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# Carcinogenesis

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London**

# Aims

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- **Become more insightful about cancer as a disease of cell biology**
- **To demonstrate how a normal cell can become a cancer cell**
- **Provide the basis to understand mechanisms of carcinogenesis**

# Learning Outcomes

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**By the end of this lecture you will be able to:**

- **Understand how important it is for cells to ‘communicate properly with each other’**
- **Give examples of different carcinogens and enumerate cancers in which they are known to play key roles**
- **Understand basic principles of cancer formation and progression**

# Today's Menu

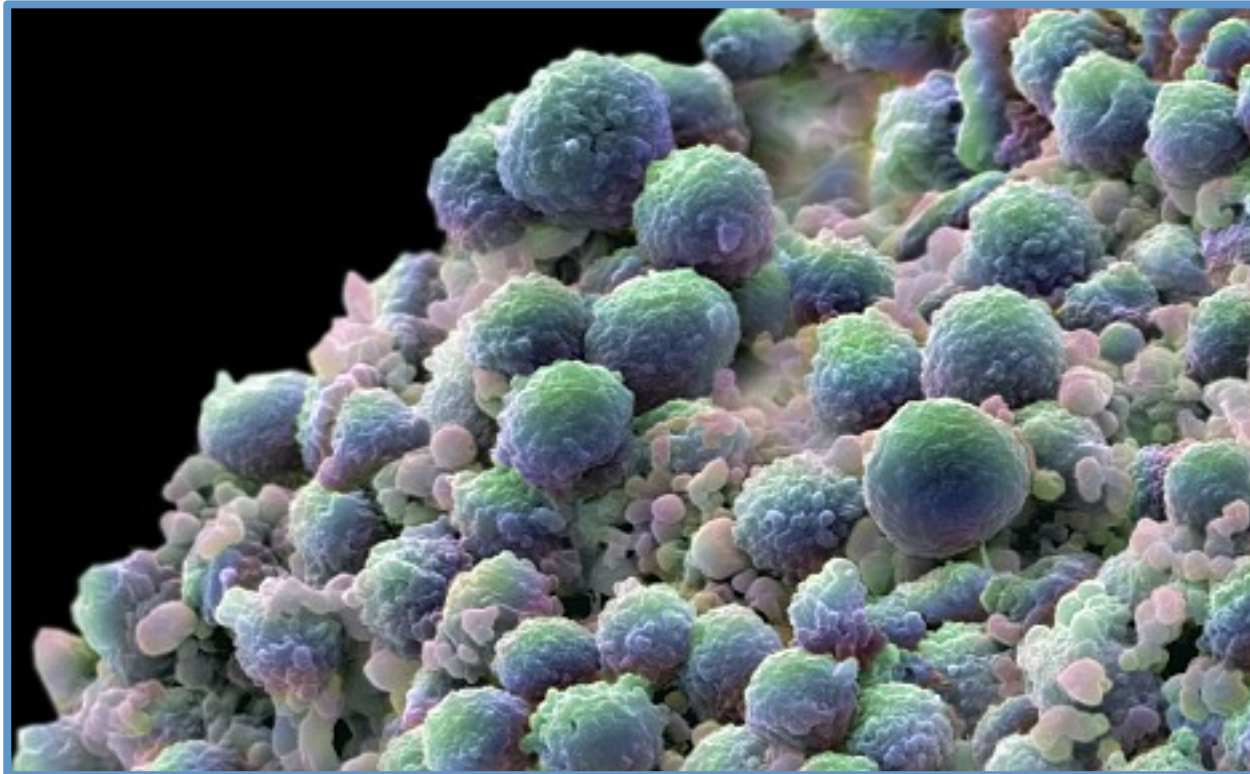
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- **Complexity of living beings and of its building blocks – the cell**
- **DNA replication, the cell cycle and apoptosis**
- **The origins of cancer**
- **Carcinogenesis**

# Unity of Design & Beauty...



... versus Chaos!



**And, yet, so much about normal biology has been learnt from studying cancer cells!**

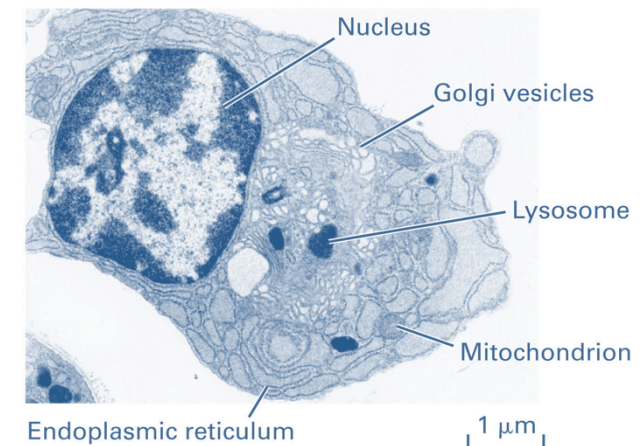
# Introduction

- The body = 80 trillion (80,000,000,000,000) cells!
- The cell = ~30 thousand (30,000) proteins!
- The nucleus = 3 metres of tightly packed DNA!

## Problem!

- \* Every day 30,000,000 die...
- \* 30,000,000 are generated by mitosis...
- \* 30,000,000 x 3 m DNA need to be copied...

(b) Eukaryotic cell



# Cell 'Multiplication'

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This is where it can all go horribly wrong...

- **complex systems, with various tissues, need to follow precise genetic instructions for the growth, maturation and maintenance of the cells**

## **Key Cellular Events:**

- Error-free DNA replication
- Cell cycle control
- Cell normal physiology
- Induction of apoptosis at key moments



# The Cells

- Each cell is a building block, a single entity, surrounded by a lipid bi-layer
- Boundaries separate them from other cells
- Eukaryotes have a membrane that isolates the DNA in the nucleus

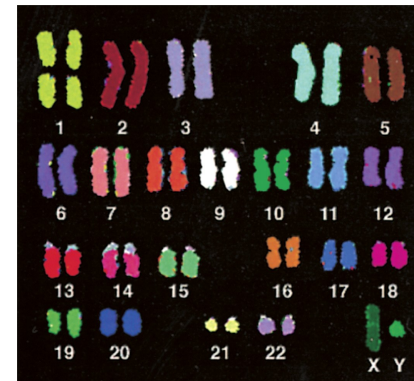


Figure 1-11b. The Biology of Cancer (© Garland Science 2007)

# Cells are autonomous entities...

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- Cells can perform many different functions almost as if they were a mini-ecosystem

\* this is good and bad...

## The good:

- Cells that can survive in several cellular contexts can adapt and serve specific functions in the body and are free to move

## The bad:

- Potential overgrowth which can ultimately lead to cancer

## **...yet they must leave in a community**

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- **Cells do not exist in a vacuum: they are surrounded by other cells and by extracellular fluids**
- **They scan the environment for cues (divide, stay still, apoptose/die)**
- **They send messages to other cells**

# The society of proteins

Proteins

do...

... not

“live” alone!

