

# 致癌物探討

招名威 教授

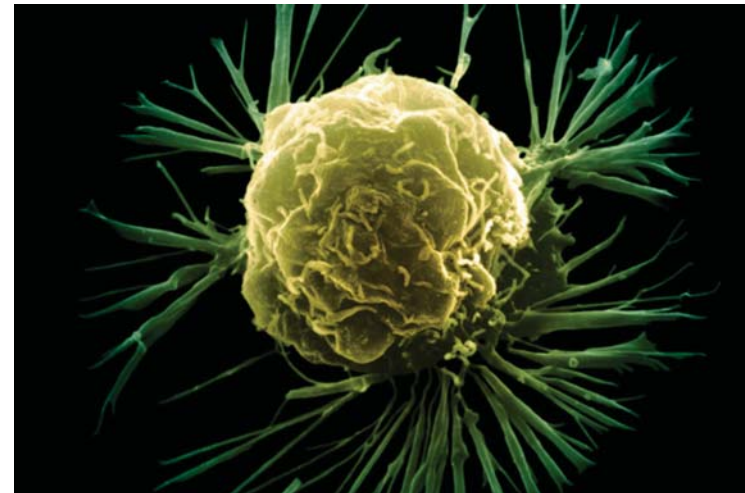
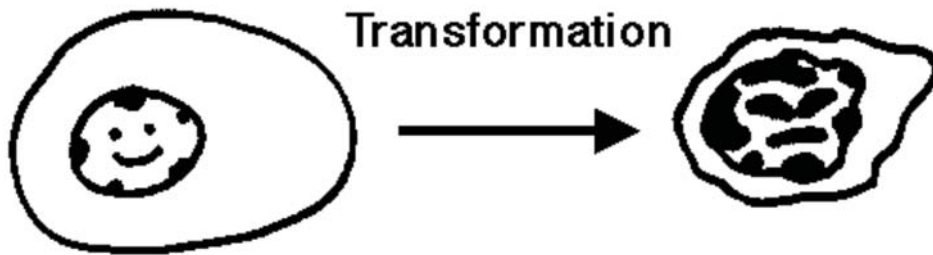
Department of BioScience Technology

Chung Yuan Christian University

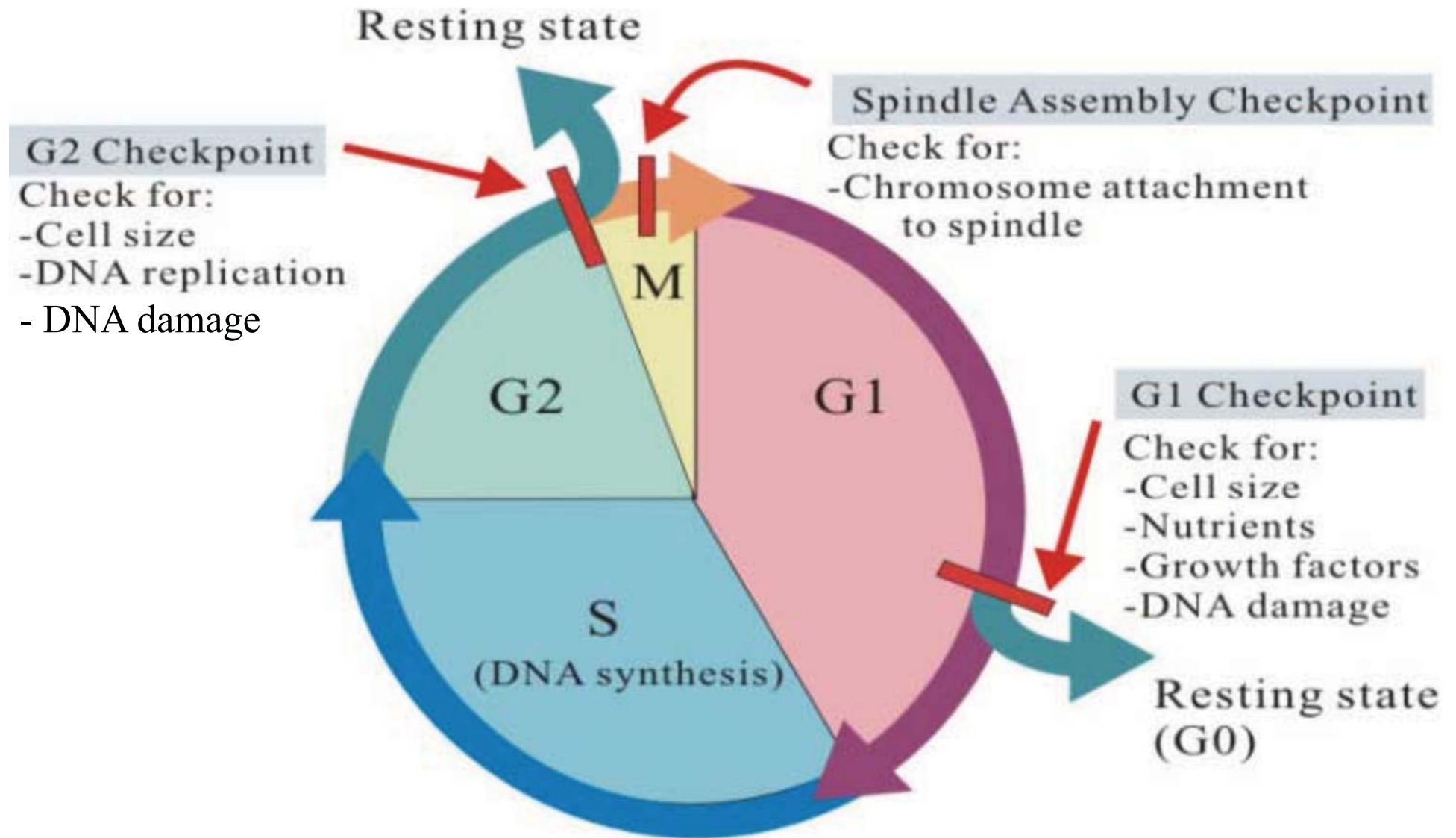
2015/08/13

# Cancer Cells

- Cancer, the 1st leading cause of death, is an example of a disease that arises from abnormalities in cell function
- Gene mutations and changes in gene expression play a central role in development of cancer
- Investigating the biology of cancer cells has deepened our understanding of normal cells



# Cell cycle checking points, part I



# DNA mutations

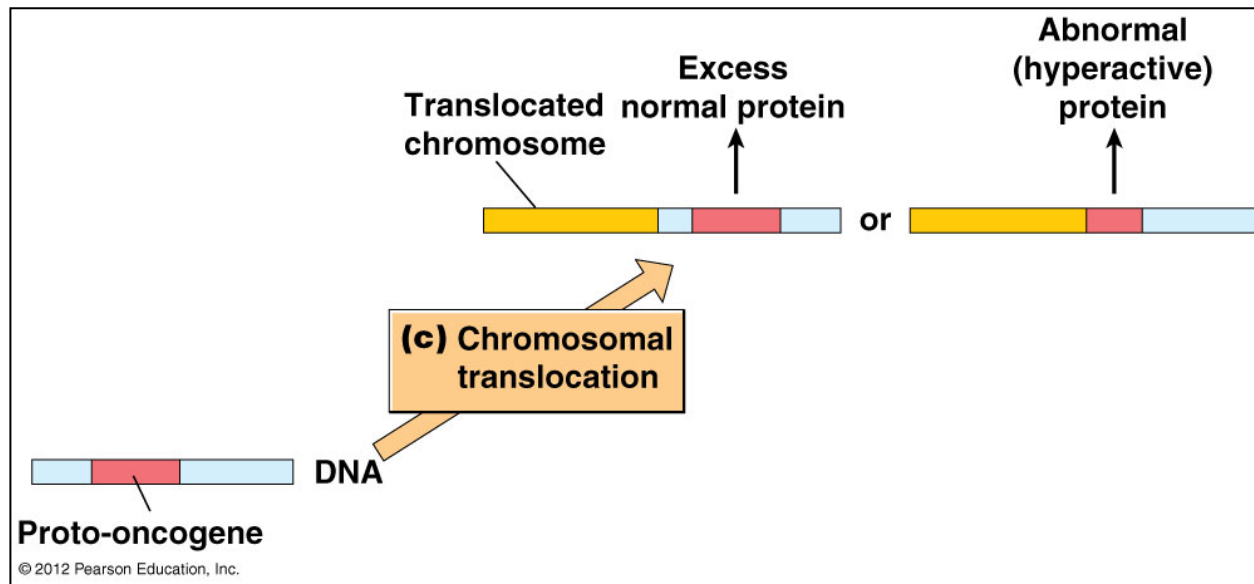
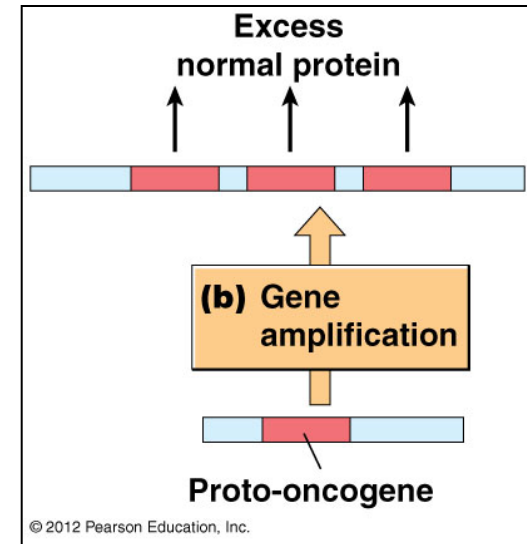
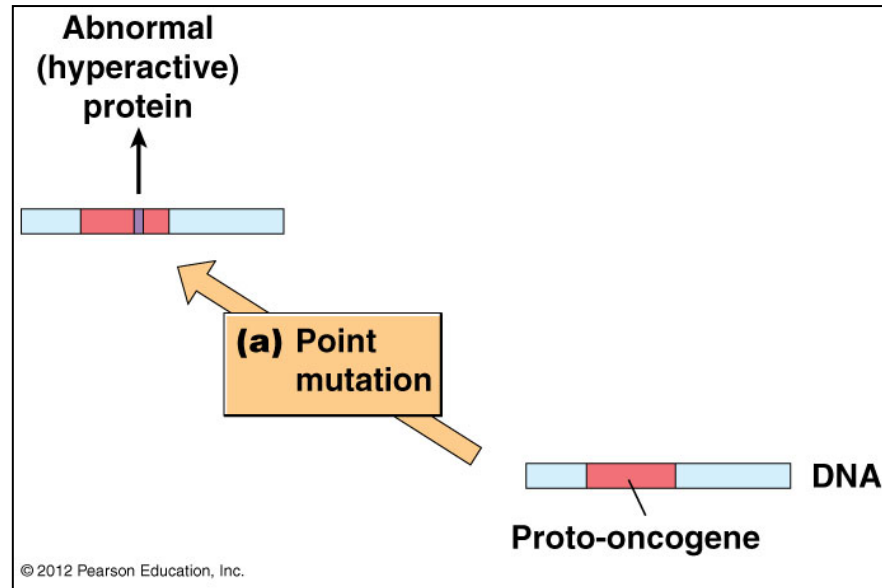
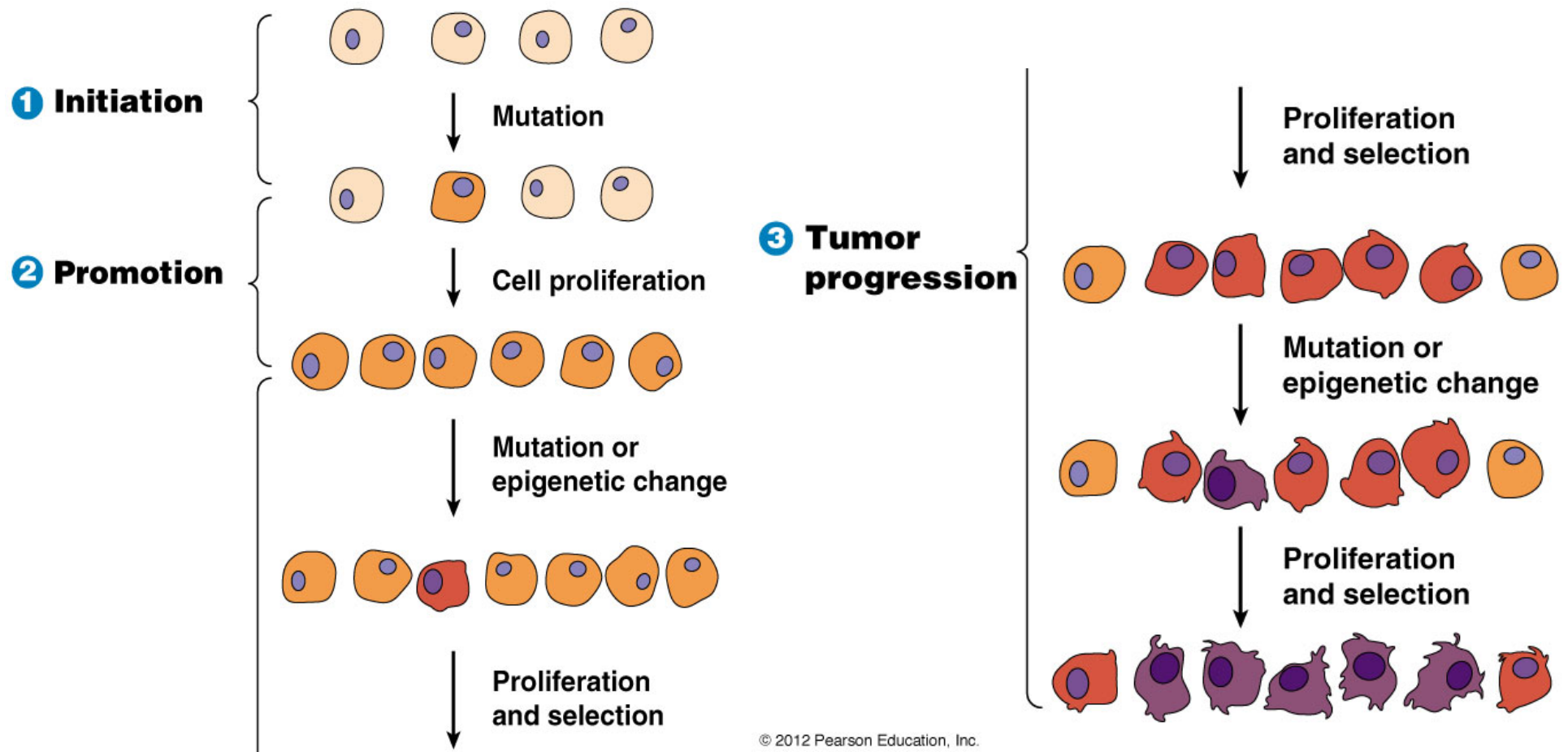


