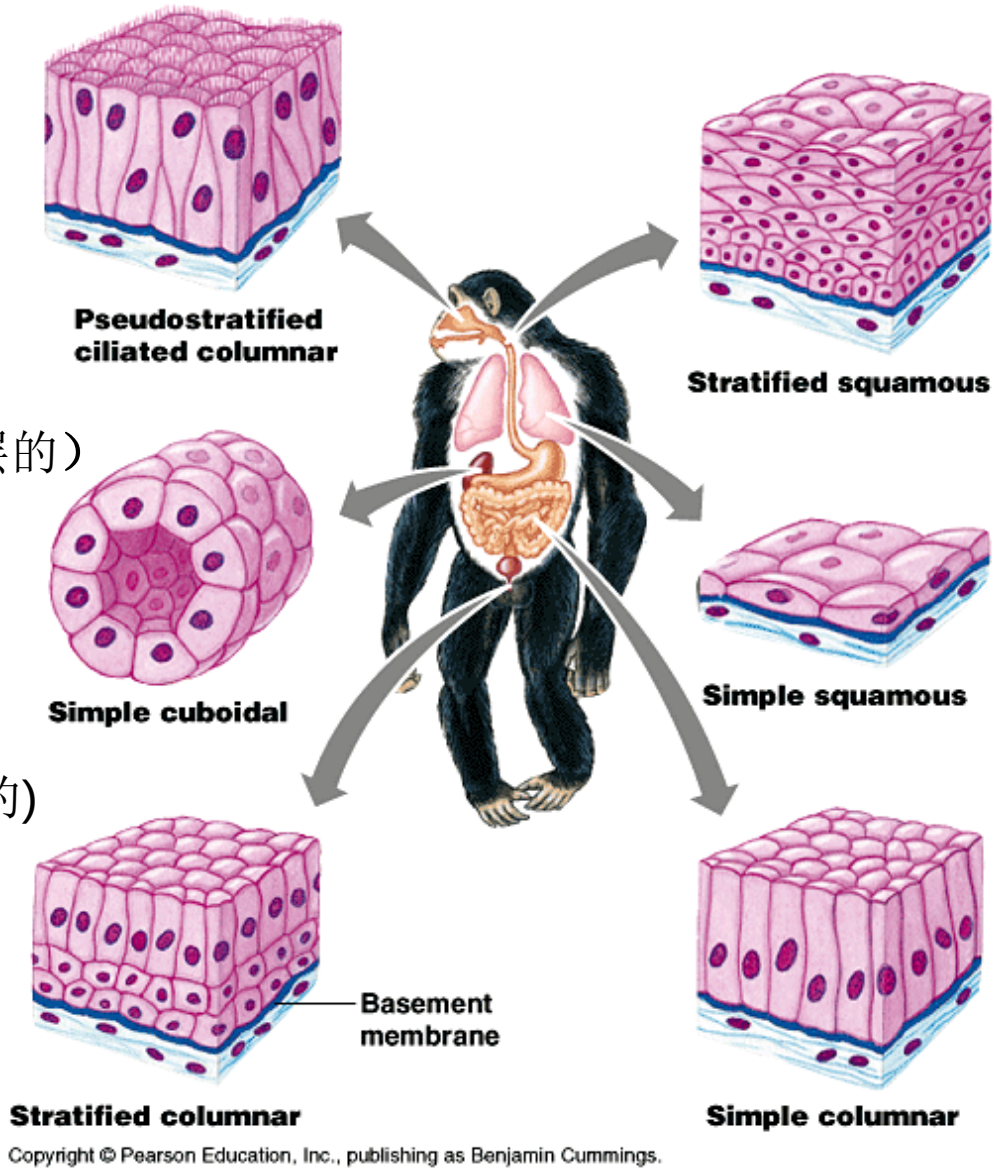
Simple: One cell layer

Stratified: two or more cell layers（分层的）

Squamous: wildth>height（鳞状的)

Columnar: Height> wildth(柱状的)

Cuboidal:wildth=height=depth (立方形的)



The Morphology of an Epithelium often Correlates with Its Function

1.Simple: One cell layer

Epithelia involved in secretion or absorption

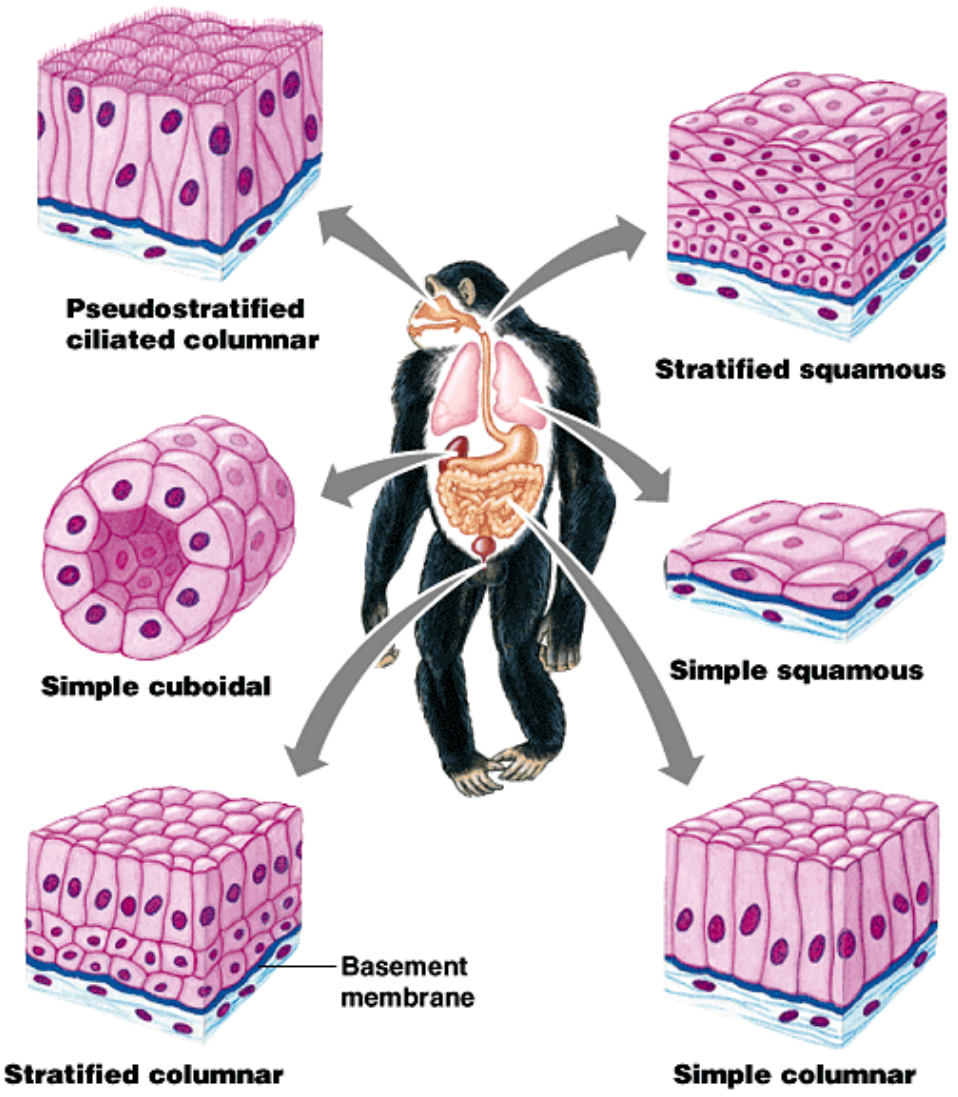
Transepithelial transport

2.Stratified: two or more cell layers

Transepithelial impermeability

3.Psedostratified:

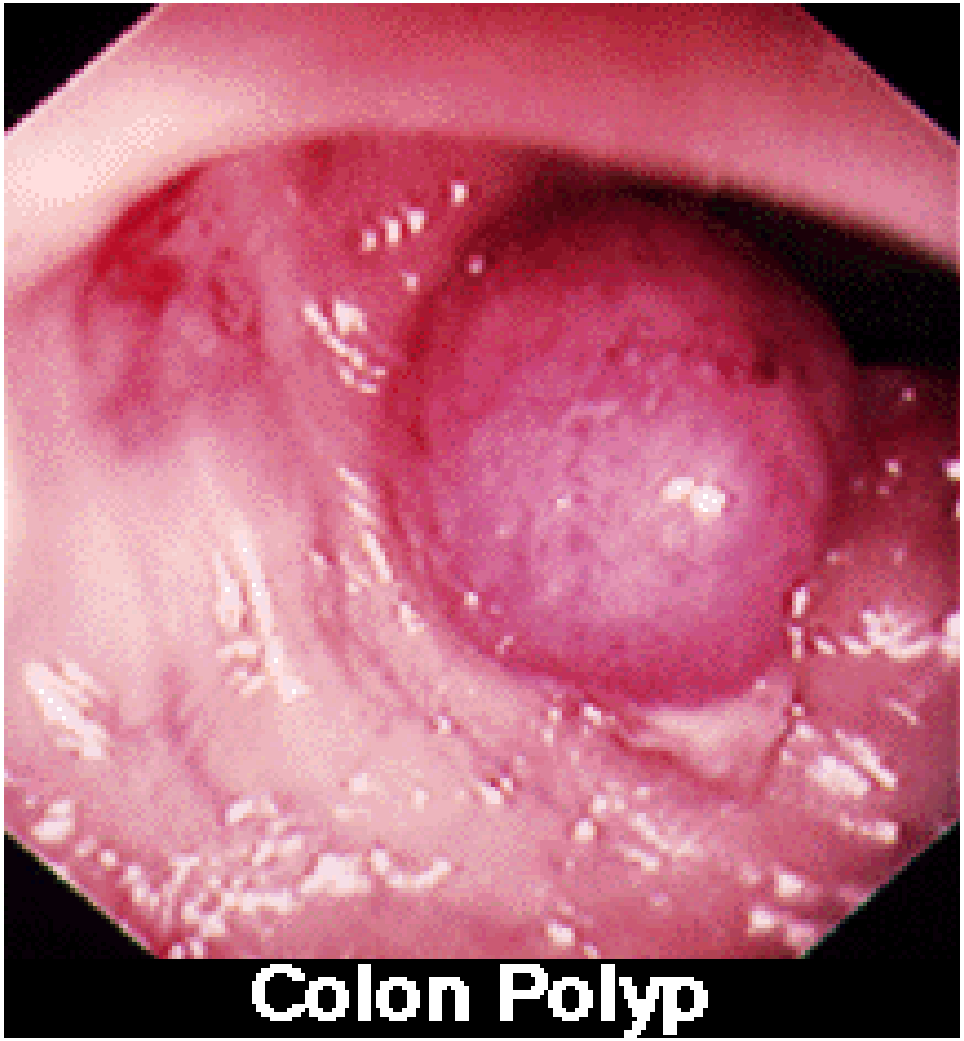
Maintain a stable population of cells to balance cell turnover