Die

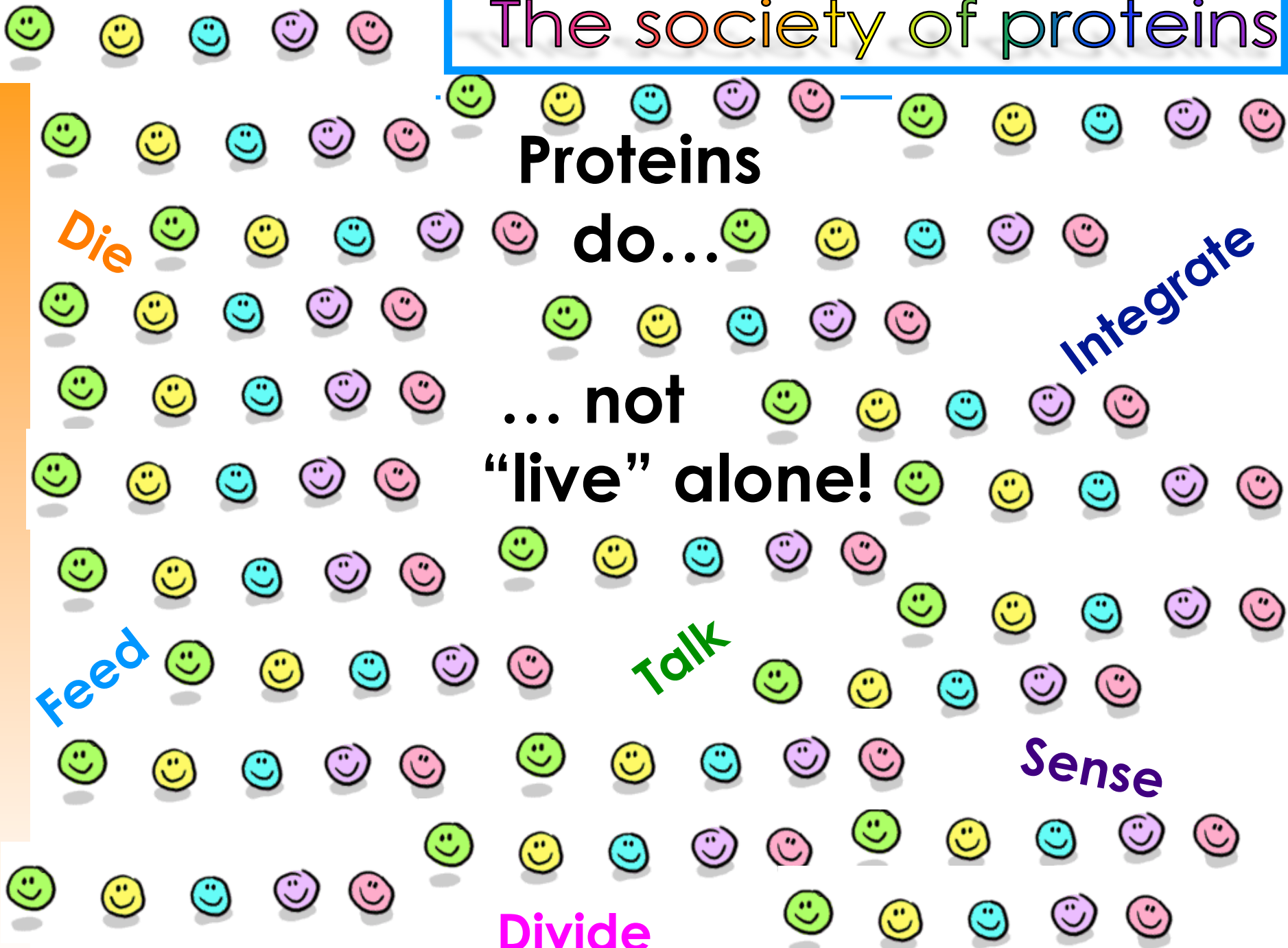
Integrate

Feed

Talk

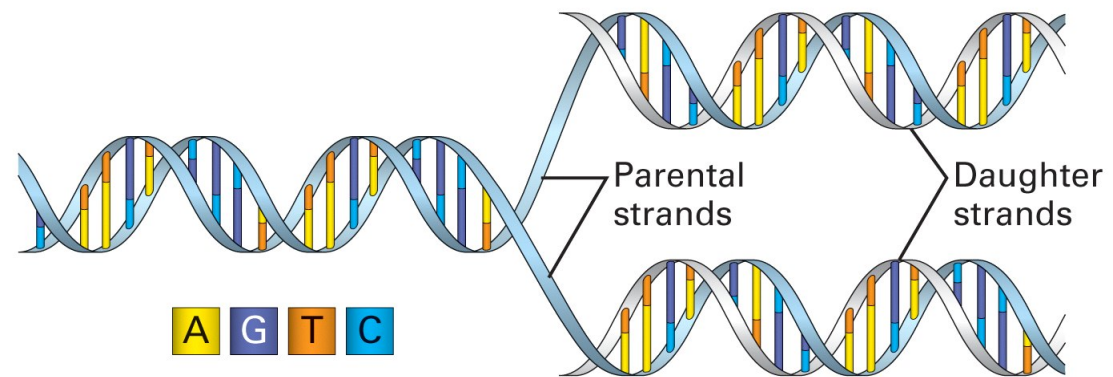
Sense

Divide



# A cell is born...

- Each cell has the potential to give rise to two daughter cells – mitosis
- The cell cycle requires the replication of DNA