Figure 24-9, Steps 1 and 2



## In Cancer cell

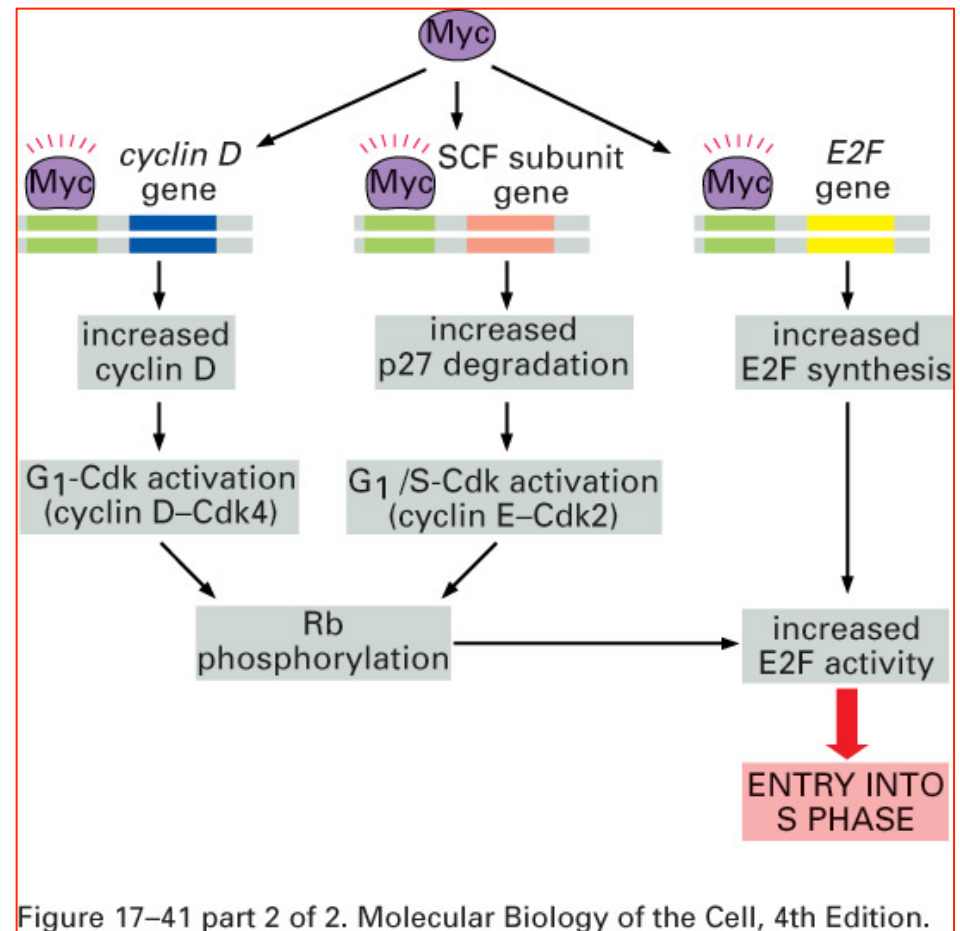
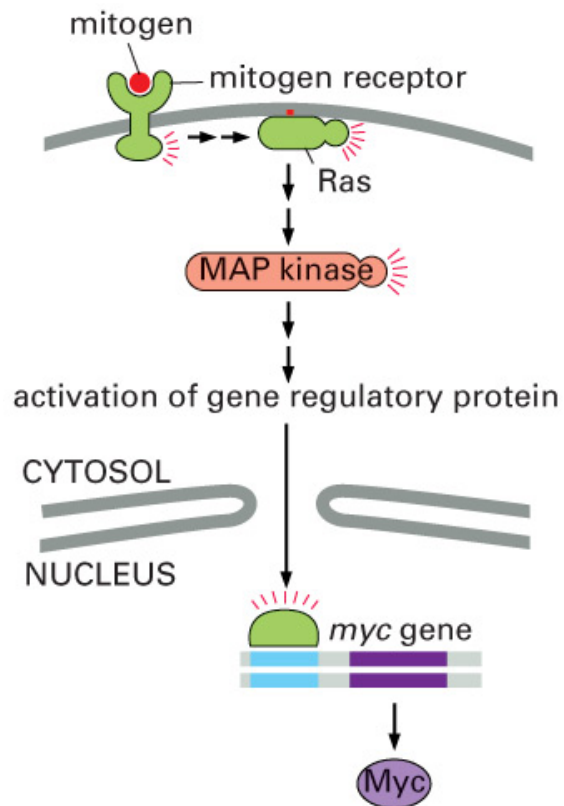


Figure 17-41 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Figure 17-41 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

# Oncogenes and Tumor Suppressor Genes

- DNA mutations in cancer originate in different ways
- However the mutations always affect genes that control cell proliferation and survival
- There are two main classes: *oncogenes* and *tumor suppressor genes*



# Inhibition of cell cycle arrest

- **Akt** inhibits cell cycle arrest through activation of a monomeric G protein called Rheb
- This leads to activation of TOR, a key regulator of cell growth
- The net effect of the PI3-kinase-Akt signaling pathway is to promote **cell survival and proliferation**
- **Some** growth factors inhibit cell proliferation, e.g., **transforming growth factor  $\beta$  (TGF $\beta$ )**
- TGF $\beta$  binding to its receptor phosphorylates **Smad** proteins that move into the **nucleus and activate expression of genes** coding for proteins that inhibit proliferation
- Two **Cdk inhibitors** that block cell cycle progression are **p15** and **p21**