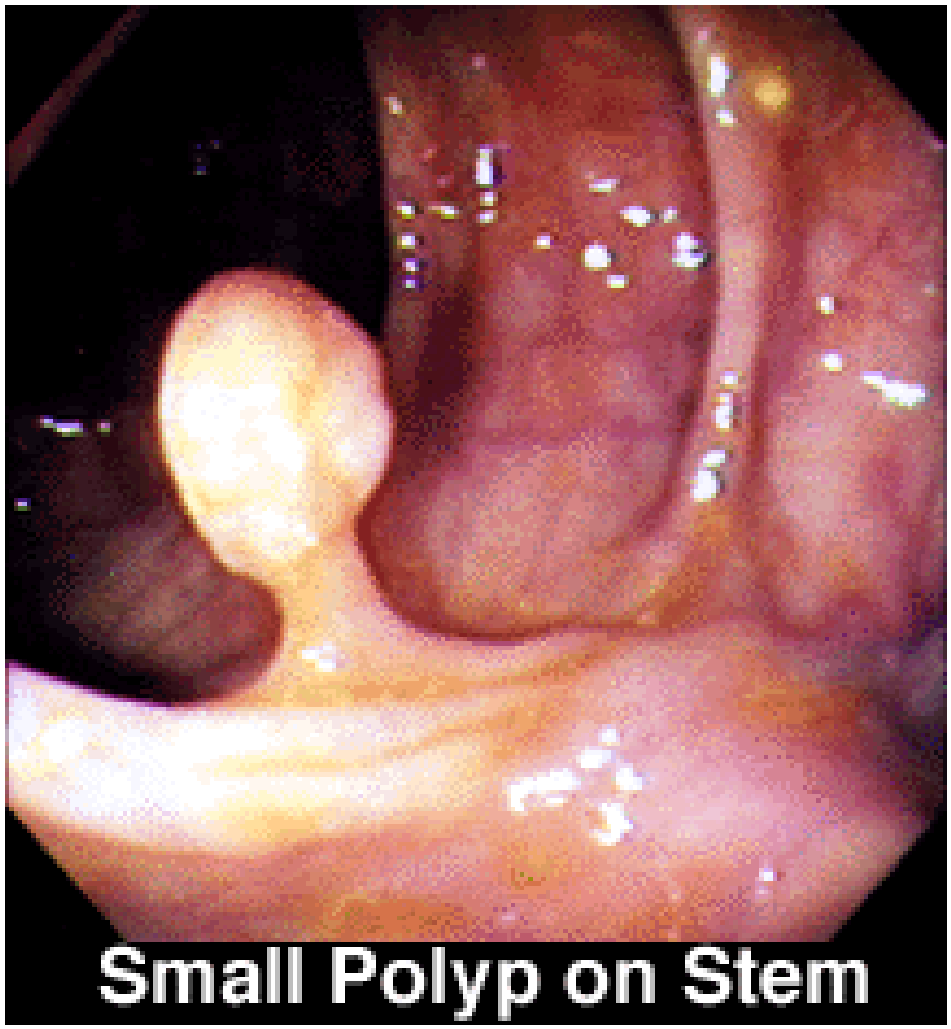
1. Adenocarcinoma ← gland epithelia

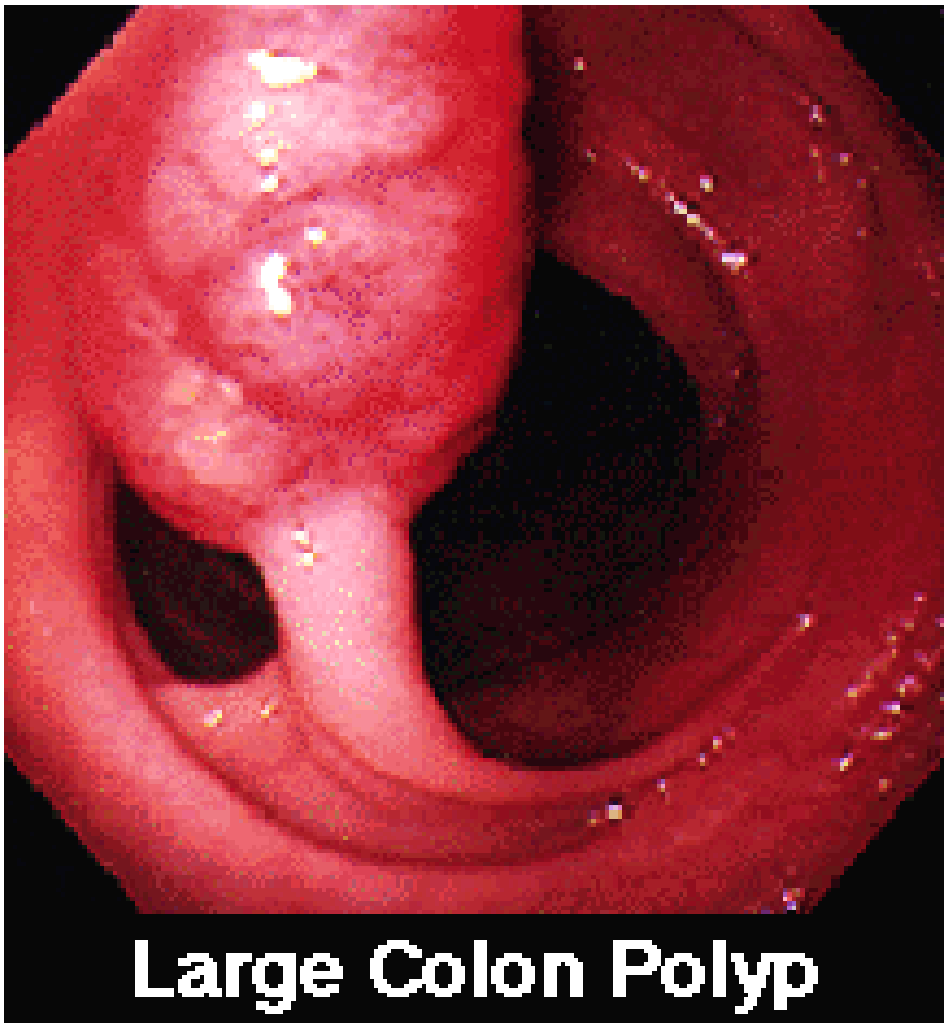
- Lung
- Stomach
- Pancreas
- Small intestine
- Colon
- Breast
- Uterus (Endometrium)
- Ovary