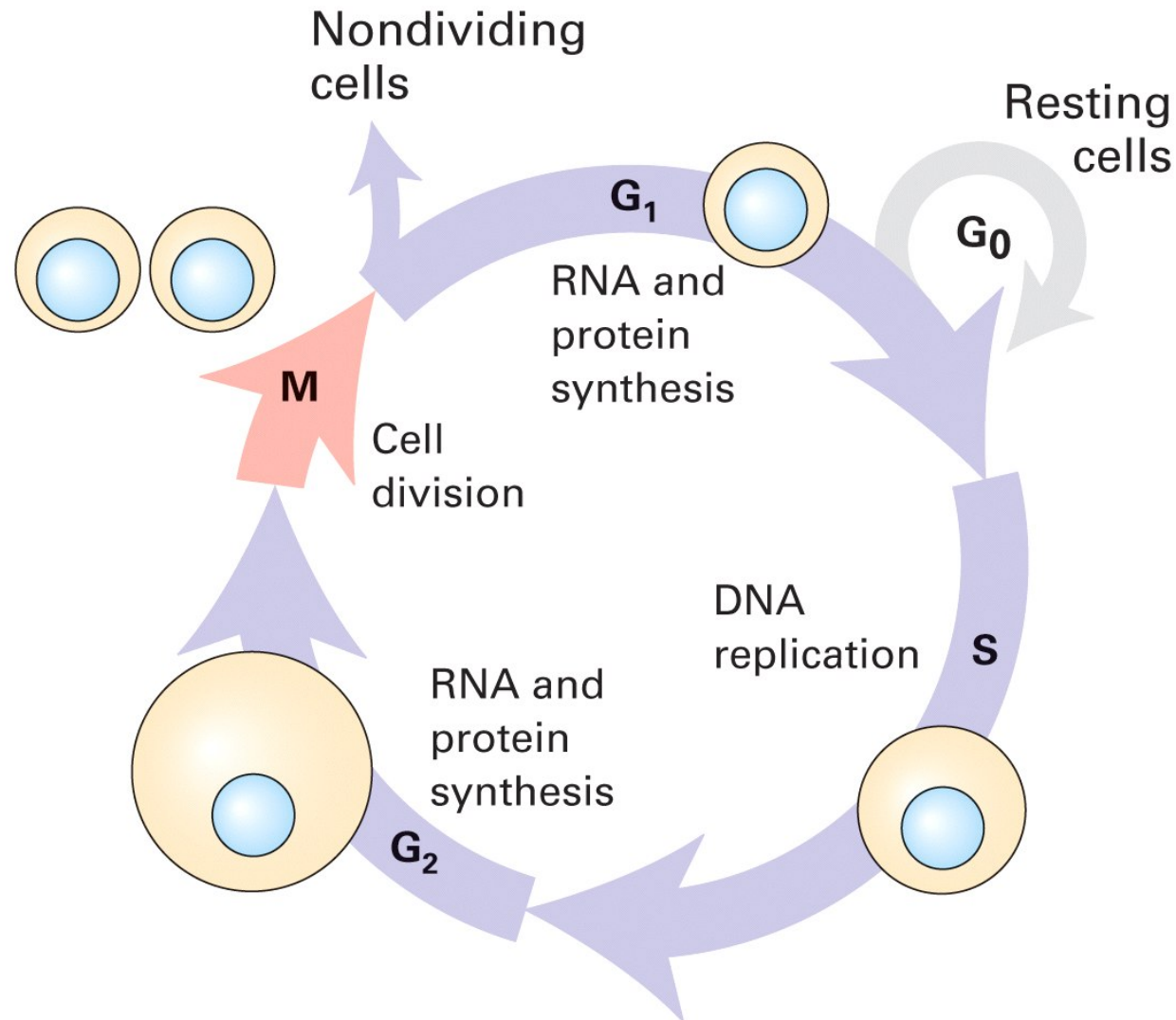


# Ingredients for a cell cycle

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- Parental cell must grow and ensure that it has enough 'goodies' (DNA, RNA, proteins, organelles, membranes, salts, fluids...) to divide between the daughter cells
- Cell must be able to coordinate the cell cycle
  - \* several checks must be in place
  - \* cycles of phosphorylation/dephosphorylation are very important - cyclins

# The Cell Cycle



# Mutations Can Arise from Replication

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- Many errors can occur during the transcription of 3 metres of DNA, which will accumulate
- Can lead to silent mutations or harmful (**small or large**) mutations:
  - \* deletion
  - \* insertion
  - \* translocation
  - \* amplification
  - \* **base substitution missense (new aa)**
  - \* **base substitution nonsense (STOP)**
  - \* **frameshift (different sequence sub.)**



# Normal Cell vs. Cancer Cell

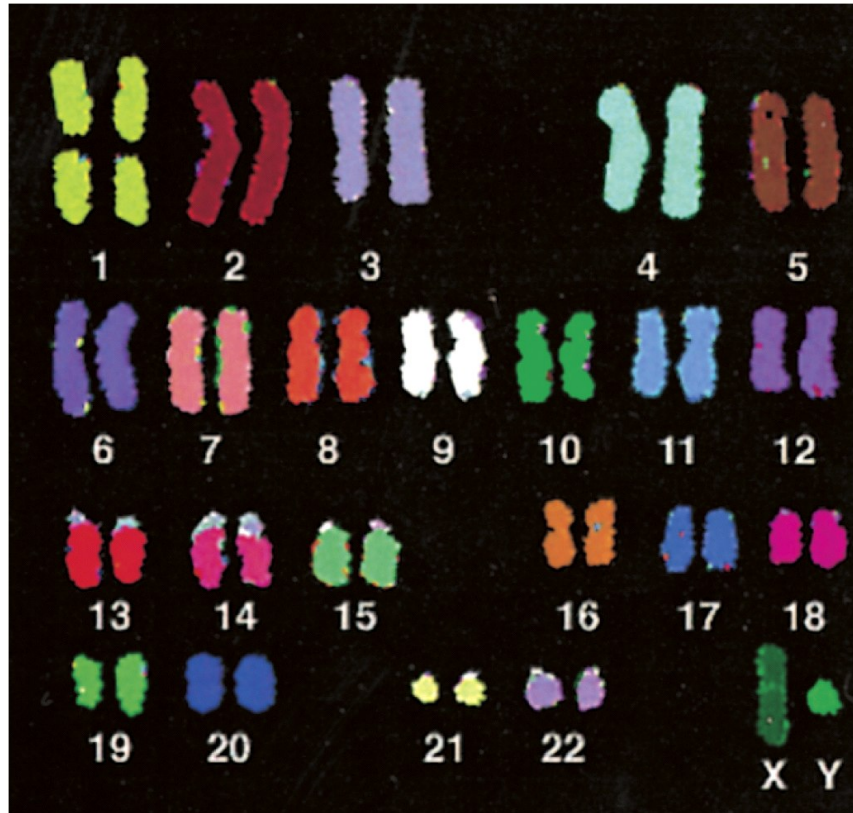


Figure 1-11b The Biology of Cancer (© Garland Science 2007)



Figure 1-11c The Biology of Cancer (© Garland Science 2007)

Weinberg (2007). The Biology of Cancer, 1<sup>st</sup> ed.  
Garland Science, New York, USA

# Cells also have a life...

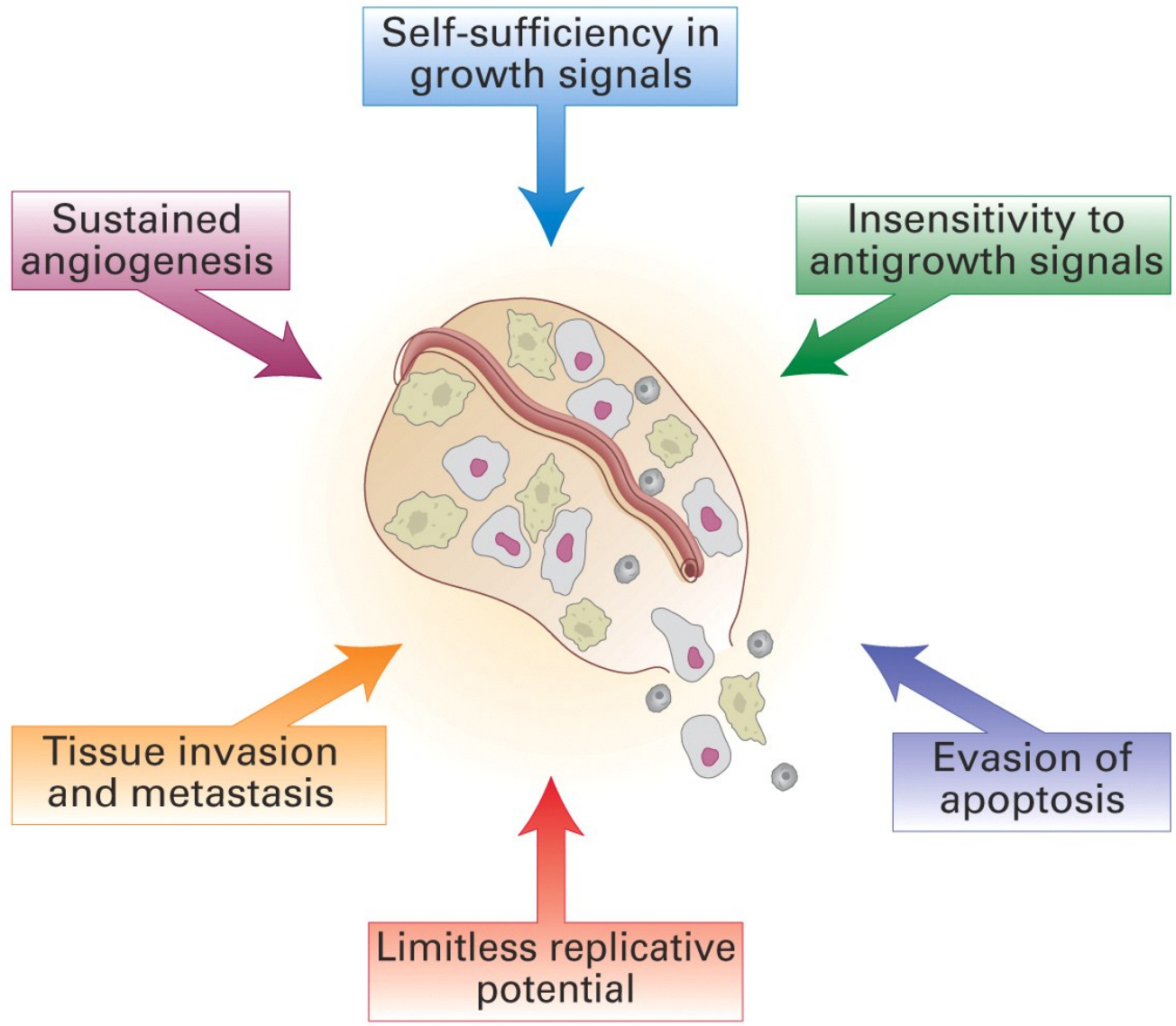
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- **Different cells have different functions**
- **Different cellular functions require a different set of proteins to execute it**
- **DNA has all the information necessary to make any given protein – the “cellular soldiers”**
- **Different kinds of proteins – different families**