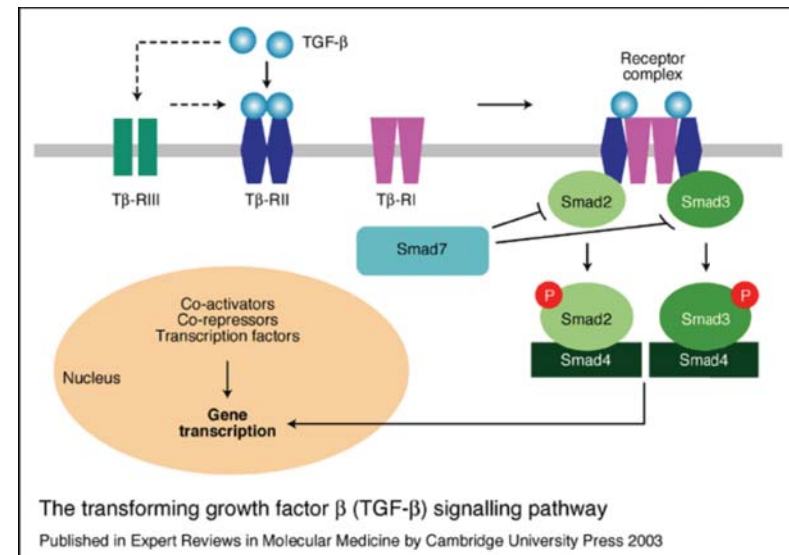
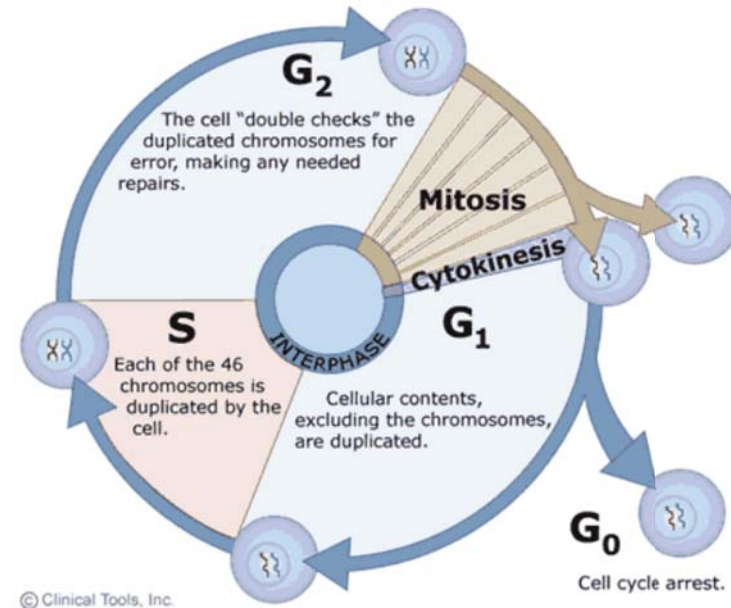
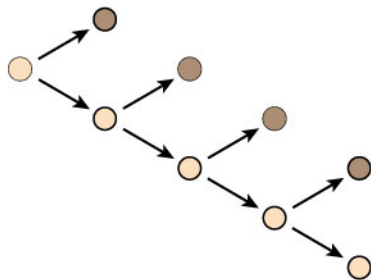
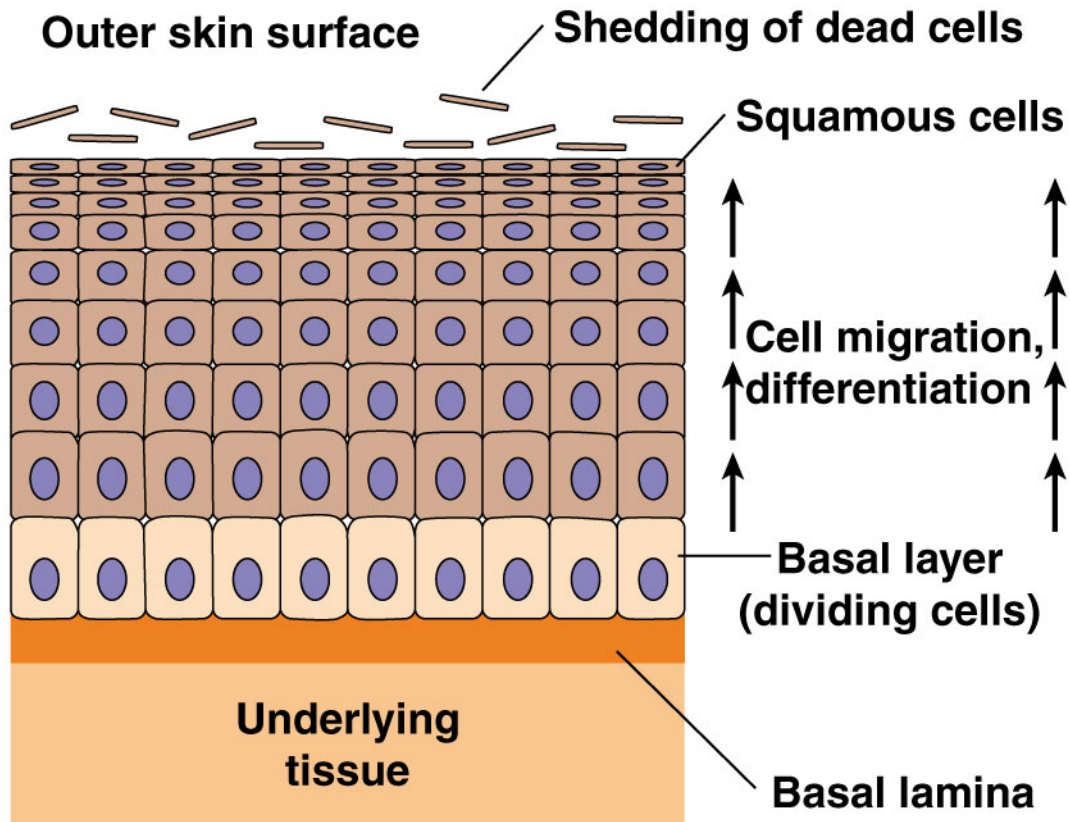


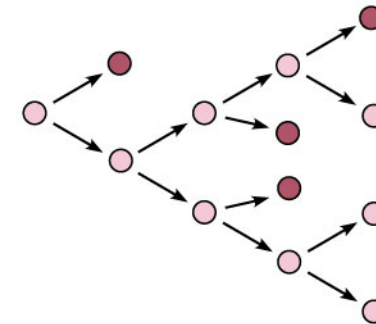
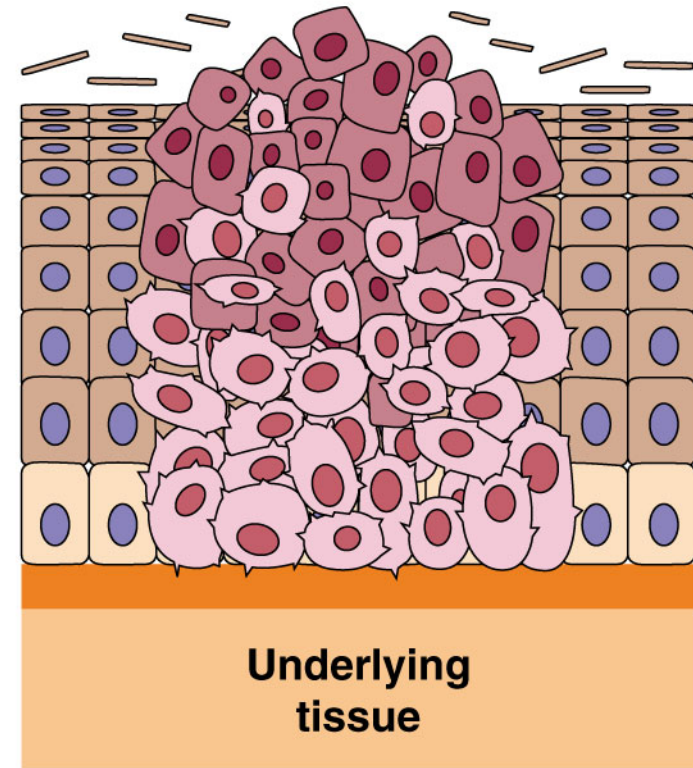