Colon

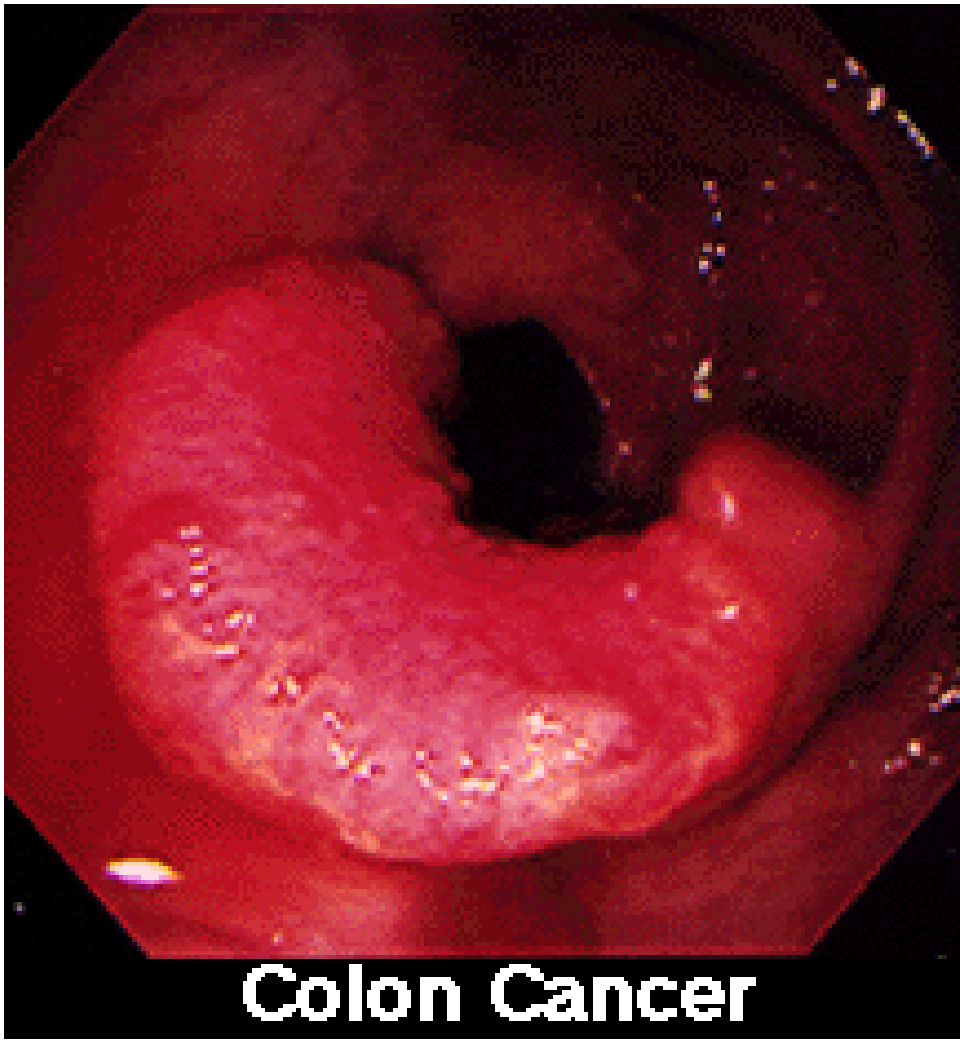


Colon Polyps

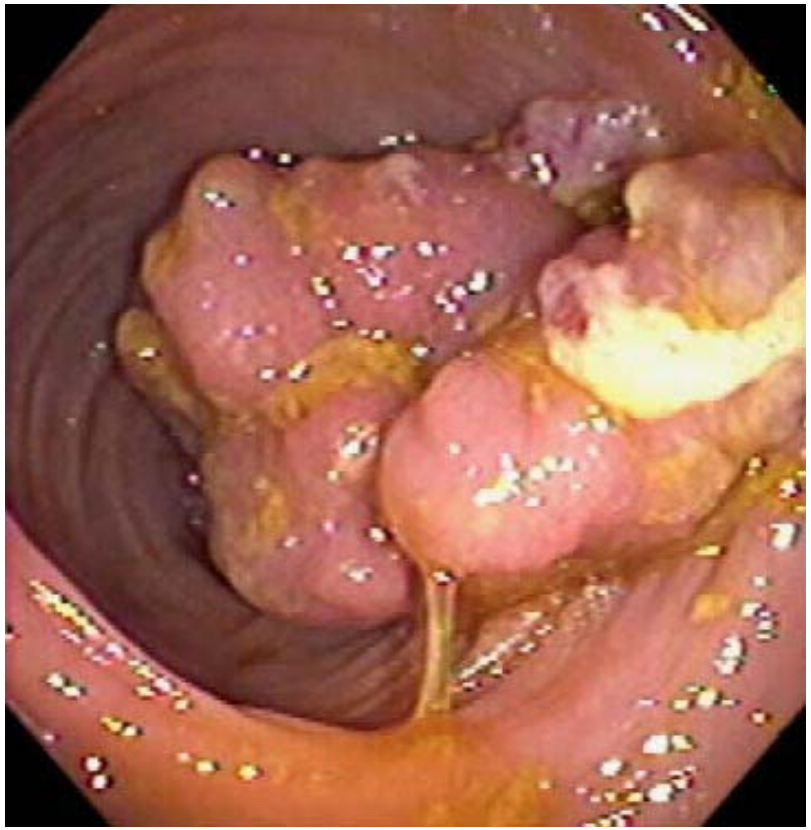


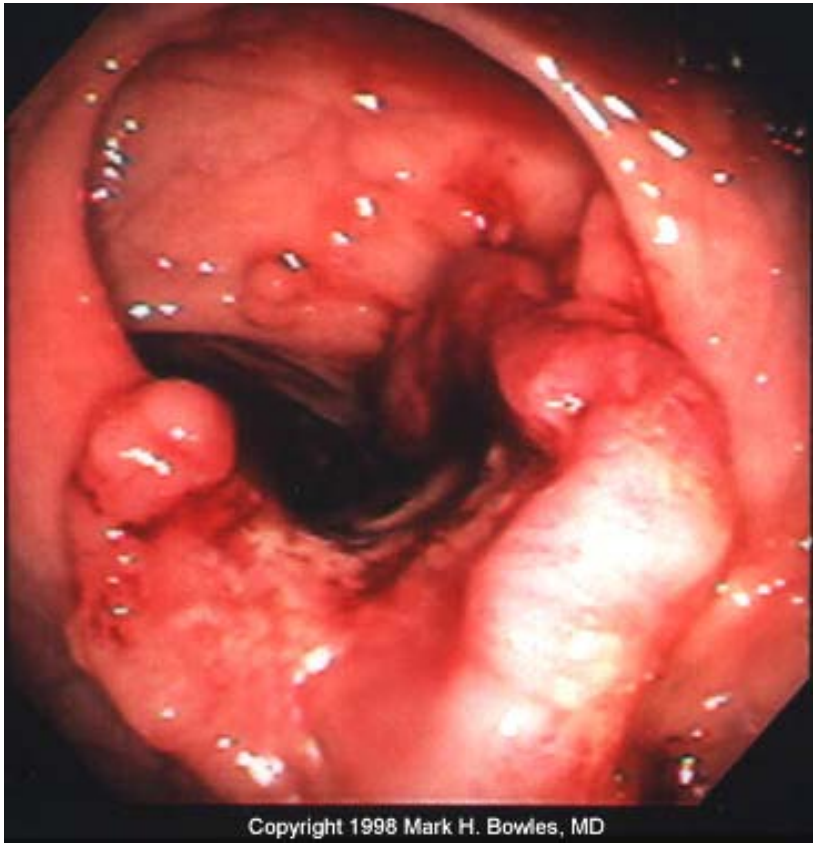


Colon cancer

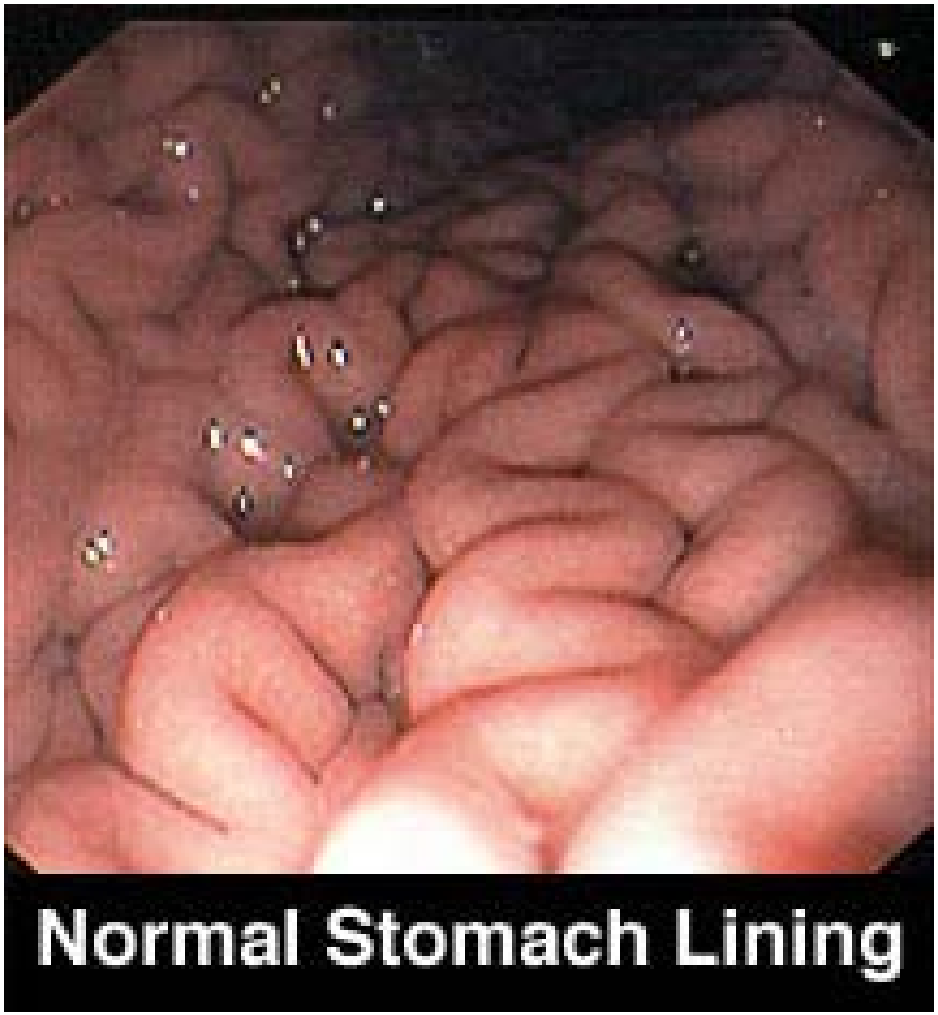


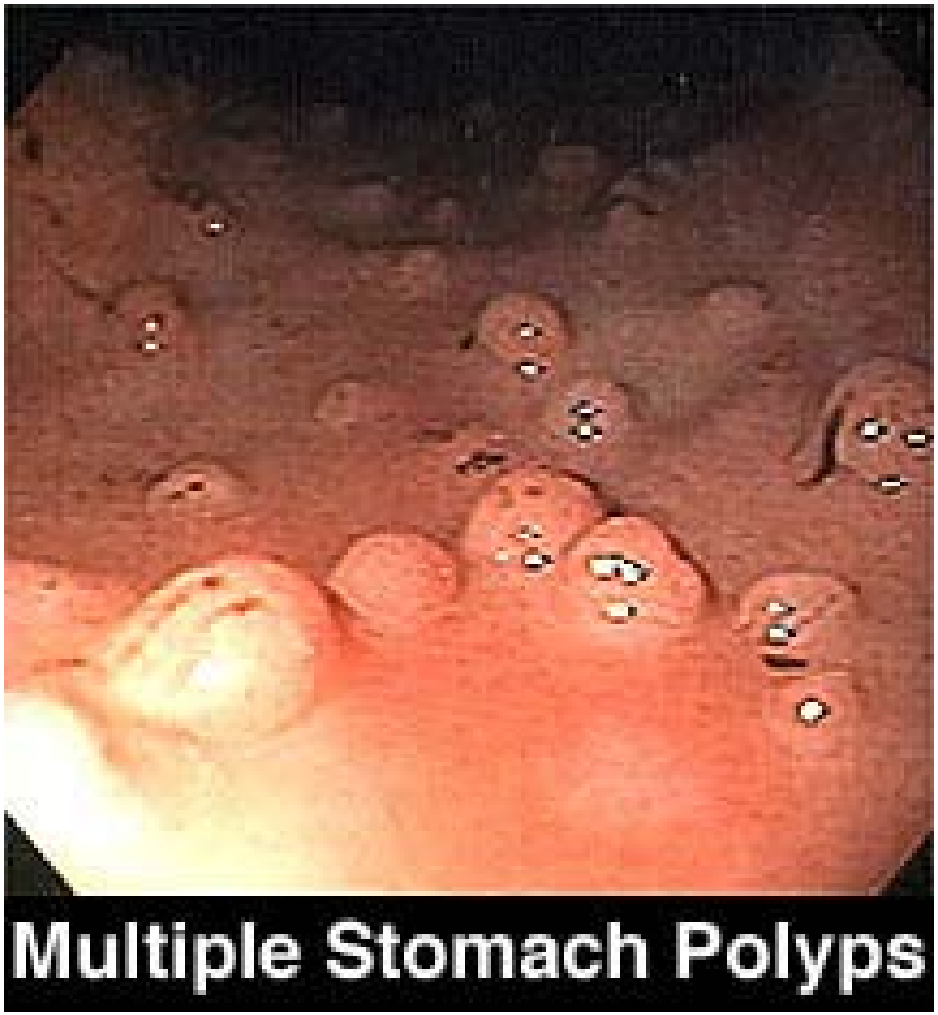
Colon polyps/cancer



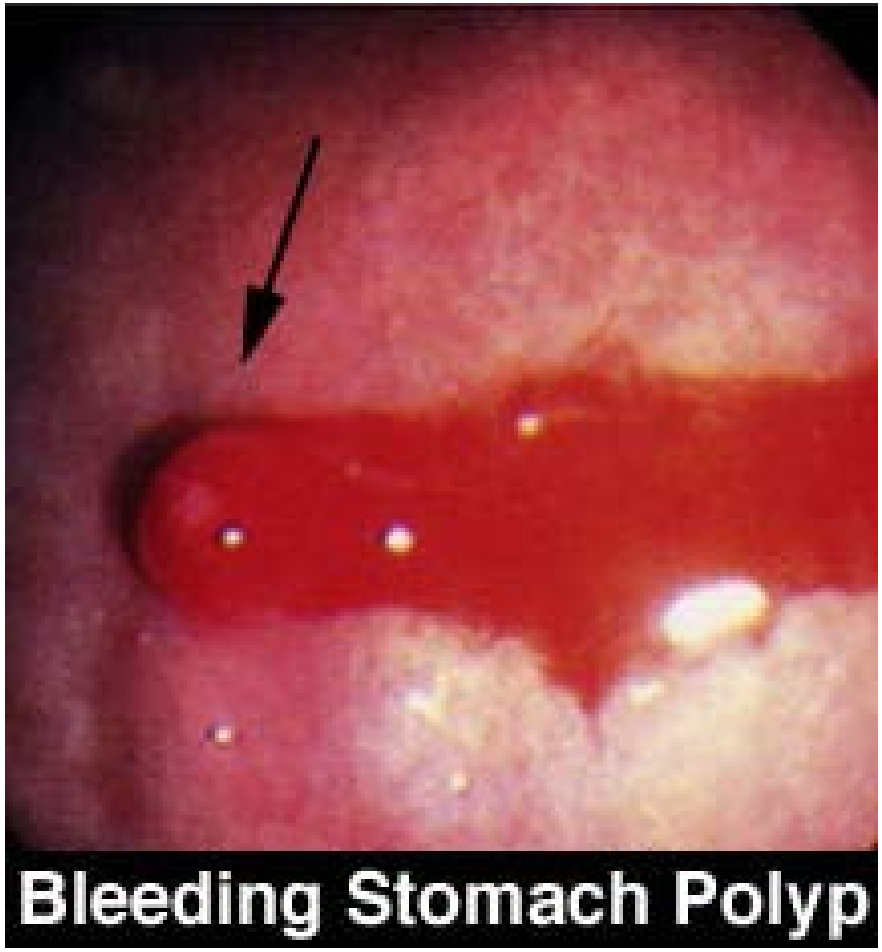


Stomach

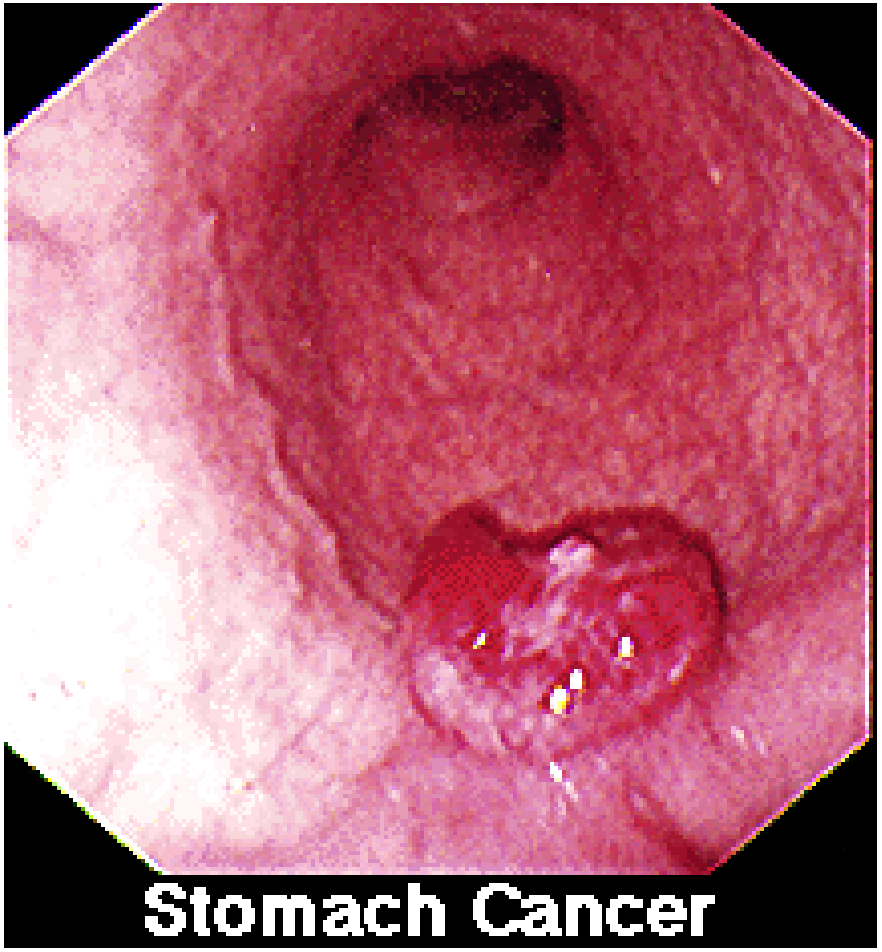