# What do cancer cells do?!?

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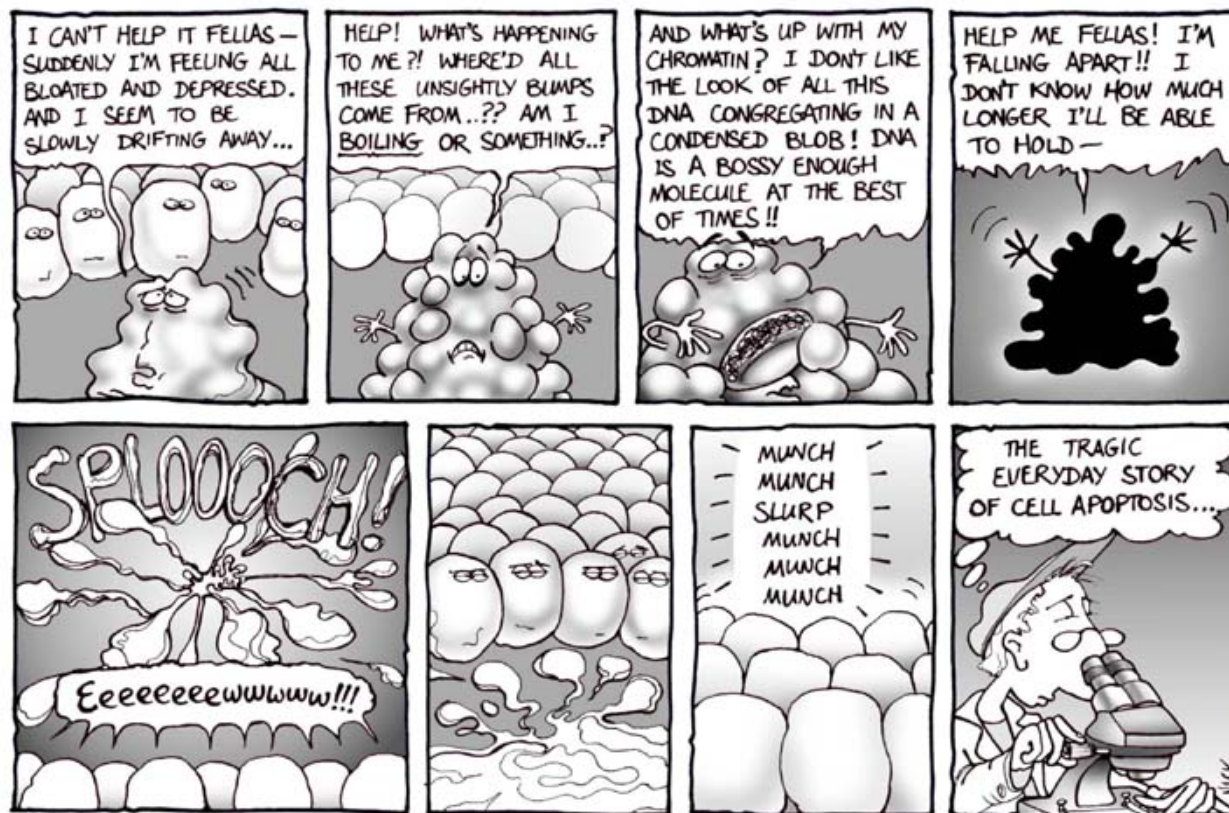
- They multiply uncontrollably – they focus their energy on their own proliferation and no longer focus on forming a functional tissue or organ
- They don't differentiate as they should – often lose organ- or tissue-specific characteristics
- They do not die when apoptosis is triggered



# But all cells must eventually die...

- 10 billion cells die every day
- Highly controlled process that involves:

- caspases
- DNA cleavage
- membrane blebbing





**What pushes cancer cells  
to adopt such  
rogue behaviour?!?**

# Cancer throughout the ages

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- **Hippocrates** used the word cancer to describe metastatic breast cancer (400 BC)



- **Robert Hooke** coined our building blocks “cells” in 1665



- **Rudolf Virchow** established that “*omnis cellula a cellula*”