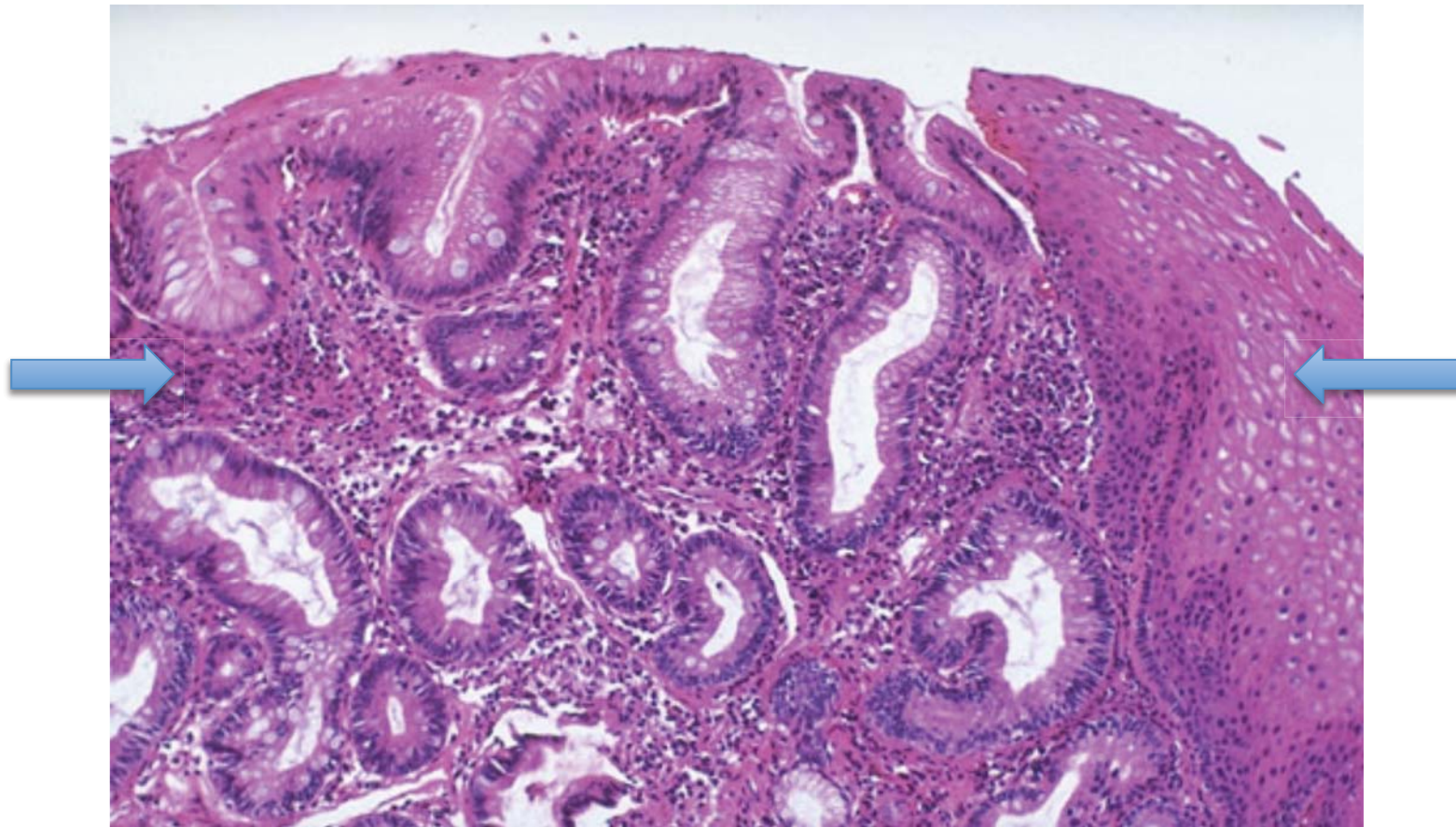
Figure 24-1

## Normal Growth



## Tumor Growth

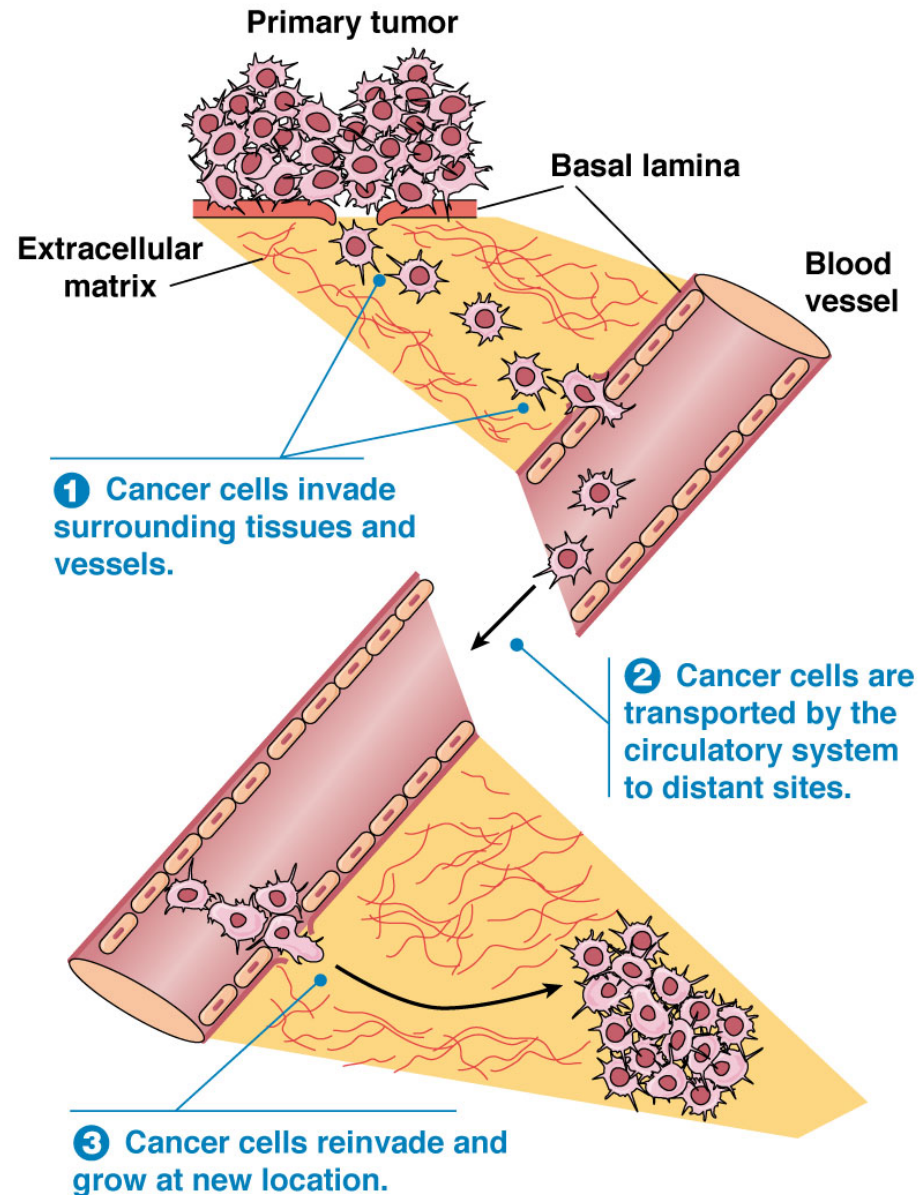




chronic gastroesophageal reflux disease

# Cancer Cells Spread by Invasion and Metastasis

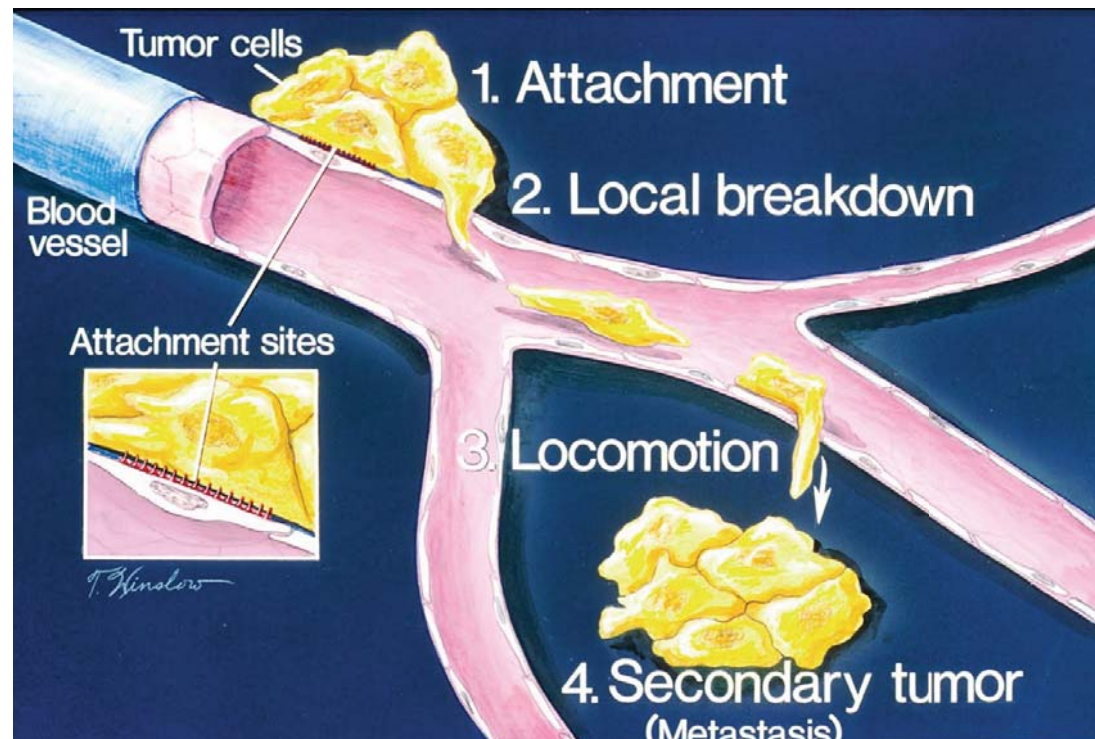
- The ability of cancer cells to spread depends on two different mechanisms
  - **Invasion** refers to the direct migration and penetration of cancer cells into neighboring tissues
  - **Metastasis** involves ability of cancer cells to enter the bloodstream and travel to distant sites
  - **Blood vessel need!**



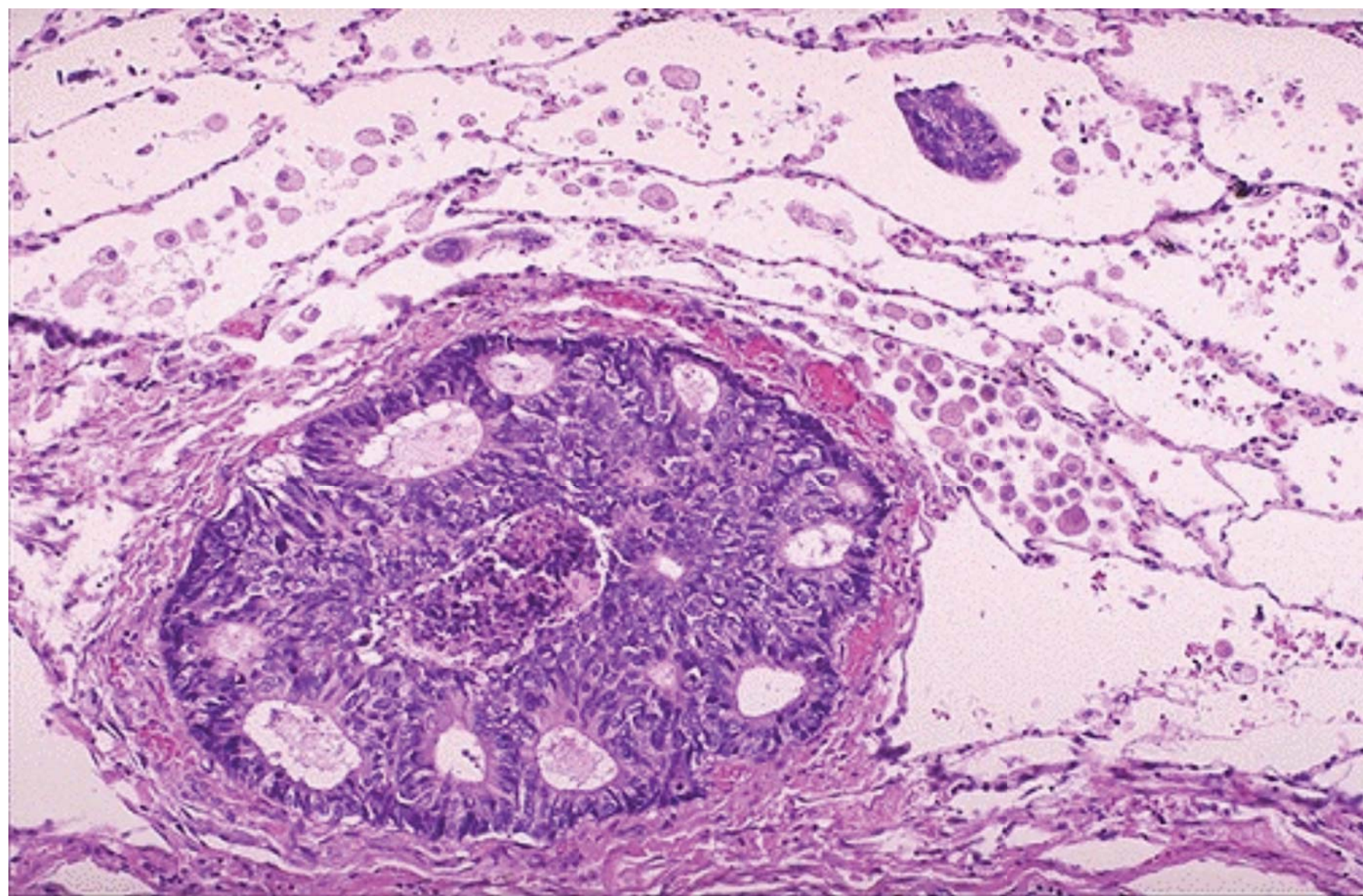


# Changes in Cell Adhesion, Motility, and Protease Production Allow Cancer Cells to Invade Surrounding Tissues and Vessels

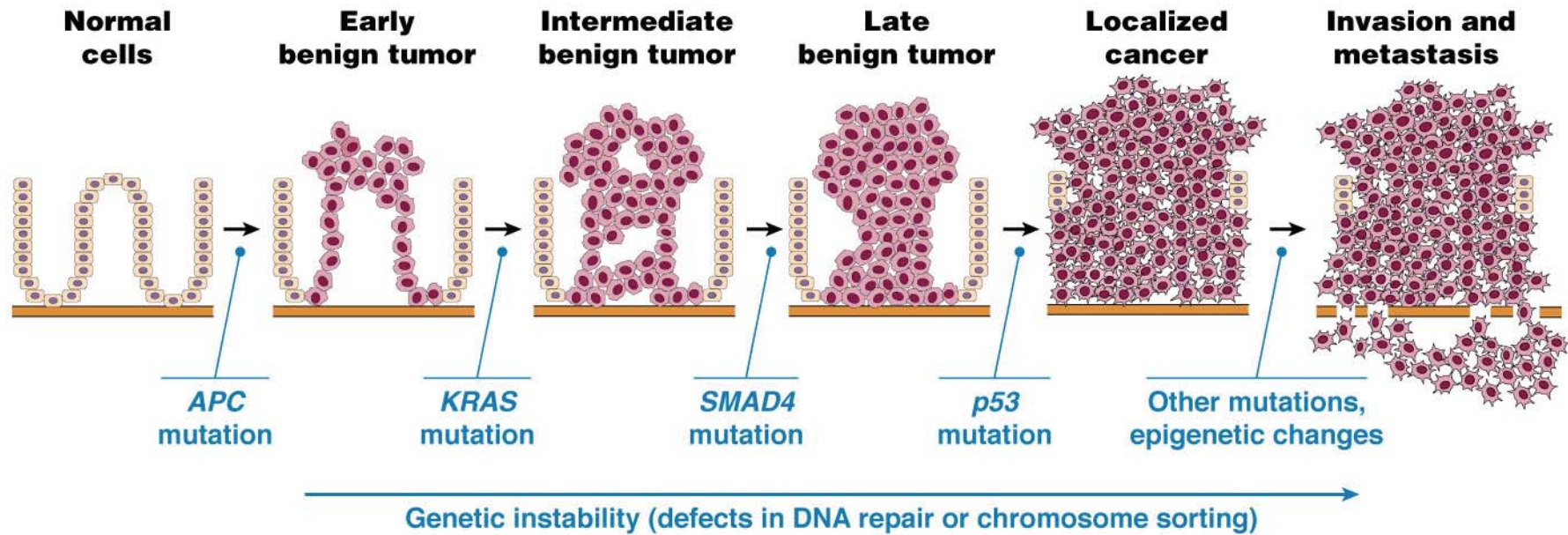
- The first step in metastasis is the invasion of surrounding tissues and vessels
- Benign tumors and normal cells remain together where they are formed
- Cancer cells are able to leave their original location through several mechanisms, the first of which involves loss of cell adhesion