www.gihealth.com/images/imgStomachCancer.gif



Bleeding Stomach Polyp

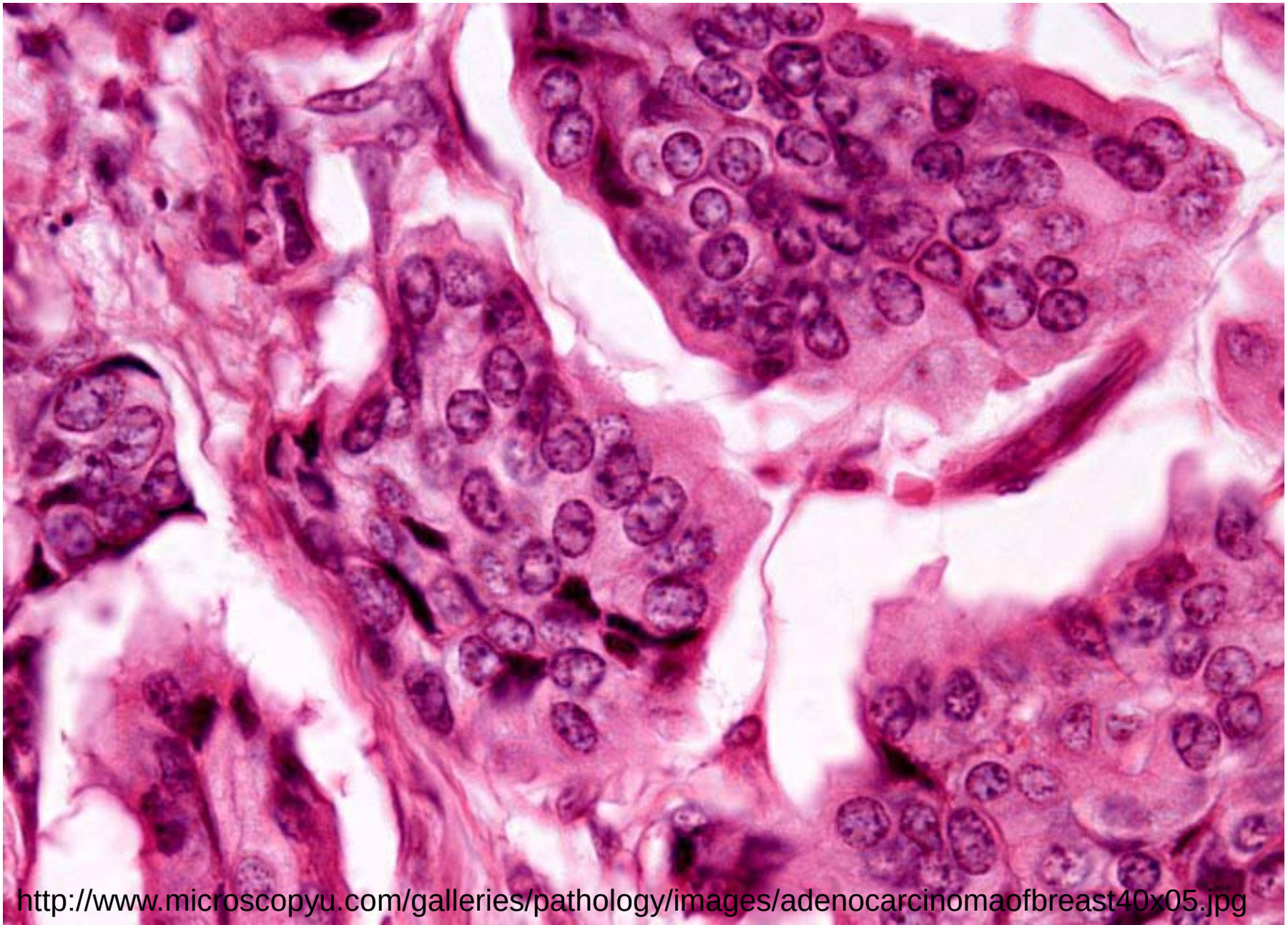


Stomach Cancer


Normal Liver

Colon Cancer spread to liver

Breast Adenocarcinoma



http://www.microscopyu.com/galleries/pathology/images/adenocarcinomaofbreast40x05.jpg

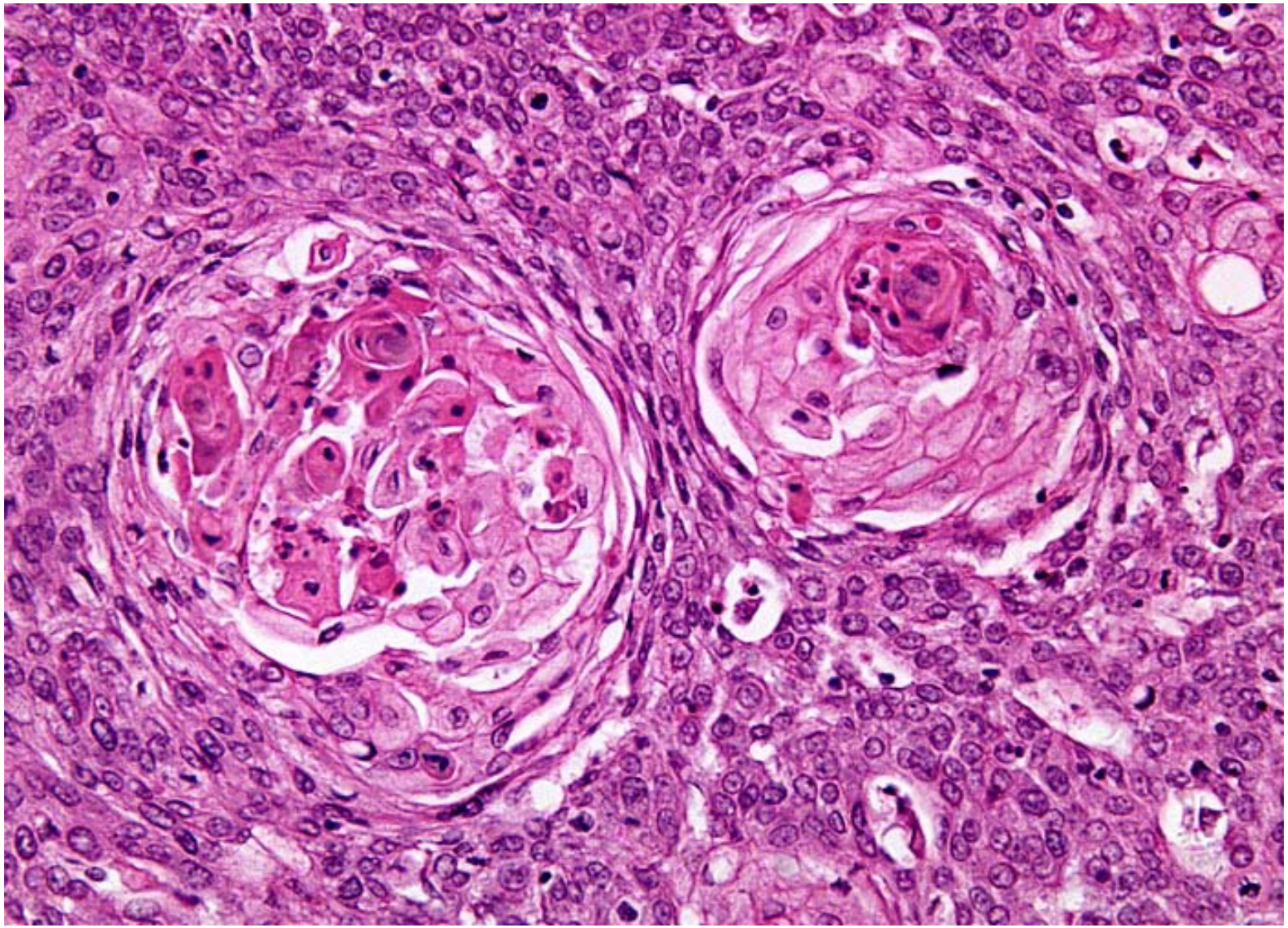
2. Squamous cell carcinoma ← Seal, protective layers