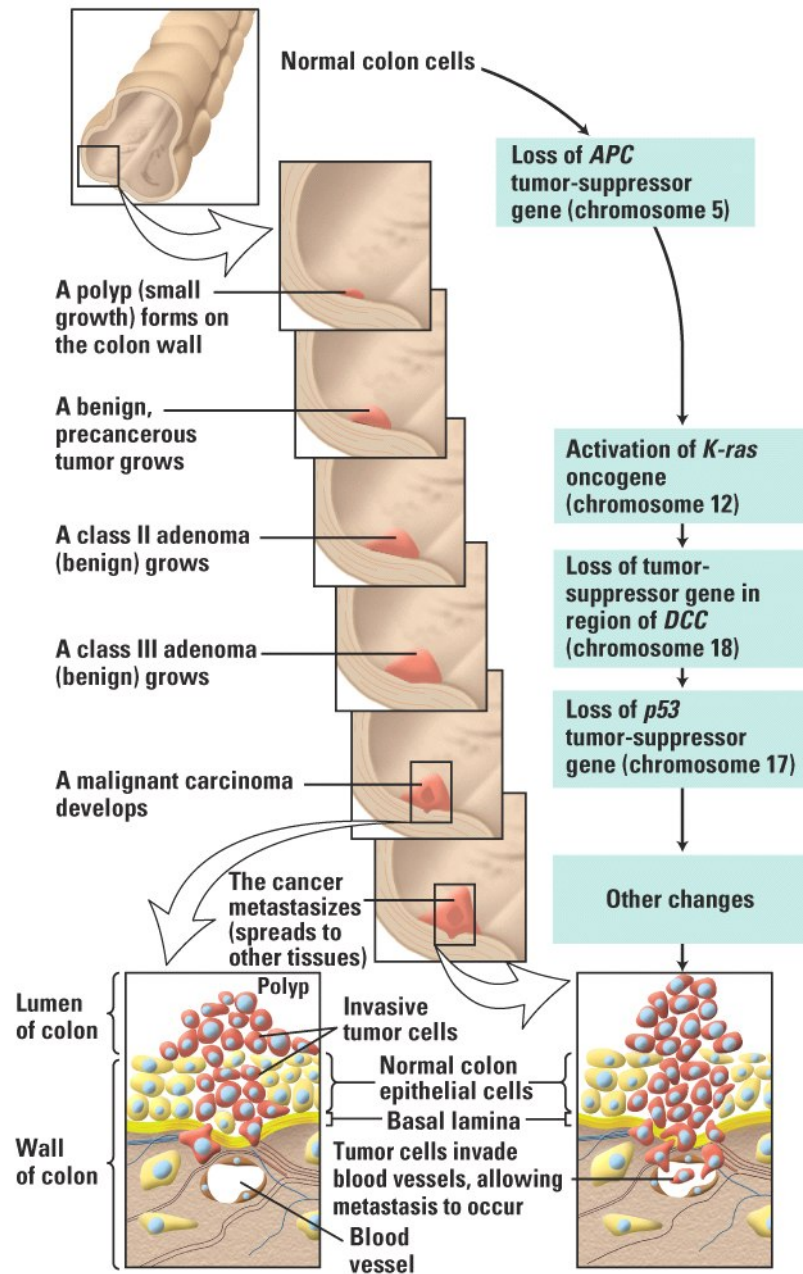


## But if all cells arise from one cell...

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- **Ultimately all cells must derive from one cell: the zygote... even tumour cells (RV)**
- **But from which cells do cancers arise from?**
- **Colon cancer will be used to exemplify and explain carcinogenesis**





**Carcinomas  
do not respect  
boundaries and  
quickly start invading  
other tissues**

# Where do cancer cells come from?!?

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- Do they arise from normal cells in an adjacent tissue(s)?
- Are they introduced in the body by infection?

## Transplants to the rescue...

\* most are rejected except between twins or closely, genetically, related people – tumours must thus arise from normal tissues... **How?!?**

# The origins of tumour cells

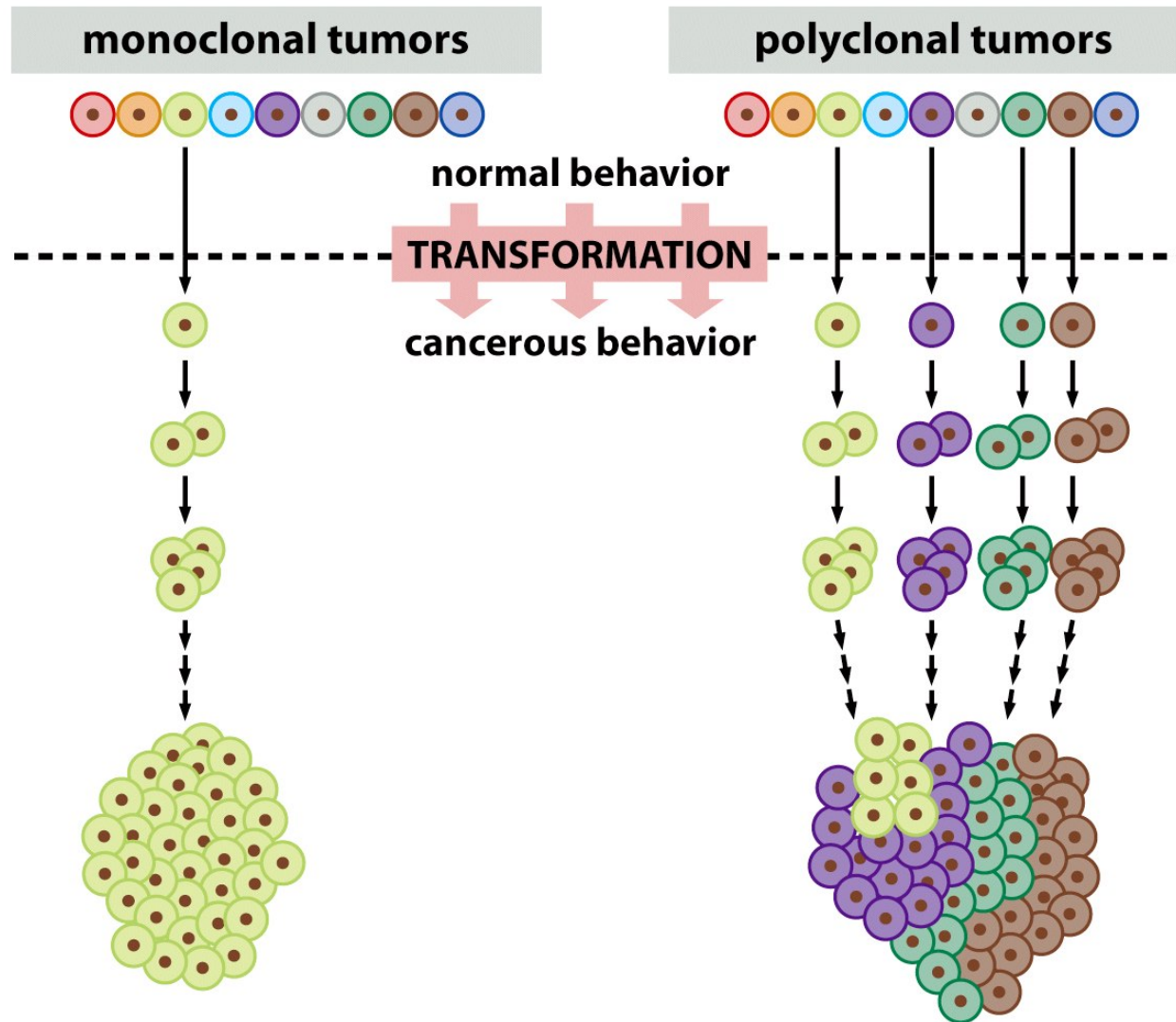


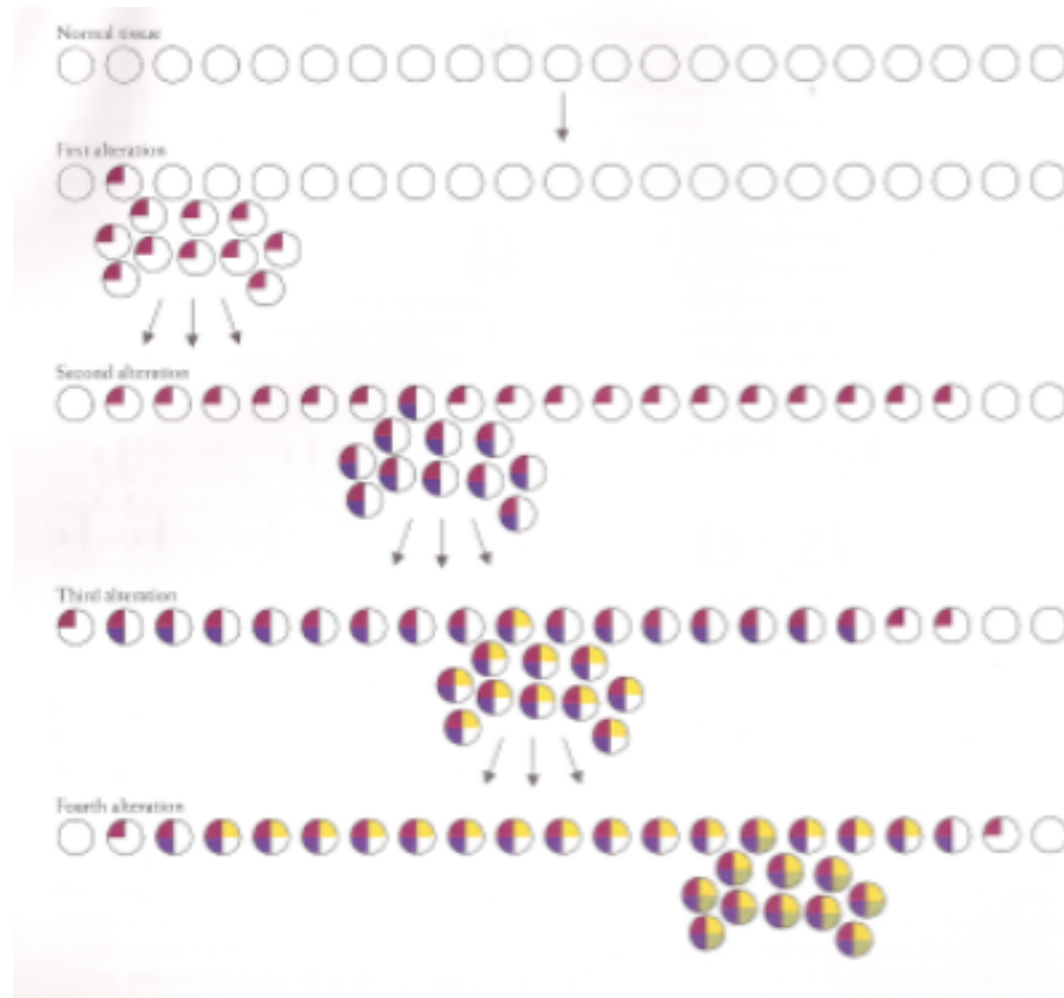
Figure 2-17 The Biology of Cancer (© Garland Science 2007)