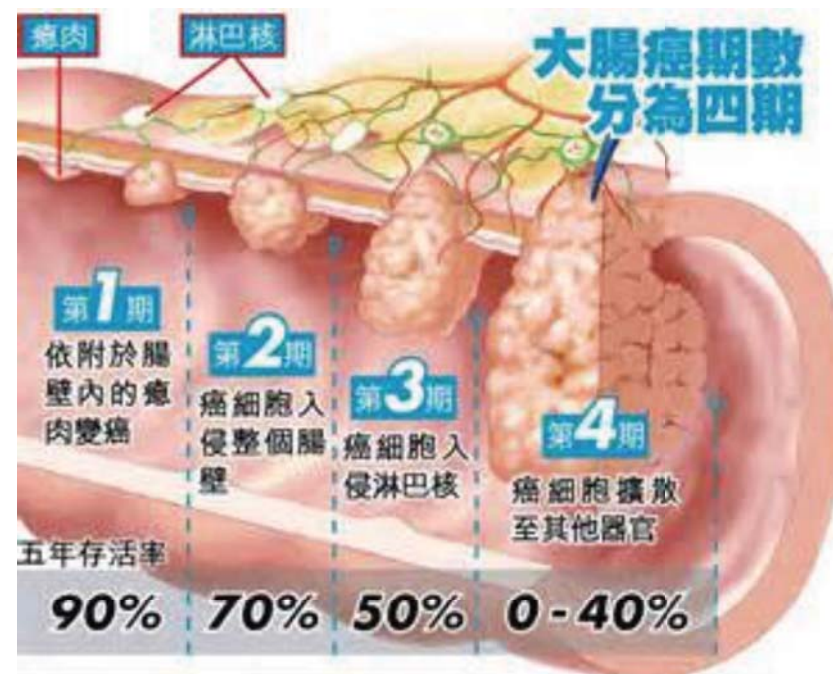




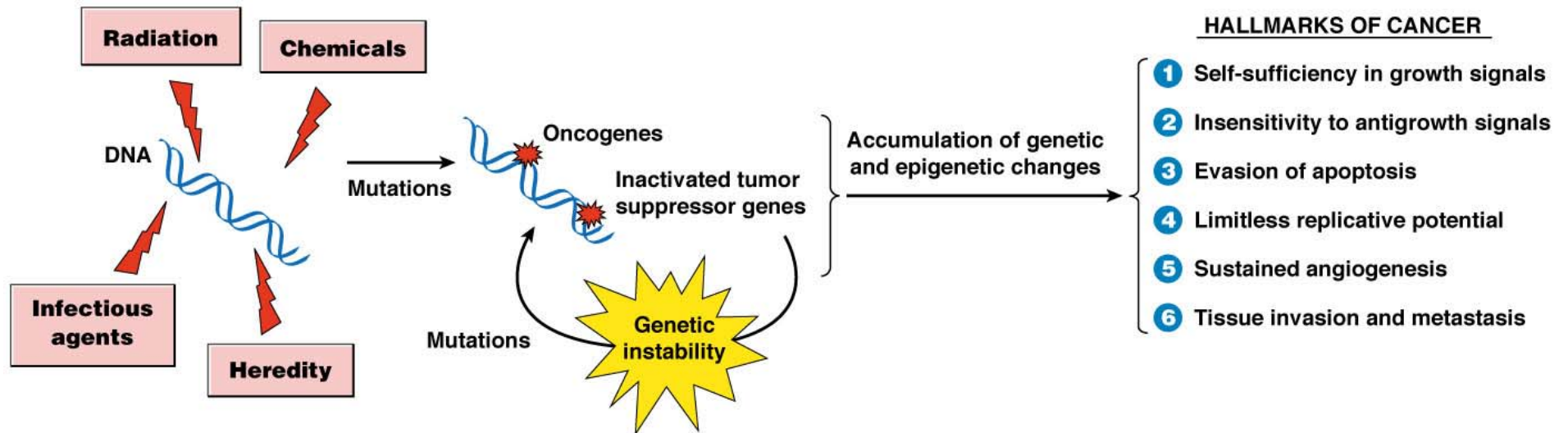




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# What's hallmarks of Cancer?



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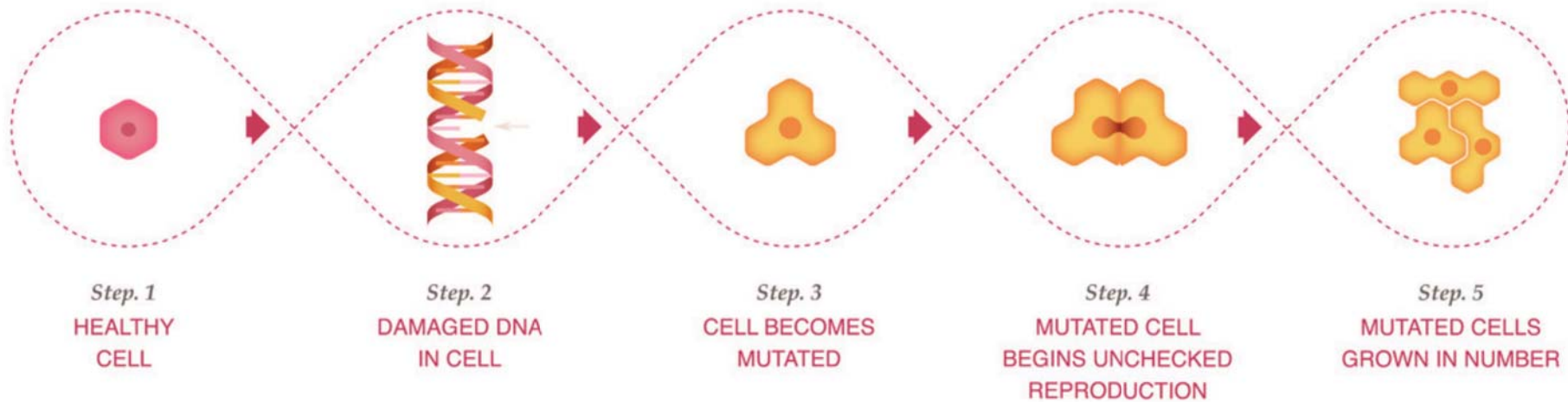
1. Normal cells require growth cells **to proliferate**, but cancer cells escape this requirement
2. Normal tissues are **protected from overproliferation** by a variety of inhibitory signals, but cancer cells are insensitive to these signals
3. Apoptosis is used by normal cells to **prevent damaged or defective cells** from continuing to divide; apoptosis is inhibited or disrupted in cancer cells
4. Normal cells have **limited replicative potential** due to telomere loss; cancer cells contain active telomerase (or other mechanisms) to maintain telomeres
5. Tumor cells cannot grow beyond a few mm **without a blood supply**; cancer cells **trigger angiogenesis** by activating genes coding for angiogenesis stimulators and inhibiting genes coding for angiogenesis inhibitors
6. Cancer cells lose adhesiveness with neighbors, invade nearby tissues, and eventually **metastasize** around the body via the circulatory system



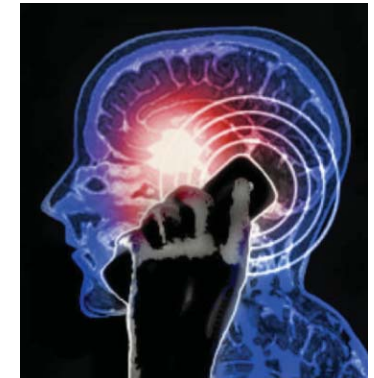
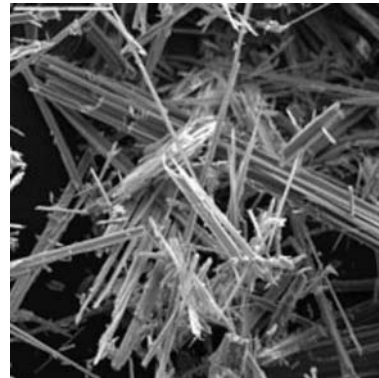
# What Causes Cancer?