- Skin
- Esophagus(食道)
- Nasal cavity(鼻咽）
- Larynx(喉)
- Cervix(宫颈)

Squamous cell carcinoma

NCI VisualsOnline

Squamous Cell Carcinoma



http://www.microscopyu.com/staticgallery/pathology/all40x04.html

3. Other types of carcinoma

- Small cell lung carcinoma
- Large cell lung carcinoma
- Hepatocellular carcinoma (Liver cancer)
- Renal cell carcinoma (Kidney cancer)
- Transitional cell carcinoma (Urinary bladder)

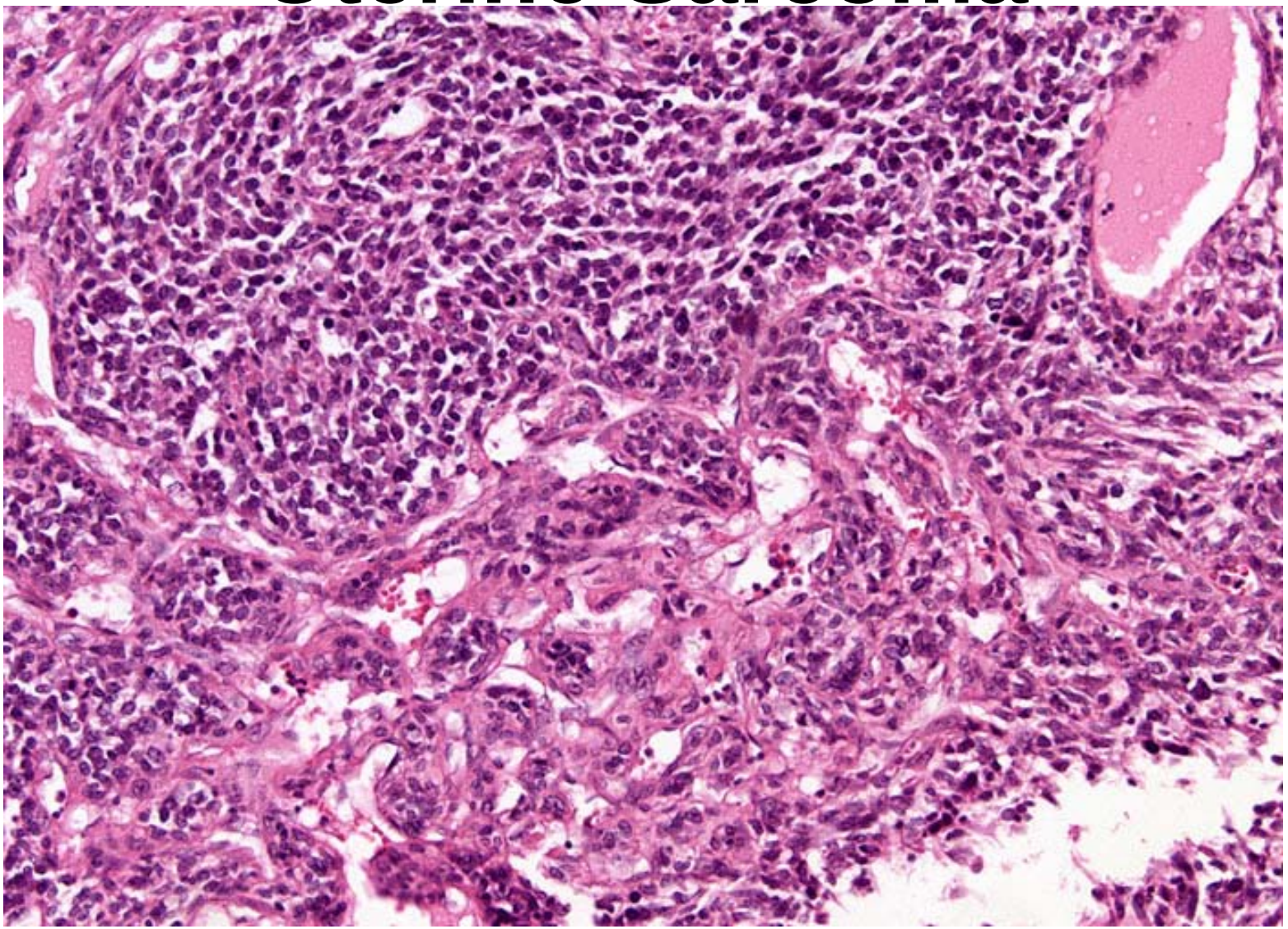
II. Sarcomas

- Derived from mesenchymal cells of connective tissues
- 1% cancer death

Types of Sarcomas

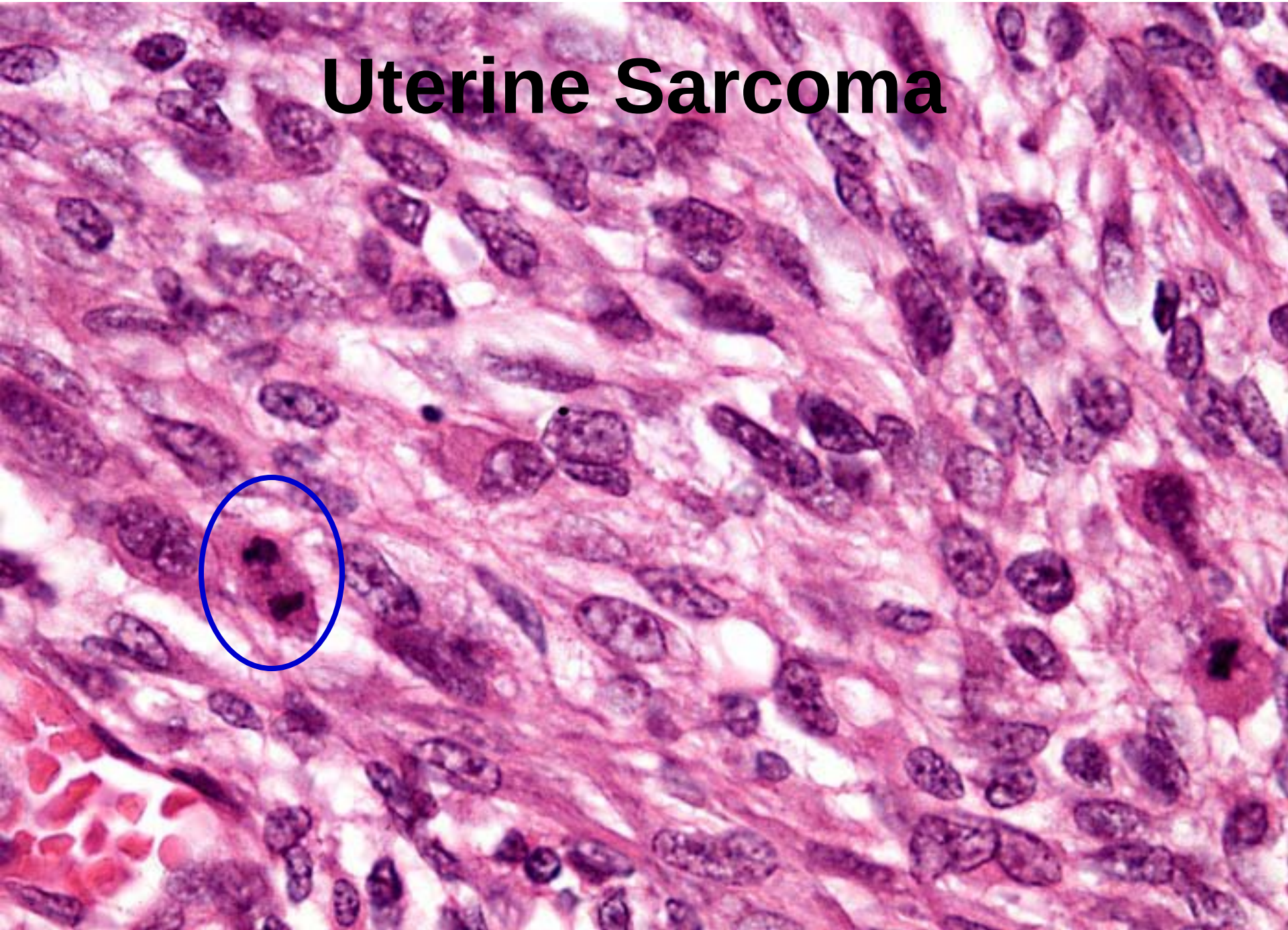
- Fibrosarcoma ← fibroblasts
- Liposarcoma← adipocytes
- Osteosarcoma ← Osteoblasts
- Leiomyosarcoma ← Smooth muscle
- Rhabdomyosarcoma ← Striated skeleton muscle
- Angiosarcoma ← precusors of endothelial cells