# So what are tumours?

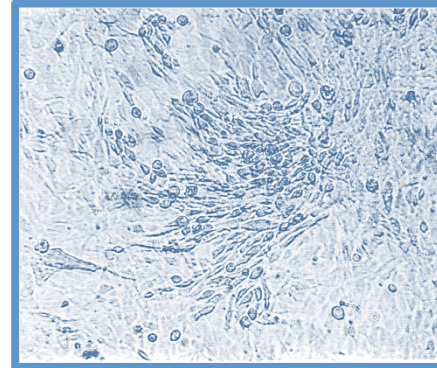
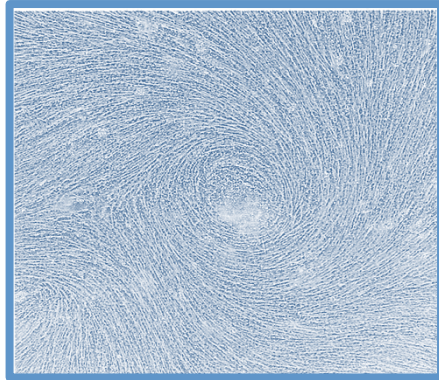
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- **Most are believed to be monoclonal**
- **Picture is more complex and some tumours may be polyclonal, depending on how many cells have initially crossed the threshold between normality and malignancy**

# A cell clone can sustain successive multiple alterations



# Normal and Cancer Cells in Culture



- \* **Loss of contact inhibition**
- \* **Disorganization**
- \* **Anchorage-independent**
- \* **Less dependent on growth factors**
- \* **Immortal!**

# Clues to What May Cause Cancer



Smoking  
lung cancer/oral cancer, etc



Pitchblende miners  
lung cancer

Infections?  
Chronic Inflammation?



X-Rays  
≠ cancers



Chimney sweepers  
scrotal cancer



Sun bathing/Sun beads  
skin cancer

# Is it an inherited disease?

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- **Darwin – theory of evolution**
- **Mendel – rules of inheritance**
- **Environmental factors**

By analysing factors such as diet, habits, life-style, occupation, sex, age, ethnic origin and geography scientists gained clues into the origins of cancer



# Cancer Incidence

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- **Cancer varies tremendously around the globe**

## Men

- \* Liver cancer: Mozambique > 70x > Norway
- \* Skin cancer: Queensland > 200x > Bombay
- \* Lung cancer: UK > 35x > Nigeria

## Women

- \* Uterus cancer: California > 30x > Japan
- \* Breast cancer: Connecticut > 15x > Uganda
- \* Ovarian Cancer: Denmark > 6x > Japan

# What causes such variation?!?

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- **Diet**
- **Tobacco**
- **Infection**
- **Sexual and reproductive behaviour**

# Viruses can cause cancer

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- **Peyton Rous** showed in 1910 that a filtrate from chicken sarcomas could induce new sarcomas in healthy chicken – **virus**
- Efforts to identify bacteria or viruses that caused cancer failed and theory fell in disrepute
- In 1966, however, he got the Nobel Prize for it!

## Peyton Rous

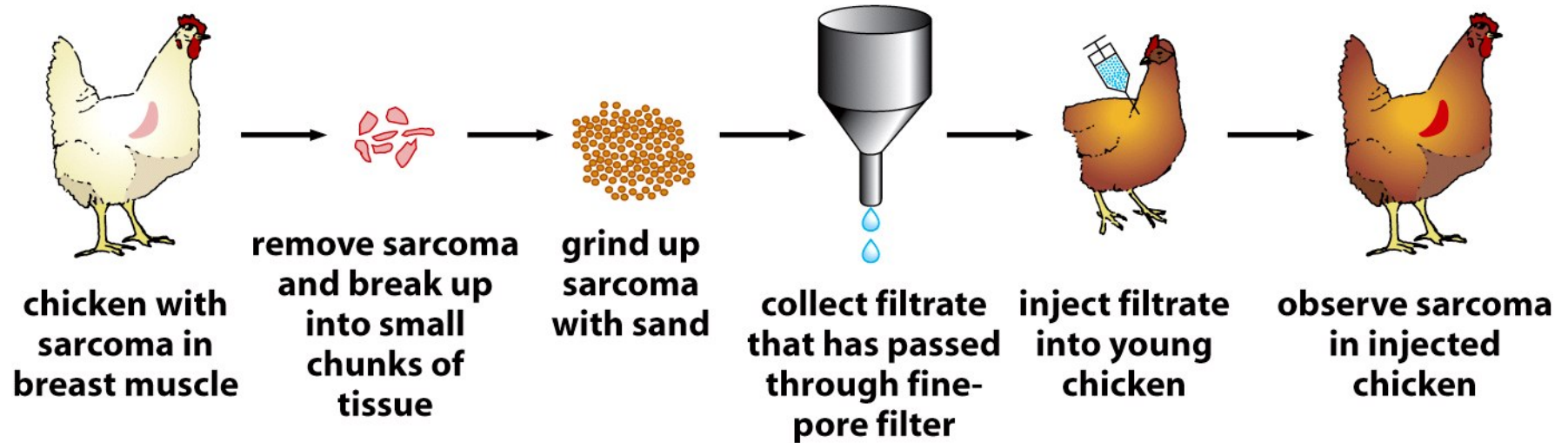


Figure 3-2 The Biology of Cancer (© Garland Science 2007)

# Viruses and Cancer

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- Rous sarcoma virus
- Polyoma
- Simian virus 40 (SV 40)

These showed that cancer could be traced to a single initiating cause (a virus particle)

