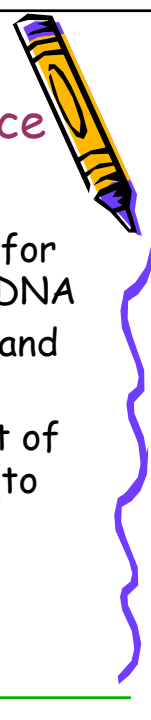


# 基因的性質和基因體

## The Nature of the Gene and the Genome


中山大學 生物科學系  
卓忠隆



## 遺傳的分子基礎

### The Molecular Basis of Inheritance

- In 1953, James Watson and Francis Crick introduced an elegant **double-helical model** for the structure of deoxyribonucleic acid, or DNA
- Hereditary information is encoded in DNA and reproduced in all cells of the body
- This DNA program directs the development of biochemical, anatomical, physiological, and (to some extent) behavioral traits



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## The Search for the Genetic Material: *Scientific Inquiry*

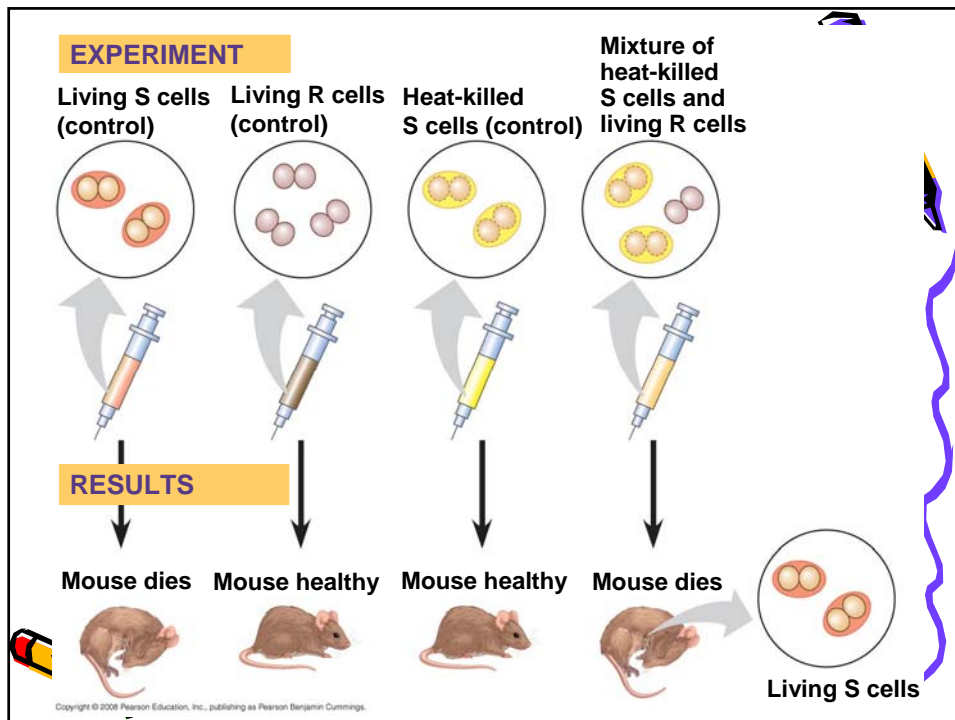
- When T. H. Morgan's group showed that genes are located on chromosomes, the two components of chromosomes—DNA and protein—became candidates for the genetic material
- The key factor in determining the genetic material was choosing appropriate experimental organisms
- The role of DNA in heredity was first discovered by studying bacteria and the viruses that infect them

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## *Evidence That DNA Can Transform Bacteria*

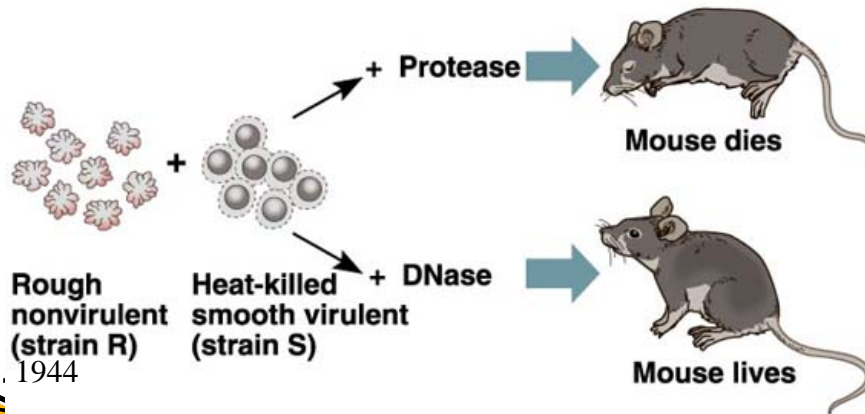
- The discovery of the genetic role of DNA began with research by Frederick Griffith in 1928
- Griffith worked with two strains of a bacterium, one pathogenic and one harmless
- When he mixed heat-killed remains of the pathogenic strain with living cells of the harmless strain, some living cells became pathogenic
- He called this phenomenon **transformation**, now defined as a change in genotype and phenotype due to taking up of foreign DNA