Uterine Sarcoma



http://www.microscopyu.com/galleries/pathology/images/sarcomaofuterus20x02.jpg

Uterine Sarcoma



III. Leukemia & lymphoma

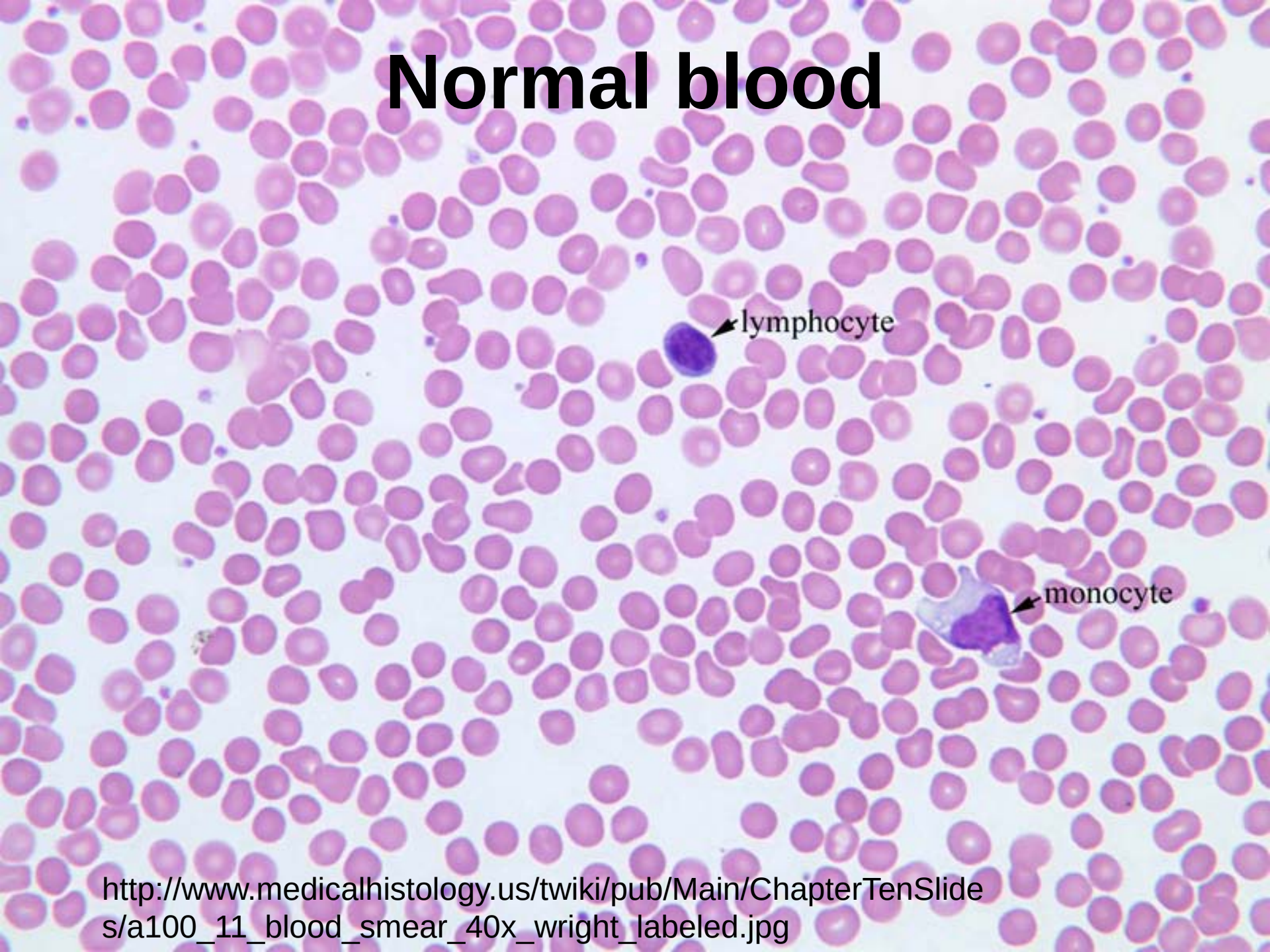
1. Lymphoma = Solid mass in lymph nodes
   - Hodgkin's lymphoma
   - Non-Hodgkin's lymphoma=lymphocytic lymphoma 15-20 subtypes
2. Leukemia=cancer cells in blood （from bone marrow)

2. Leukemia: cancer cells in blood

- Acute lymphocytic leukemia (ALL)
  - 80% from B cells, 20% from T cells
  - Distinguished by cell surface markers
- Chronic lymphocytic leukemia

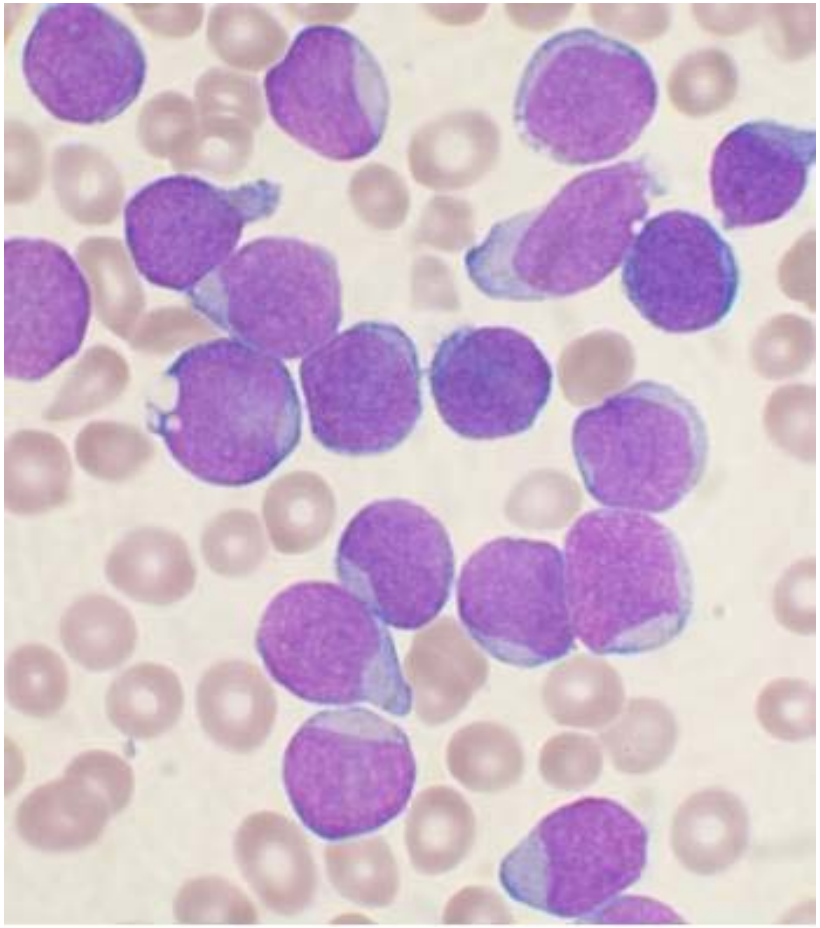
- Acute myelogenous leukemia (AML)
  - Small rim of cytosol, large nucleus
  - Pre-granulocytes (precursors of monocyte/macrophage)
- Chronic myelogenous leukemia
  - Bone marrow derived
- Multiple myeloma ← Plasma cell derived

Normal blood

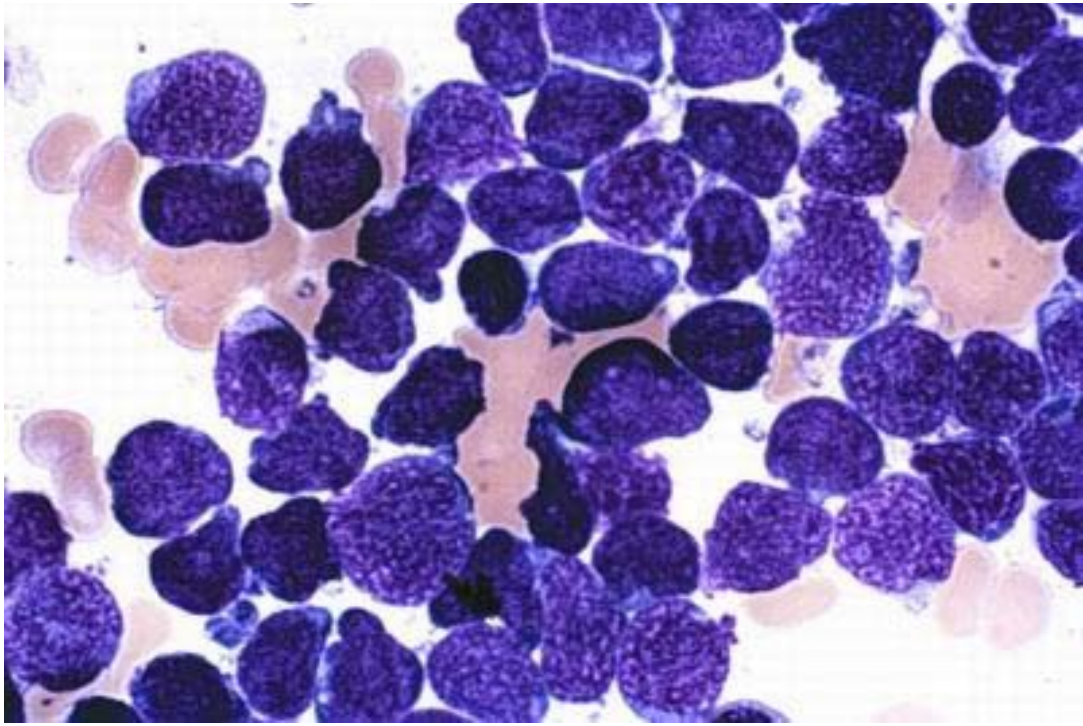


http://www.medicalhistology.us/twiki/pub/Main/ChapterTenSlides/a100_11_blood_smear_40x_wright_labeled.jpg

Acute lymphocytic leukemia (ALL)