*fig. 4a*

CANCER CELL  
REPRODUCTION



1. Carcinogens
2. Infection
3. Diet
4. Radiation
5. Heredity
6. Physical agents
7. Hormones
8. Others



# 世衛對致癌物分類

## 第1類：致癌物

**定義：**有足夠證據證明致癌；或是有充足證據證明致癌的同時，於動物實驗有足夠證據證明致癌，以及有強烈證據證明於人類患癌扮演重要角色

**例子：**柴油廢氣、石棉、芥子氣、酒精、煙草、二手煙  
**已被歸類數目：**108

## 第2A類：或許致癌

**定義：**有限證據證明致癌，並有充足證據證明令動物患癌

**例子：**長及短波紫外綫、硝酸鹽、高溫油炸  
**已被歸類數目：**62

## 第2B類：有可能致癌

**定義：**有限證據證明致癌，並有不夠充足證據證明令動物患癌

**例子：**哥羅方、鉛、汽油  
**已被歸類數目：**271

## 第3類：致癌性不能歸類

**定義：**證據不足以證明致癌

**例子：**咖啡因、膽固醇、石油、茶  
**已被歸類數目：**509

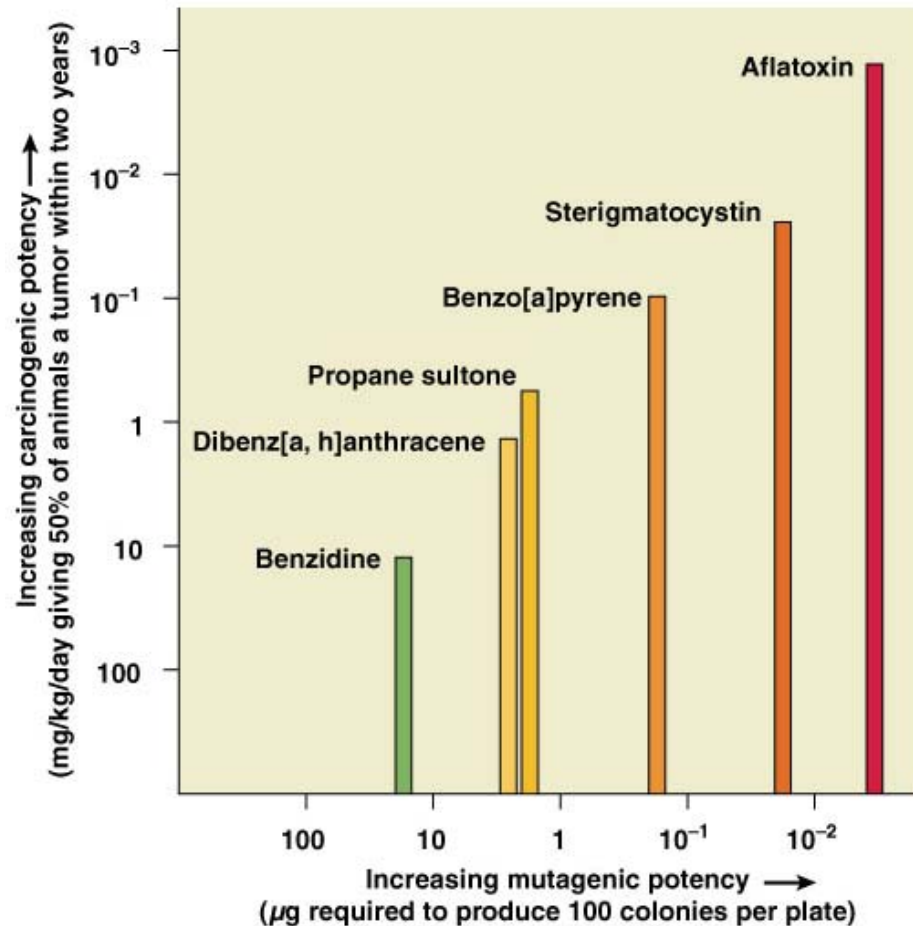
## 第4類：或許不致癌

**定義：**有證據顯示不致癌

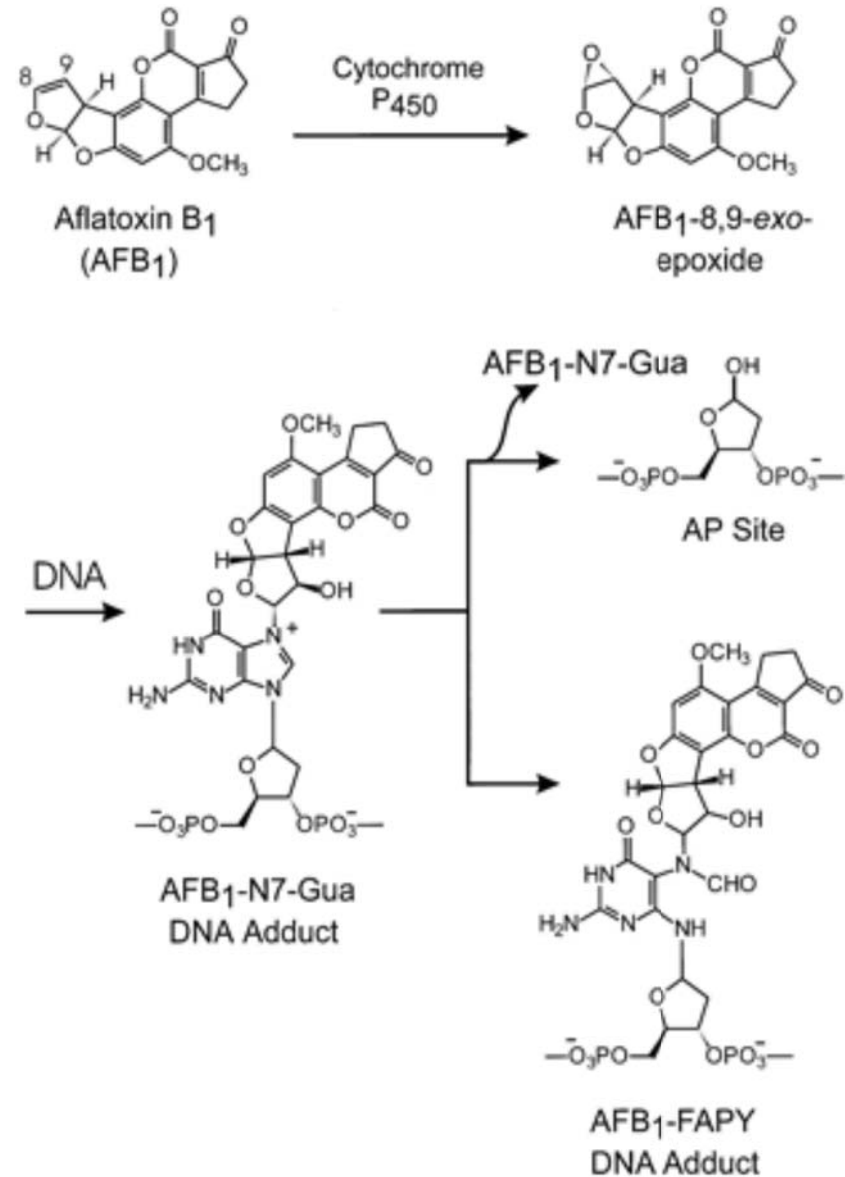
**例子：**己內酰胺  
**已被歸類數目：**1

資料來源：世衛

# Carcinogen and Carcinogenesis



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## 台灣地區食品中毒發生狀況, 1999 to 2013



Cases

•4,560

Illness

•65,674

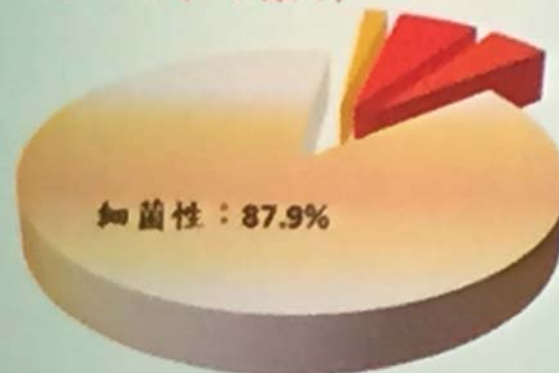
Death

•14

## 台灣地區食品中毒發生狀況, 1999 to 2013



### 原因判明案件



化學性：農藥、重金屬、亞硝酸鹽

天然毒素：植物性、麻痹性貝毒、河豚毒、  
組織胺、黴菌毒素

- 細菌性 87.9%
- 化學性 1.6%
- 天然毒素 5.9%
- 其他 4.6%

其他原因包含：諾羅病毒、過氧化氫等

# 世界衛生組織評出**十大垃圾食品**

1. 油炸類食品 2. 醃製類食品 3. 加工類肉食品 4. 餅乾類食品 5. 汽水可樂類食品



6. 方便類食品 7. 罐頭類食品 8. 話梅蜜餞類食品 9. 冷凍甜品類食品 10. 燒烤類食品



資料來源：聯合國世界衛生組織



# Where is the food toxin routing from?

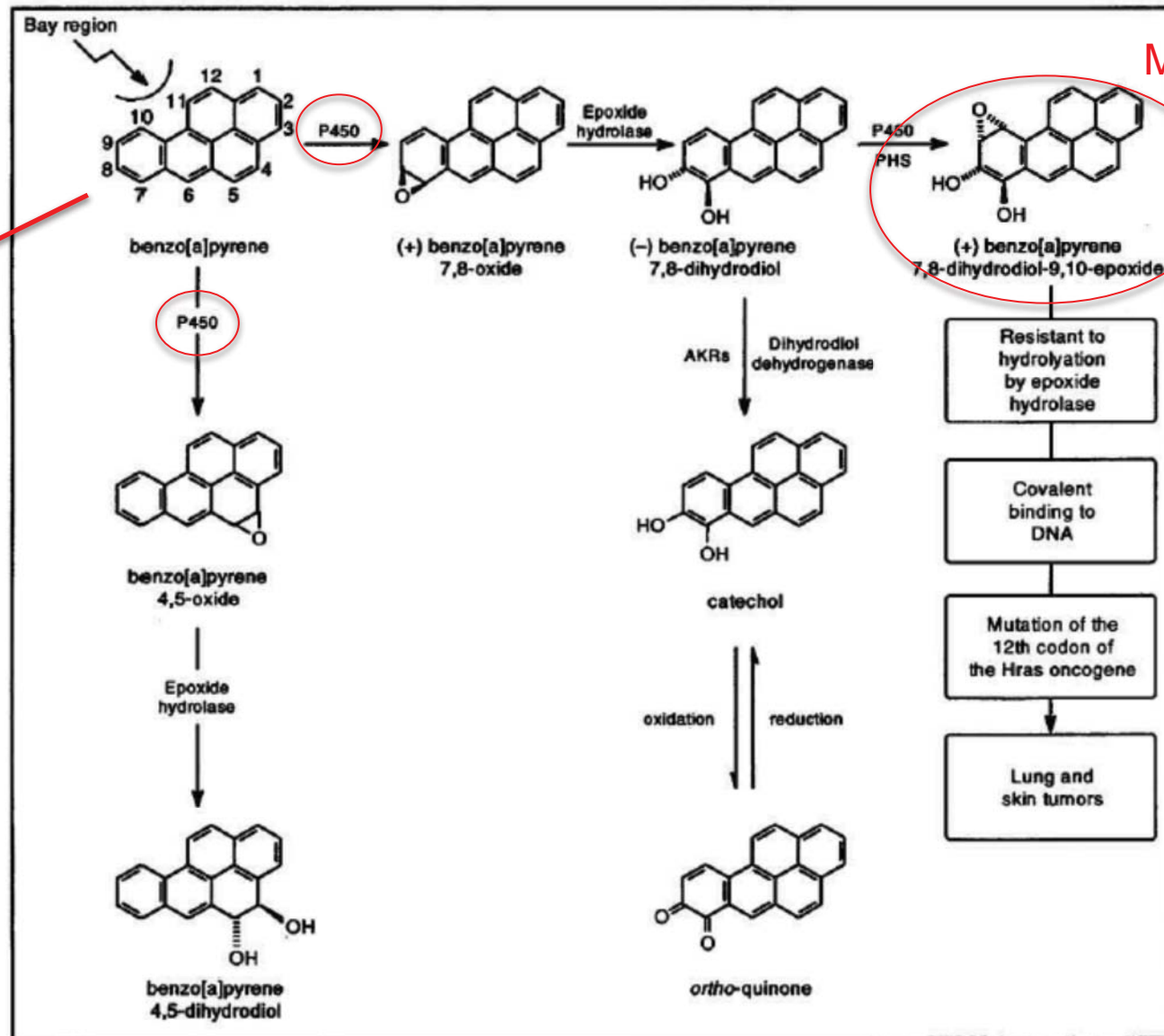


高溫烹飪燒烤的毒害		
食物成份	所致毒物	健康危害
蛋白質類	異環胺等	大腸癌、乳癌等
油脂類	多環芳香碳氫化合物 (PAH)	胃腫瘤、肝腫大
澱粉類	丙烯胺 (AL)	泌尿系統癌及突變
醣類	先進糖化終產物 (AGE) 等	老化等疾病

資料來源：林口長庚醫院林杰樑醫師

# Metabolism: Phase II reaction, NOT 100% in one product

Example:

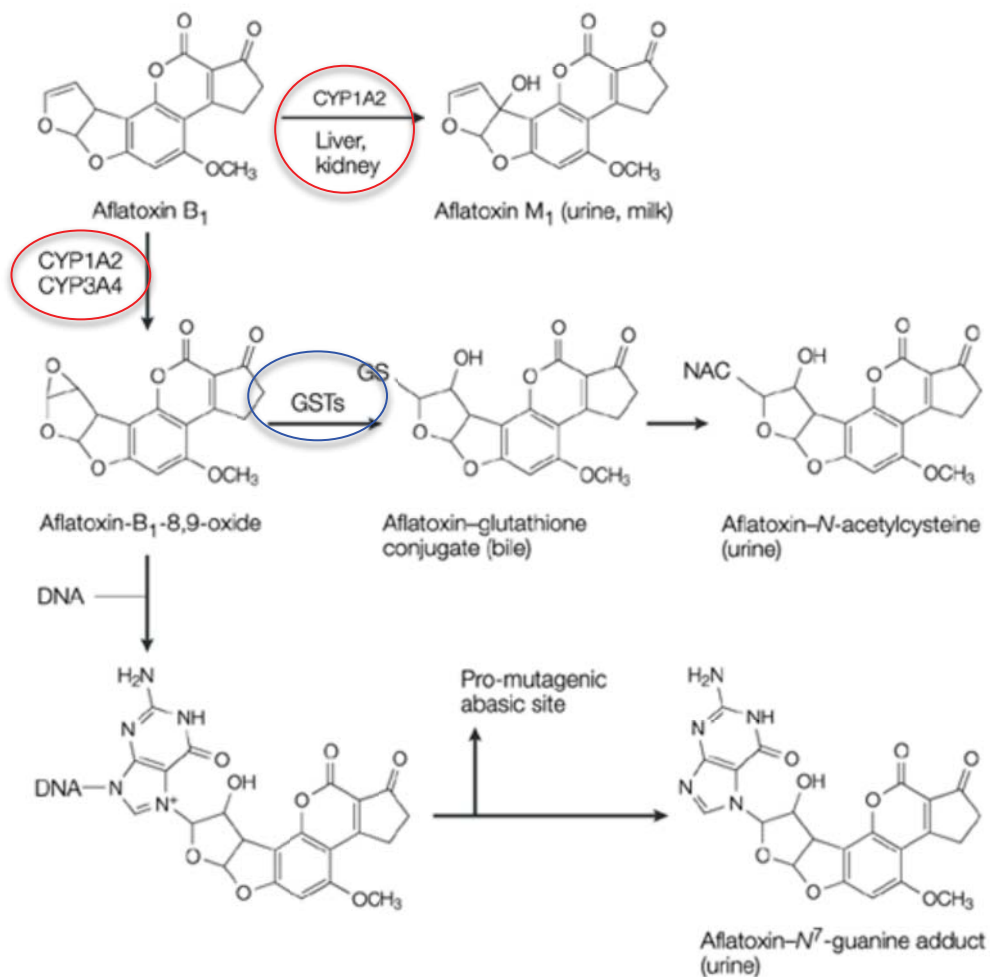


Most ~90%

Figure 6-6. Role of epoxide hydrolase in the inactivation of benzo[a]pyrene 4,5-oxide and in the conversion of benzo[a]pyrene to its tumorigenic bay-region diolepoxide.