**But how?!? How can a virus induce cancer in such a complex environment?**

# Transformation of Cells in Culture

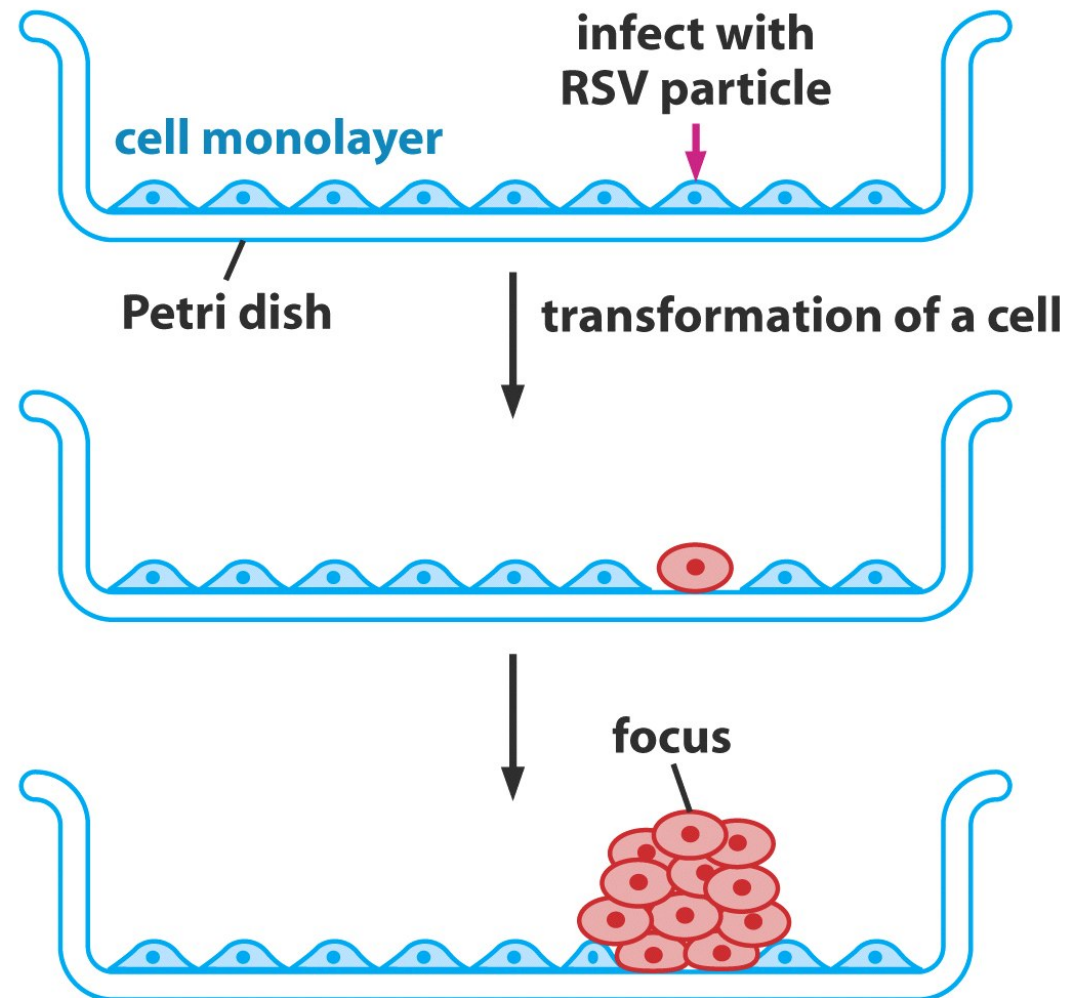


Figure 3-7a The Biology of Cancer (© Garland Science 2007)

# Radiation and Cancer

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- Repeated exposure to X-Rays correlated with subsequent cancer onset – e.g. Marie Curie
- Skin, leukaemias and bone cancers – not explained by local irritation (inflammation)
- **Herman Muller** noticed > mutant off-spring in flies subjected to X-Rays (later seen with chem.)

Thus radiation can affect cells by damaging their DNA (mutations)

# Normal Cell vs. Cancer Cell

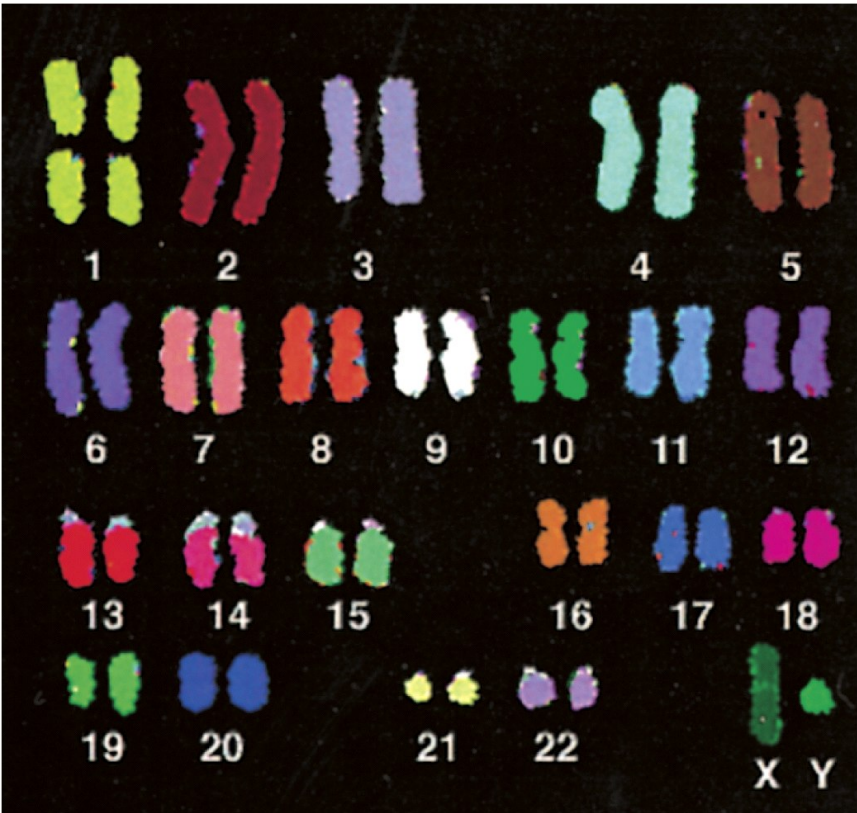


Figure 1-11b The Biology of Cancer (© Garland Science 2007)

## Theodor Boveri, 1914

Weinberg (2007). The Biology of Cancer, 1<sup>st</sup> ed.  
Garland Science, New York, USA



Figure 1-11c The Biology of Cancer (© Garland Science 2007)



# Chemical Carcinogenesis


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- **Coal tar induced skin cancer in rabbits when applied on their ears (1918)**
- **DNA known to be the genetic material by late 1940s**
- **Carcinogens likely to damage DNA**
- **Carcinogens often found bound to DNA...**

# Mutagenicity Test

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- Some chemical are potent inducers of cancer, others are weak inducers.
- **Bruce Ames (1975)** developed a reliable, cheap and easy test to measure mutagenicity
- The test used *Salmonella typhimurium* and a target gene that controlled His metabolism

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- 
- **Chemical mutagenesis = 2-step process**
  - **Cells alter the inert pro-mutagen chemically**
  - **Resultant mutagen can now interact with DNA**  
≠ chemical structure → ≠ information content
  - **Potent carcinogens were shown to be potent mutagens!**