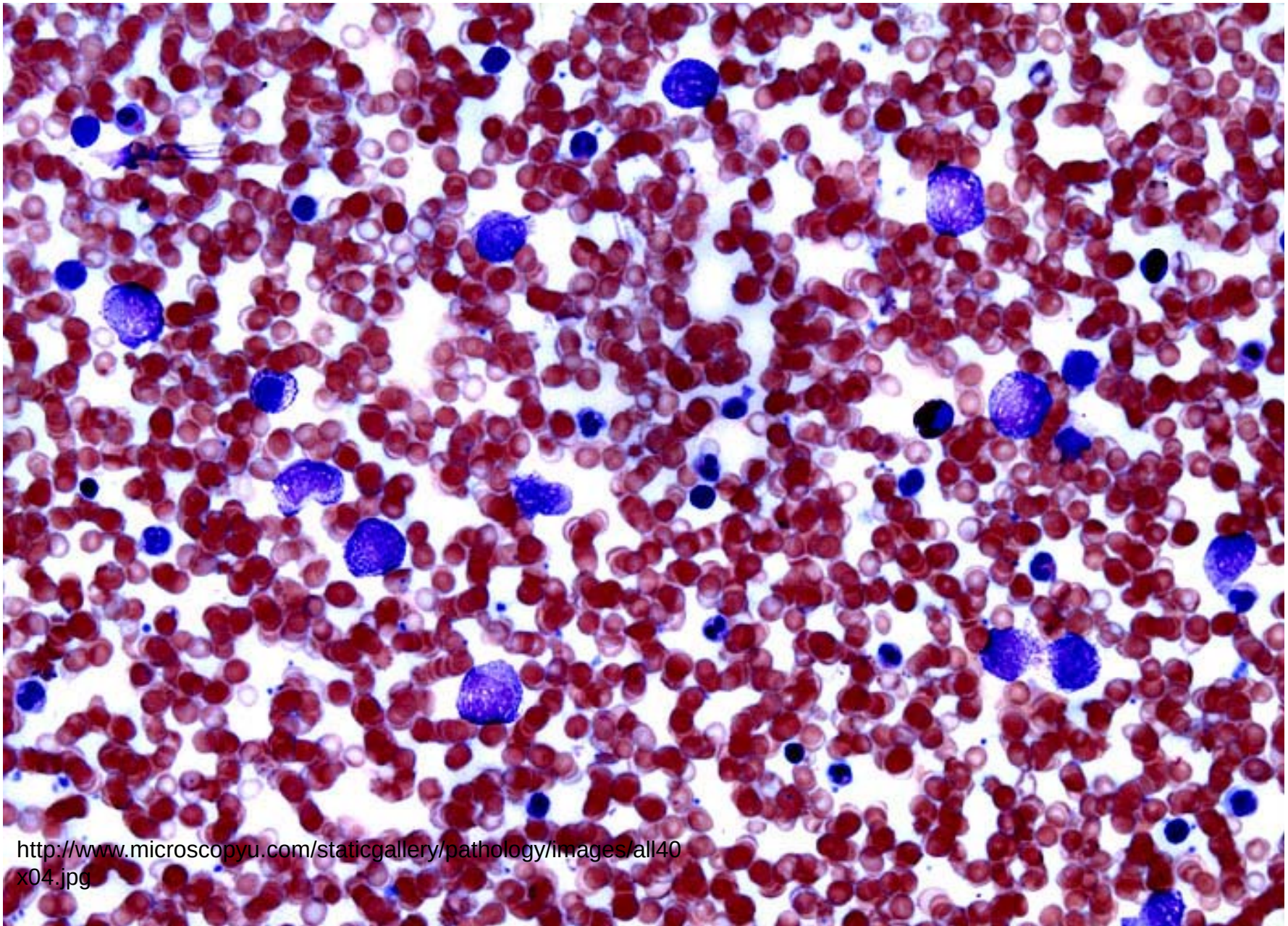


http://spittoon.23andme.com/wp-content/uploads/2009/08/Acute_leukemia-ALL.jpg



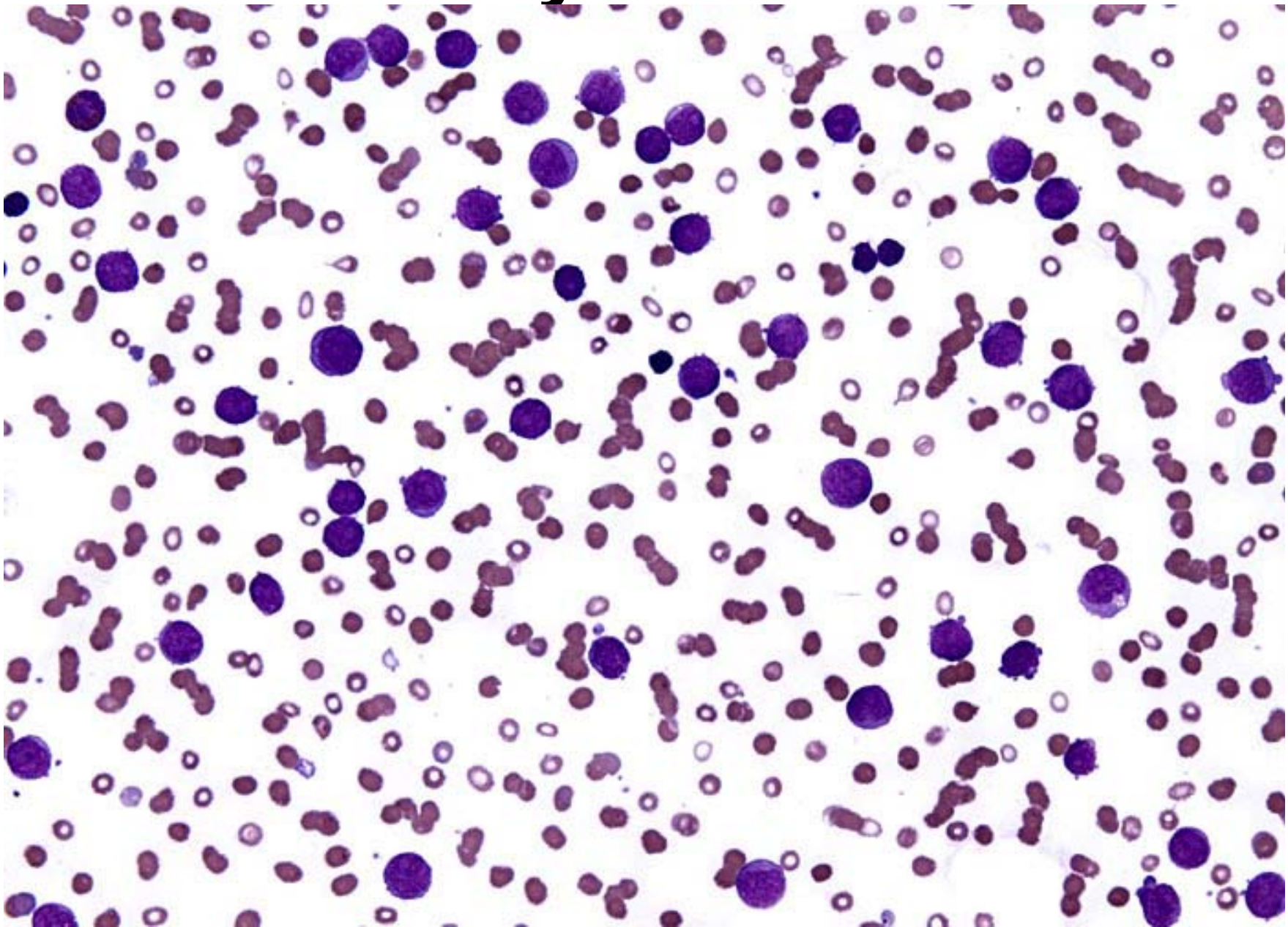
http://www.pharmacy-and-drugs.com/illnessessimages/acute-lymphoblastic-leukemia1.jpg