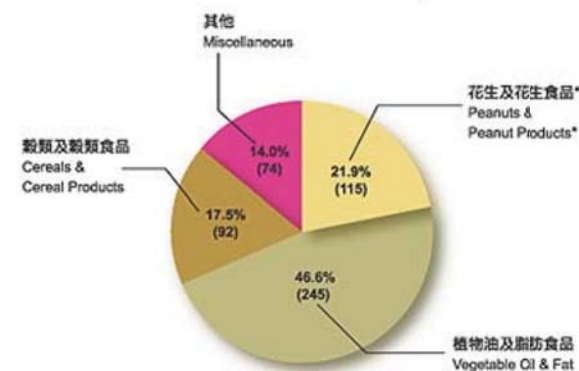


# Gerald Wogan's finding



Nature Reviews | Cancer

香港的黃曲霉毒素監察結果 (1998 - 2000 )  
Surveillance Results - Aflatoxin (1998 - 2000 )



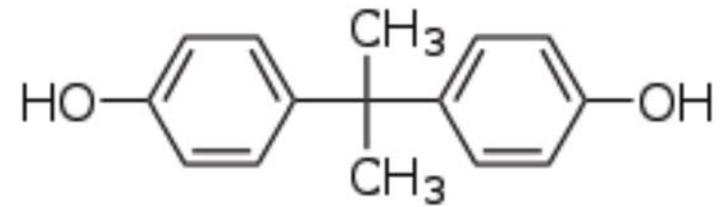
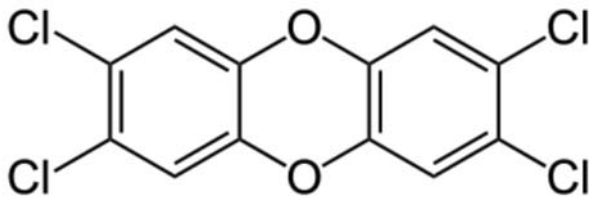
樣本總數 Total number of samples 526

\*包括花生油 Including Peanut Oil

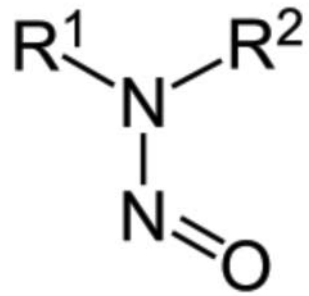


你聽過環境荷爾蒙嗎？？

➡ 內分泌干擾素：模擬人體荷爾蒙可擾亂內分泌的物質



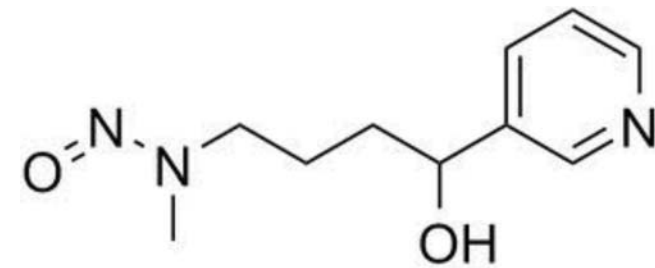
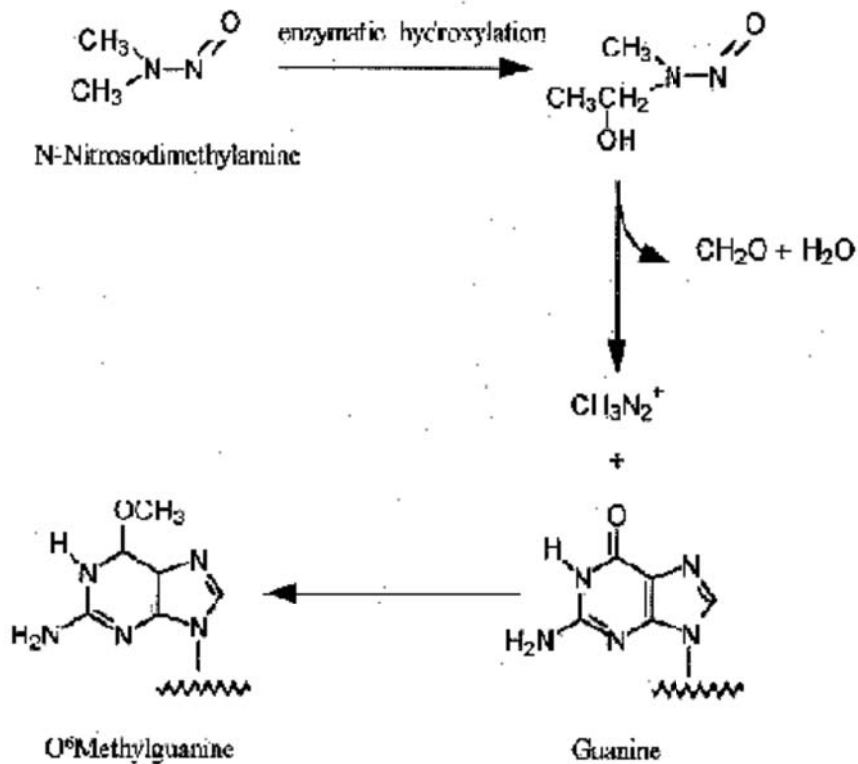
# Nitrosamine



(一) 含亞硝酸鹽食物與含胺類食物合吃

(二) 直接吃含亞硝胺的食物

(三) 含硝酸鹽的蔬菜或食物，由腸胃道細菌代謝後，在腸胃道中合成亞硝胺

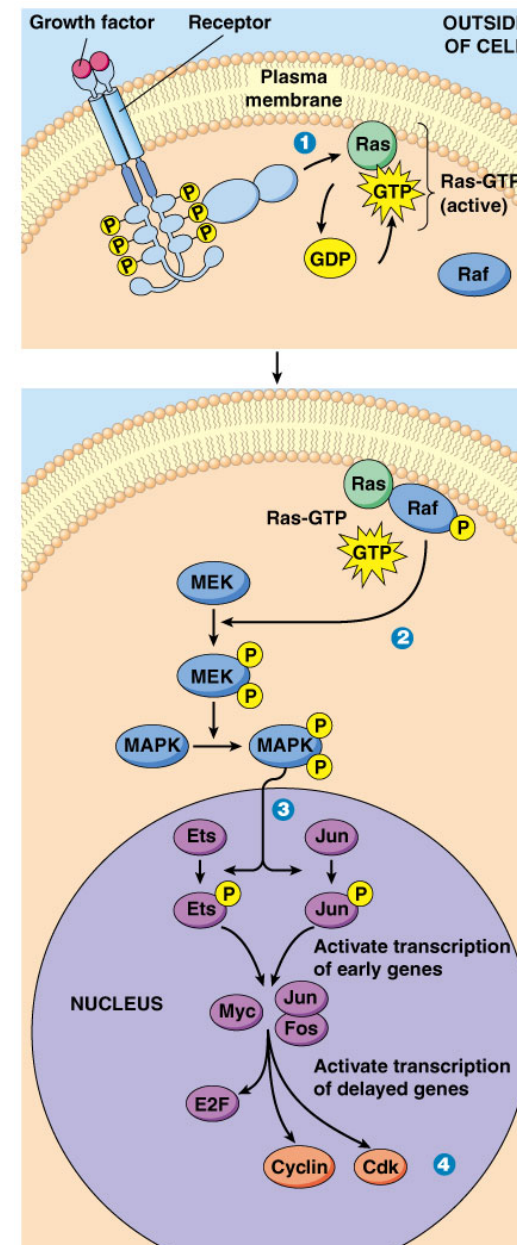


NNAL



# Growth Factors and Cell Proliferation

- In simple unicellular organisms presence of nutrients in the environment is the primary factor determining whether cells grow and divide
- In multicellular organisms extracellular signaling proteins, growth factors, control the rate of cell proliferation
- Growth factors are called *mitogens*





## 美國正式宣布基因改造食品有毒！

共享 2014-04-27



【新三才綜合報道】以下是整理的一些幫助家長怎樣識別基因改造食品的文章，為了下一代，為了自己及家人，請一定要看！

看到《今日頭條》法國科學家實驗證明基因改造玉米誘發腫瘤。看到被做實驗的小白鼠身上長出來大大的腫瘤和痛苦的樣子，實在感到恐怖。美國環境醫學科學研究院推出報告稱：「一些動物實驗表明，食用基因改造食品有嚴重損害健康的風險，包括不育，免疫問題，加速老化，胰島素的調節和主要臟腑及胃腸系統的改變」。美國科學院環境醫學研究院得出的結論引起了轟動。



周處除三害

美國正式宣布基因改造食品有毒！

【各國趣聞】巴西篇

麥當勞早餐霸主地位岌岌可危

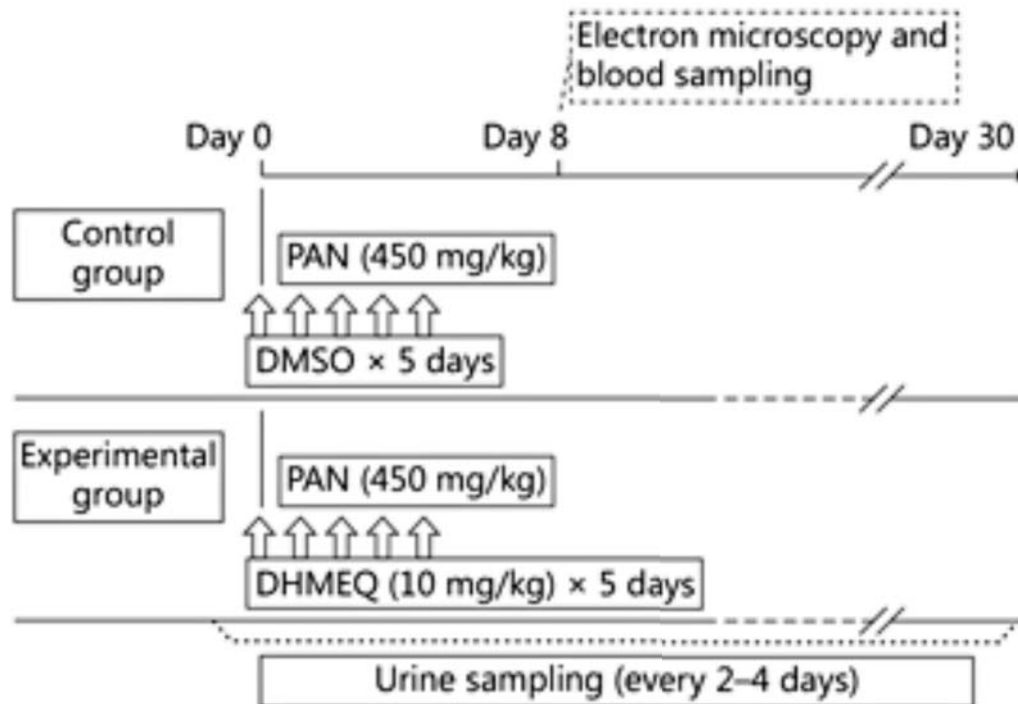
凱特全家在紐西蘭首都的一天  
擦眼鏡 (圖)