# Ames' Test

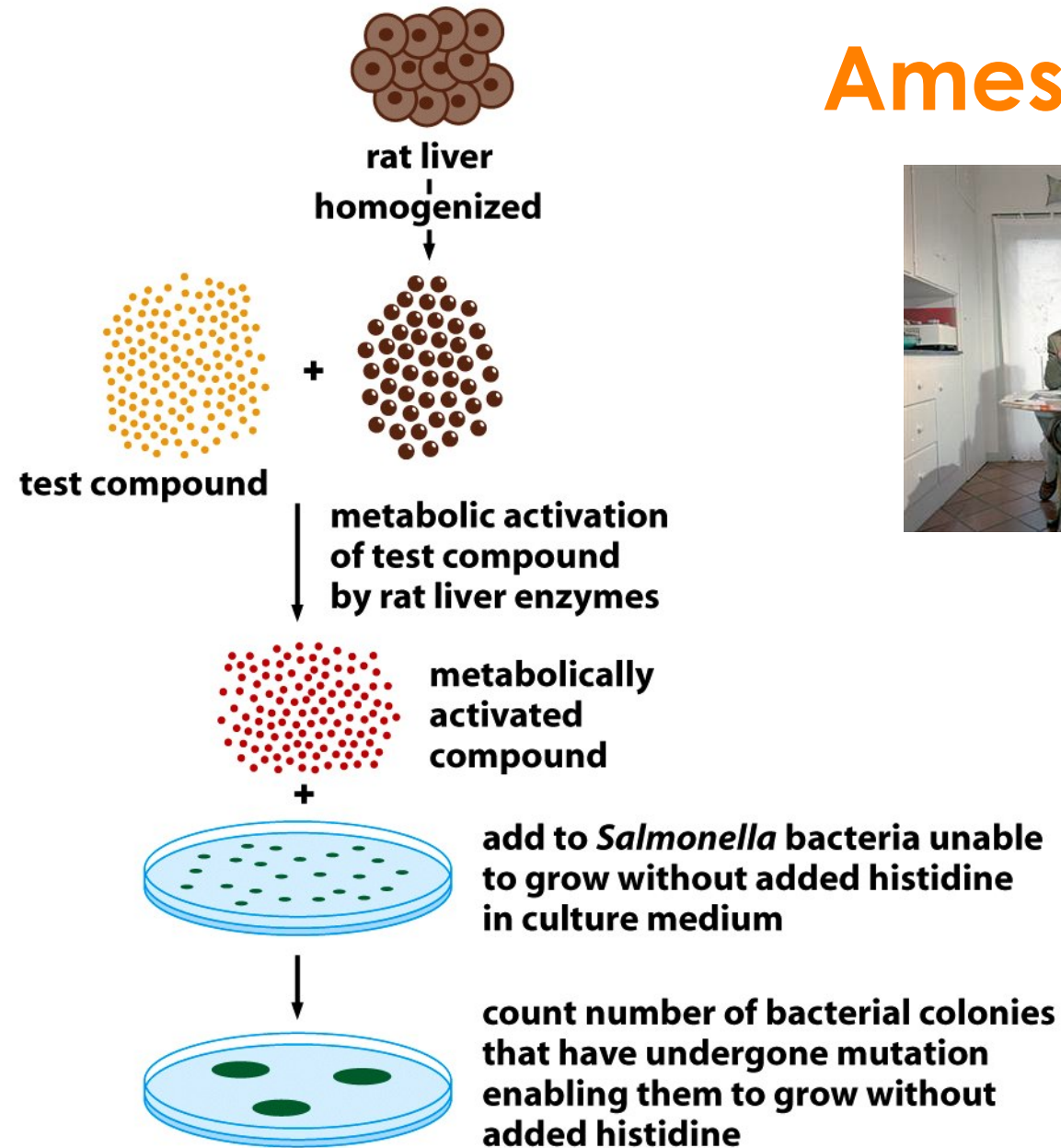


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# Conclusion

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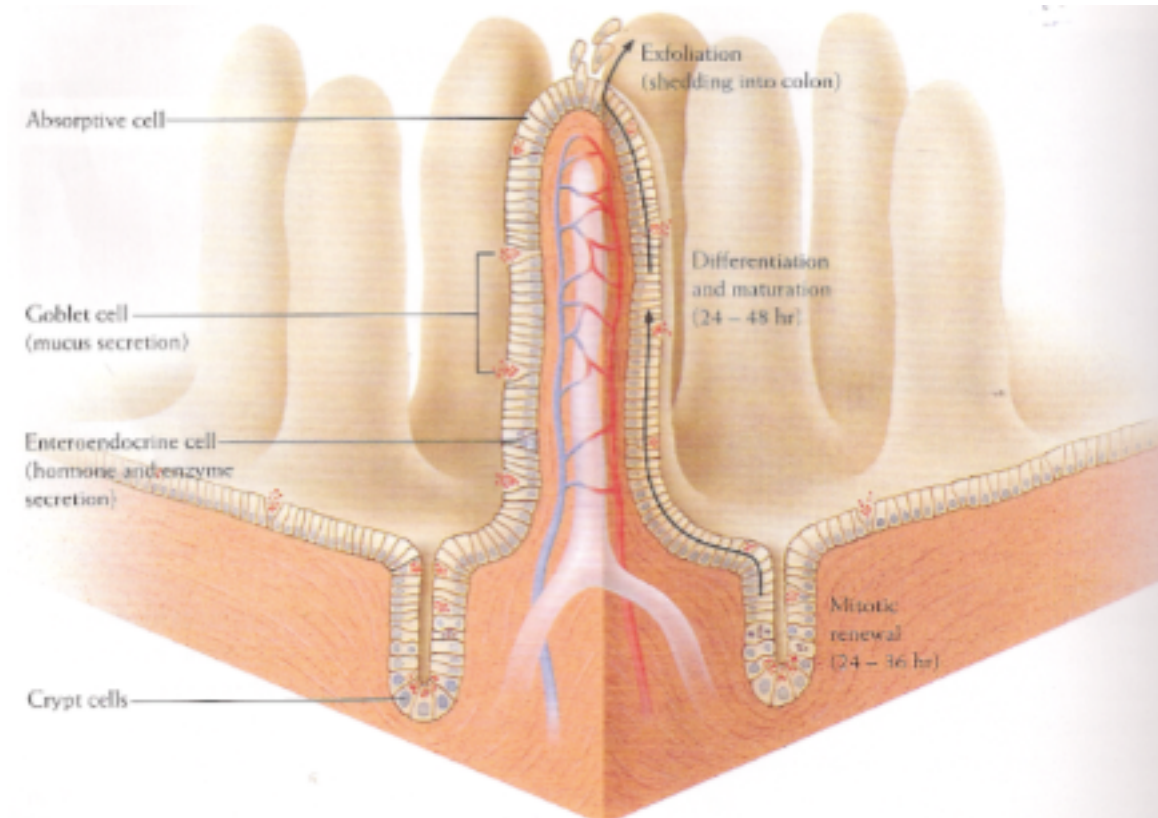
- **Cancer is a disease of cell biology**
- **Cancer is highly complex and it arises due to errors in our DNA – these can be inherited or induced by environmental factors**
- **Mutagens must target specific molecules – these will be the topic of the next lecture**

# Bibliography

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- Weinberg (2007). **The Biology of Cancer**, 1<sup>st</sup> ed. Garland Science, New York, USA
- Lodish *et al.* (2004). **Molecular Cell Biology**, 5th ed, W.H. Freeman & Co., NY, USA
- Varmus & Weinberg (1993). **Genes and the Biology of Cancer**, 1<sup>st</sup> ed, W.H. Freeman & Co., NY, USA

# Colon Carcinogenesis



**Carcinomas do not respect boundaries and quickly start invading other tissues**