Acute Myelomonocytic Leukemia-AML

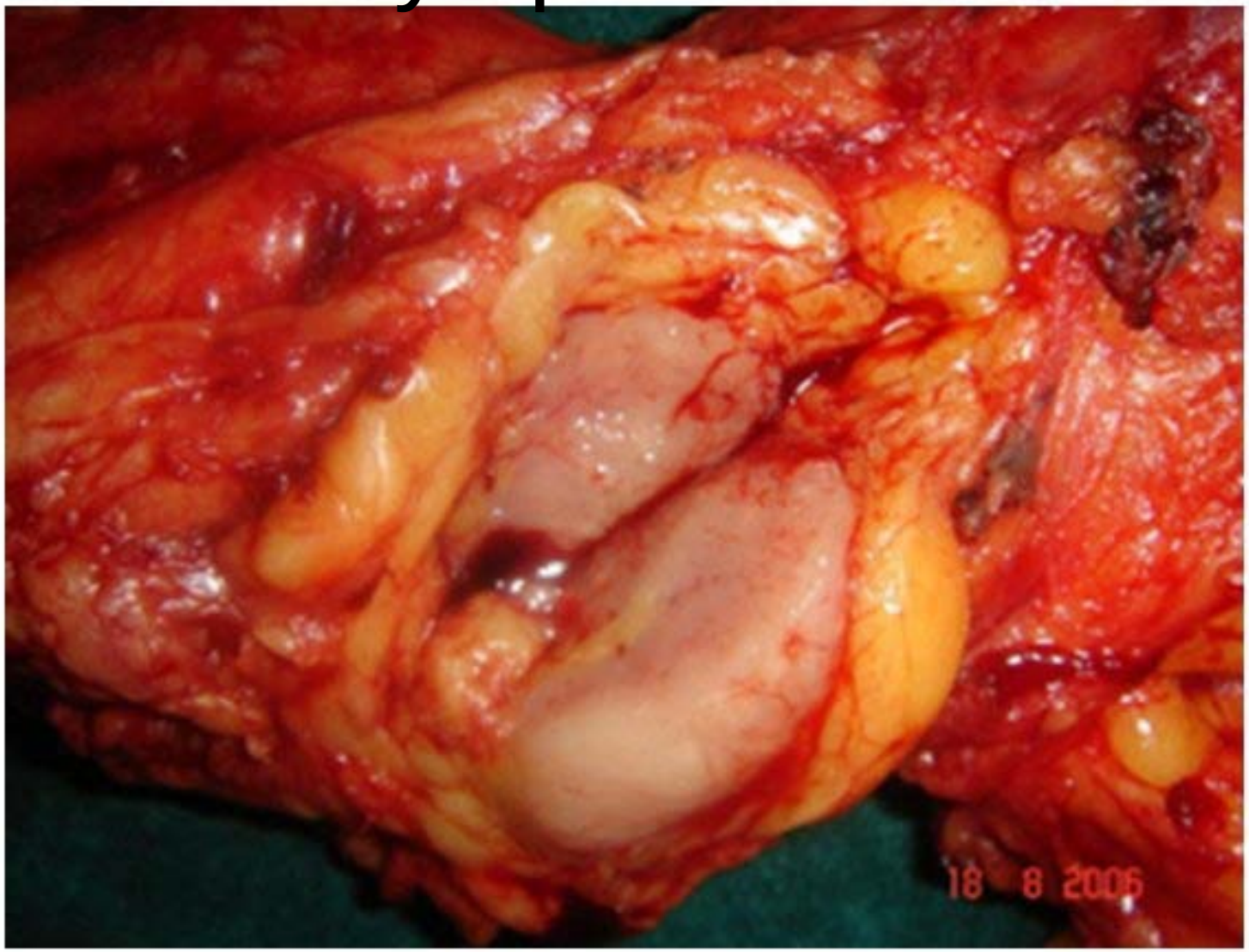


http://www.microscopyu.com/staticgallery/pathology/images/all40x04.jpg

Granulocytic Leukemia

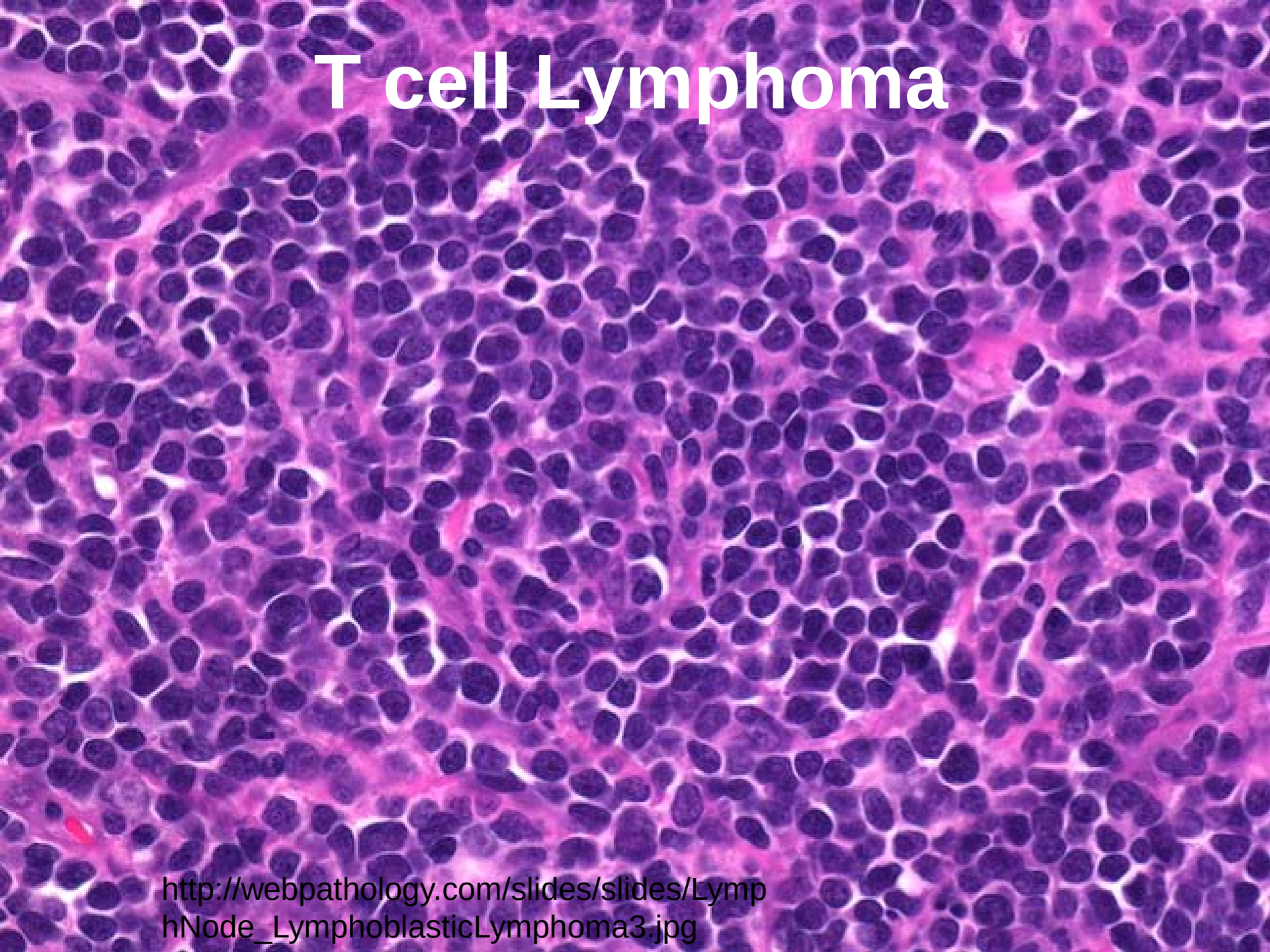


Lymphoma



http://www.ispub.com/ispub/ijs/volume_9_number_2/primary_non_hodgkin_lymphoma_of_the_breast/lymphoma-fig3.jpg

T cell Lymphoma

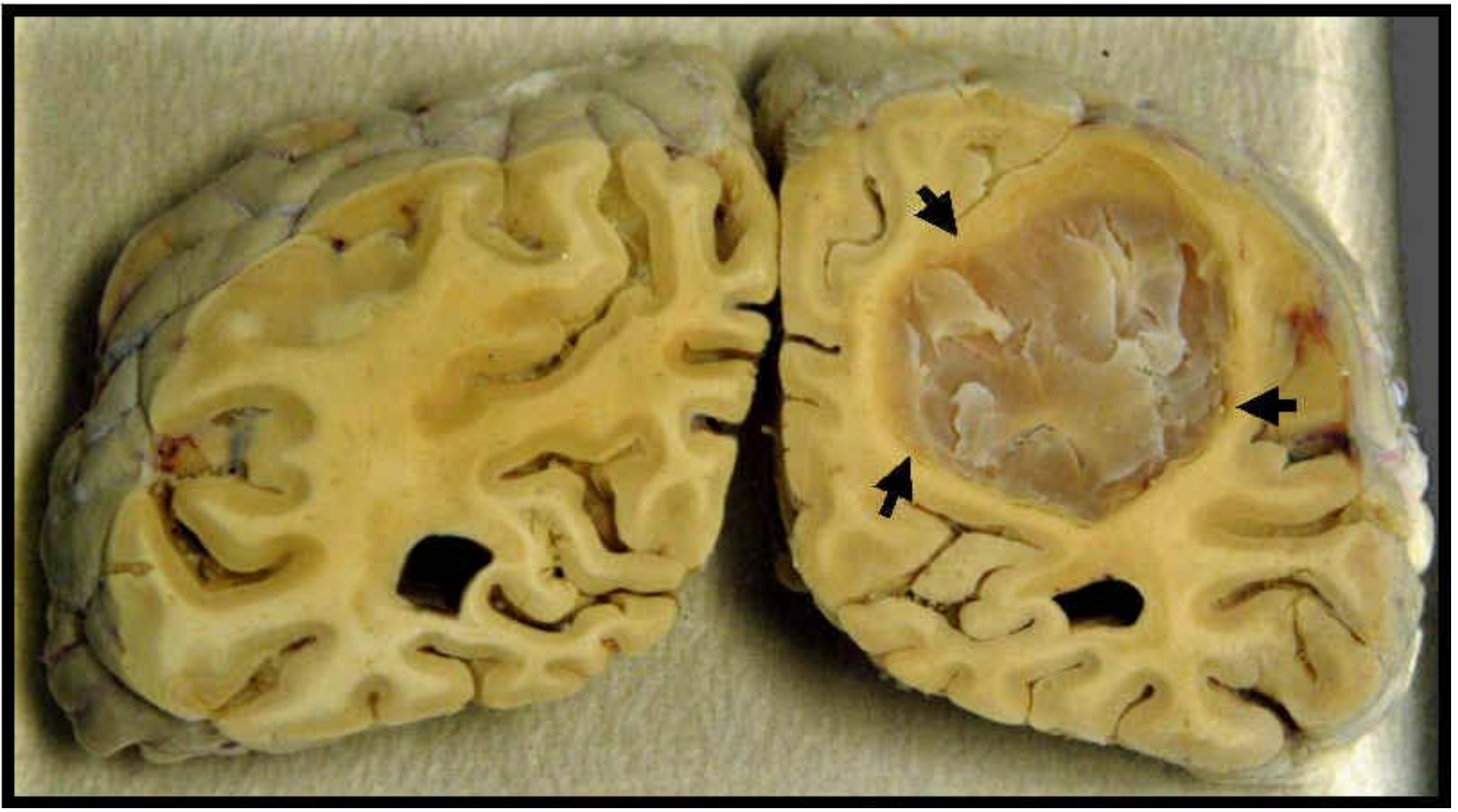


http://webpathology.com/slides/slides/LymphNode_LymphoblasticLymphoma3.jpg

IV. Neuroectodermal tumors

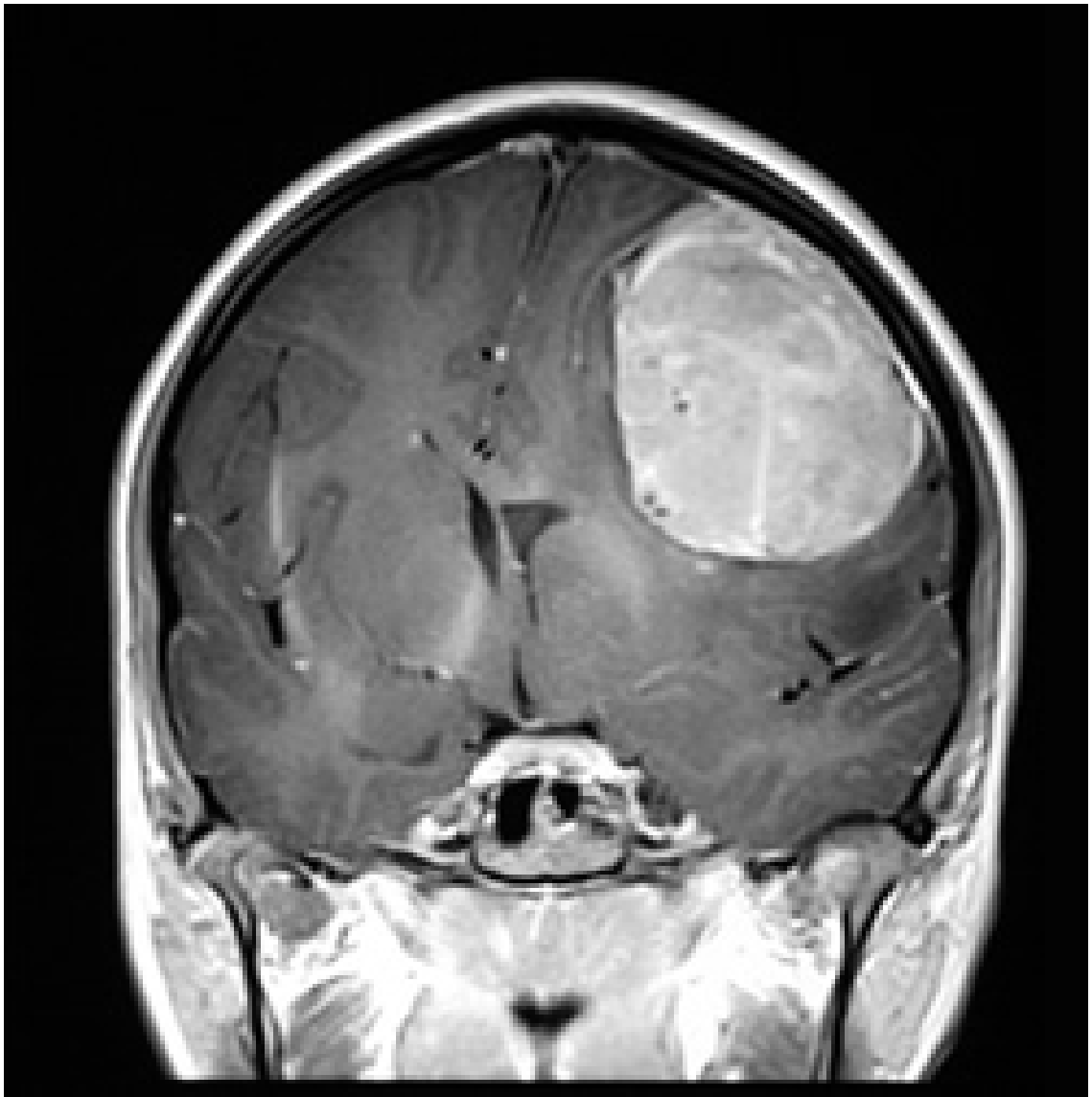
- CNS (central nervous system)
- PNS (Peripheral nervous system)

- 1.3% diagnosed cancer→2.5% cancer death
  - Glioma
  - Glioblastoma
  - Neuroblastoma
  - Schwannoma
  - Medulloblastoma



http://www.uthsc.edu/pathology/Brain/brain.5.jpg

Brain Imaging



V. Other tumors

- Melanoma ← melanocytes （黑色素细胞）
- Tumors of unknown origin

Moles and melanoma

Melanomas

melanoma.at/images/ melanoma_1.jpg

Definitions in Oncology. (Part 1)

Neoplasma:

"Neo"=New

"Plasma"= formation;

Abnormal* *new cell proliferation of* *altered* *cells

- **Heritably Altered**
- **Relative autonomous growth**
- **Can be benign or malignant (See later)**

Neoplasma:

"Neo"=New

"Plasma"= formation;

Tumor:

Solid mass,

- **tumor means a neoplasm that has formed a lump**

Summary: Cancer classification

I. Carcinoma ← epithelia
   1. Adenocarcinoma ← gland epithelia
   2. Squamous cell carcinoma ← protective sheets
   3. Other types of epithelia
II. Sarcoma ← Mesenchymal cells of connective tissue
III. Leukemia and lymphoma
IV. Neuroectodermal tumors
V. Can't fit in the above 4 / origin unknown

Questions?