### 相關文章

基因改造食品強制標示 華盛頓州  
中農業部頒轉基因食品安全證引擔憂  
地方危機不斷 中國怎麼了  
奧勒岡州發現的基因改造小麥  
明尼蘇達州湖中發現大量有毒化學物  
歐洲人對基因改造農作物GMO疑慮  
科學家對轉基因食品發出安全警告  
美國正式宣布基因改造食品有毒！  
英國或允許基因改造的試管嬰兒  
轉基因食品危害的65種科學證據  
阿根廷的不良種子與基因改造農作物  
雀巢等品牌嬰兒輔食被曝含有毒重金  
8字開頭的水果請不要買  
中藥的有毒與無毒(圖)  
基因改造食物的大新聞  
廣西發現兩萬斤有毒蔬菜 數噸已經  
歐盟將批准最新基因改造玉米  
歐洲議會決議 禁止種植基因改造玉

## 致癌性試驗 (Carcinogenicity Study)

- (1) 未來須經持續給藥6個月以上之試驗物質
- (2) 過去之數據顯示此類別之試驗物質可能引起致癌性者
- (3) 試驗物質之作用機制推測可能有致癌性者
- (4) 重覆劑量毒性試驗之結果顯示有腫瘤生成現象的試驗物質
- (5) 物質之成分或其代謝產物長期滯留在組織中，產生局部的組織作用或病理生理反應
- (6) 基因毒性試驗結果顯示有致突變性存在之試驗物質等，均應進行致癌性測試





# Air pollutant Exhaust Particles is everywhere

- People walking around in cities are breathing in pollutant exhaust particles
- Epidemiology studies: A rise in particle in ambient urban air correlates to increasing incidence of chronic lung and cardiovascular diseases: asthma, atherosclerosis
- Acute lung effects: cough or shortness of breath
- Acute cardiovascular events: myocardial infarction (MI) & thrombus formation can be seen within 48 hr

*Sydbom et al., Eur Respir J., 17:733-746, 2001*

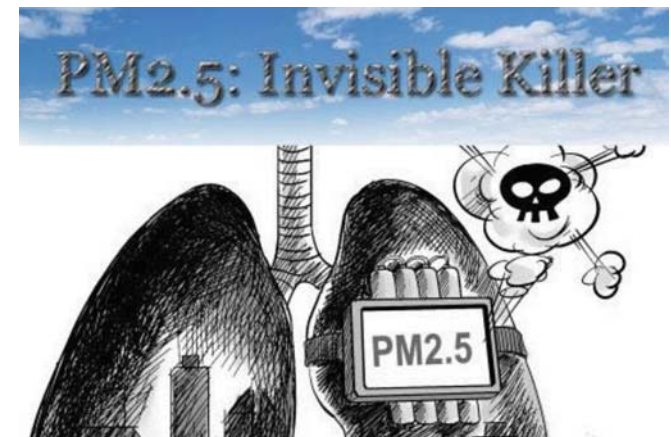
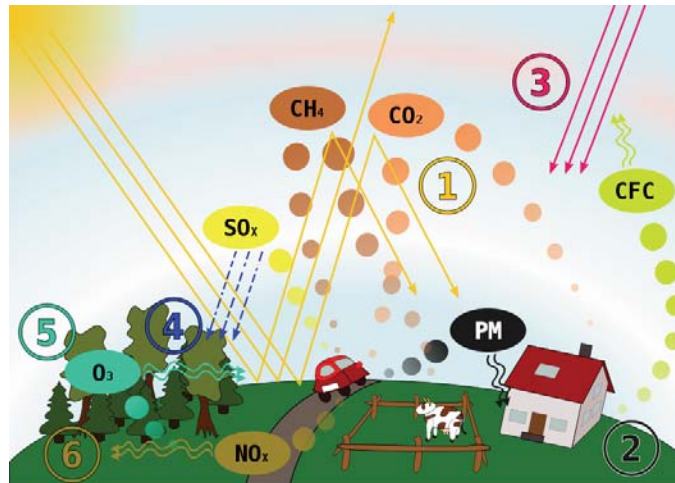
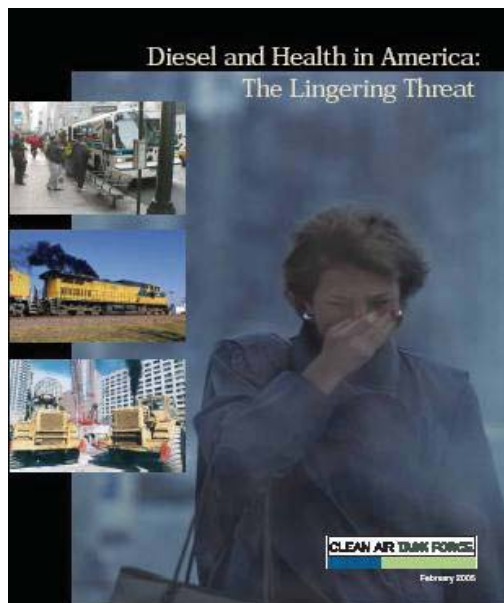
*Nemmar et al., Pathophysiol Haemost Thromb. 32(5-6):349-350, 2002*

*Nemmar et al., Circulation, 110(12):1670-7, 2004*

*Mills et al., N Engl J Med., 357(11):1075-82, 2007*

*Brook, Clinical Sci., 115, 175-187, 2008*

*Lucking et al., Eur Heart J., 29(24):3043-51, 2008*





Eq = to calculate O<sub>2</sub> diffusion capacity

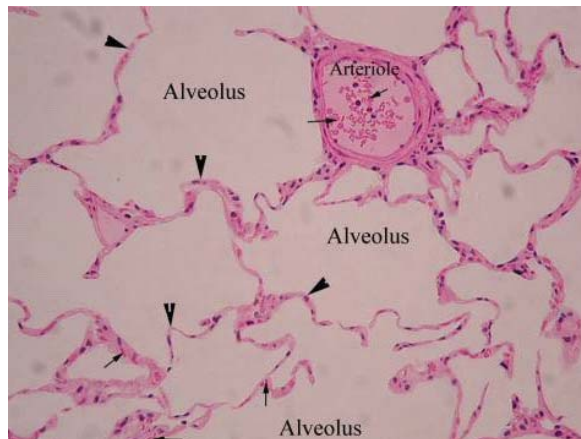
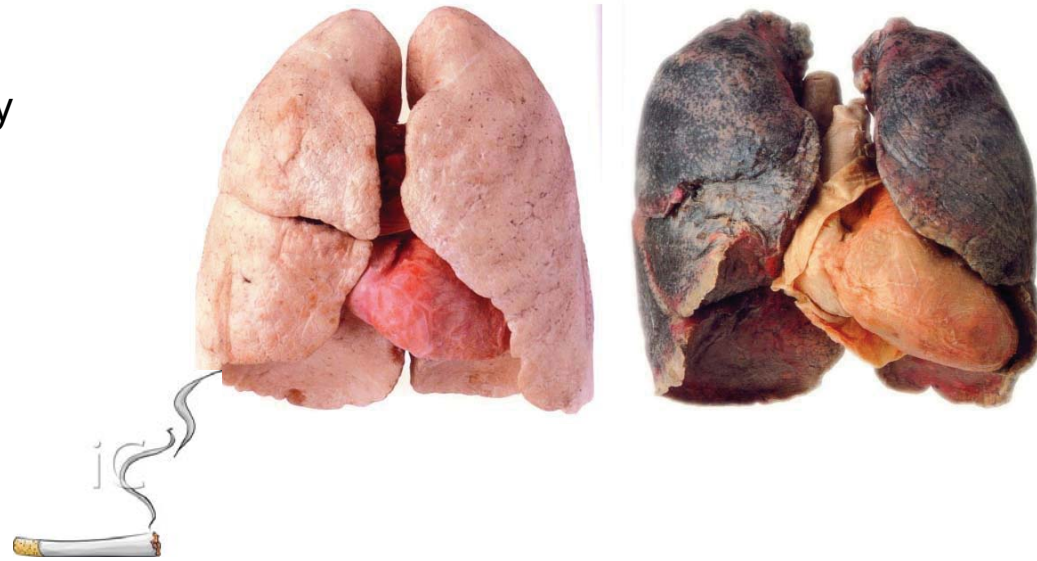
$$D_{LO_2} = \frac{\dot{V}_{O_2}}{P_{AO_2} - P_{aO_2}}$$

D<sub>LO<sub>2</sub></sub>: diffusion capacity

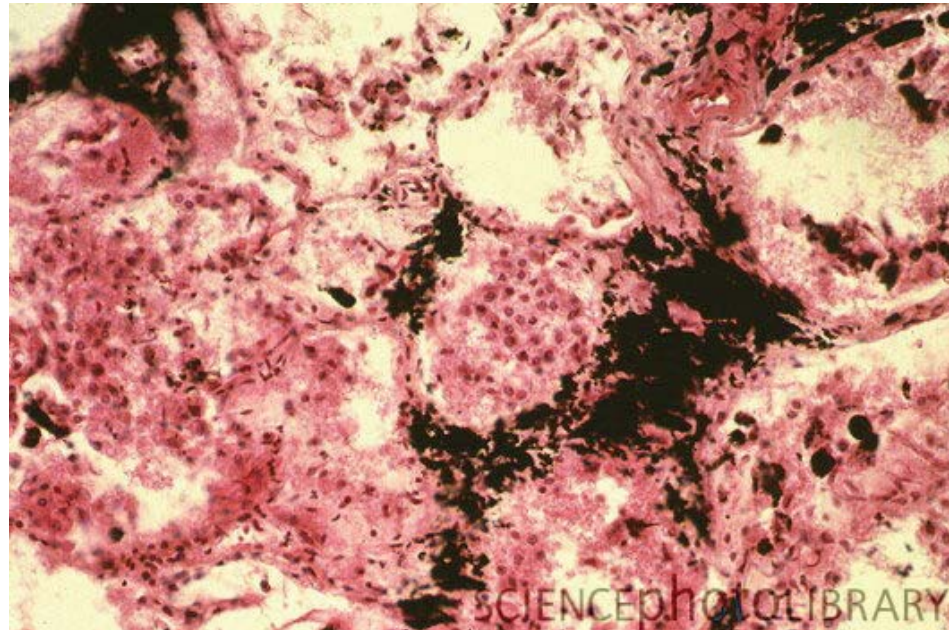
V<sub>O<sub>2</sub></sub>: rate oxygen been uptaken

P<sub>aO<sub>2</sub></sub>: partial pressure in artery

P<sub>AO<sub>2</sub></sub>: partial pressure in alveoli



δP<sub>O<sub>2</sub></sub>=60 mmHg



P<sub>aO<sub>2</sub></sub> decreasing, δP<sub>O<sub>2</sub></sub> > 60 mmHg ---→ low O<sub>2</sub>



# Glyphosate

What you **don't**  
know might be  
**KILLING YOU**

[NourishingLiberty.com](http://NourishingLiberty.com)