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- In 1944, Oswald Avery, Maclyn McCarty, and Colin MacLeod announced that the transforming substance was DNA
  - Their conclusion was based on experimental evidence that only DNA worked in transforming harmless bacteria into pathogenic bacteria
  - Many biologists remained skeptical, mainly because little was known about DNA
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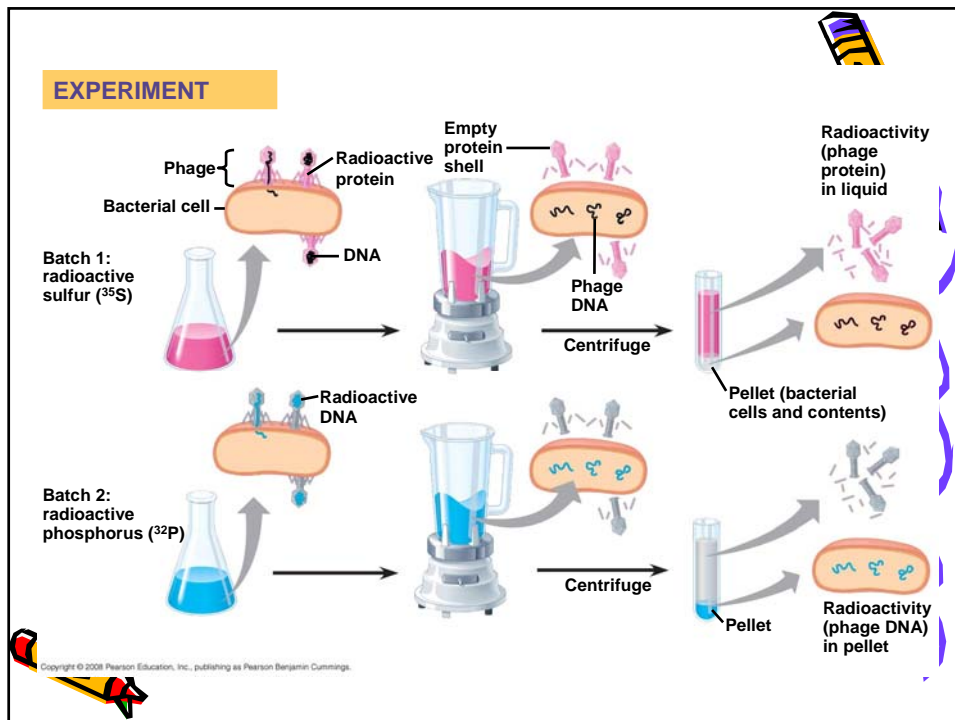
## AVERY'S BOMBSHELL: DNA transforms bacteria



1944  
Avery, MacLeod, McCarty (Rockefeller Institute)

### *Evidence That Viral DNA Can Program Cells*

- More evidence for DNA as the genetic material came from studies of viruses that infect bacteria
- Such viruses, called **bacteriophages** (or **phages**), are widely used in molecular genetics research
- In 1952, Alfred Hershey and Martha Chase performed experiments showing that DNA is the genetic material of a phage known as T2



- To determine the source of genetic material in the phage, they designed an experiment showing that only one of the two components of T2 (DNA or protein) enters an *E. coli* cell during infection
- They concluded that the injected DNA of the phage provides the genetic information

## *Additional Evidence That DNA Is the Genetic Material*

- It was known that DNA is a polymer of nucleotides, each consisting of a nitrogenous base, a sugar, and a phosphate group
- In 1950, Erwin **Chargaff** reported that DNA composition varies from one species to the next
- This evidence of diversity made DNA a more credible candidate for the genetic material
- **Chargaff's rules** state that in any species there is an equal number of A and T bases, and an equal number of G and C bases

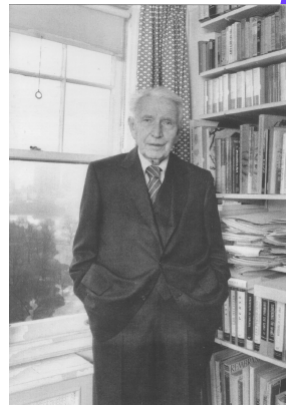
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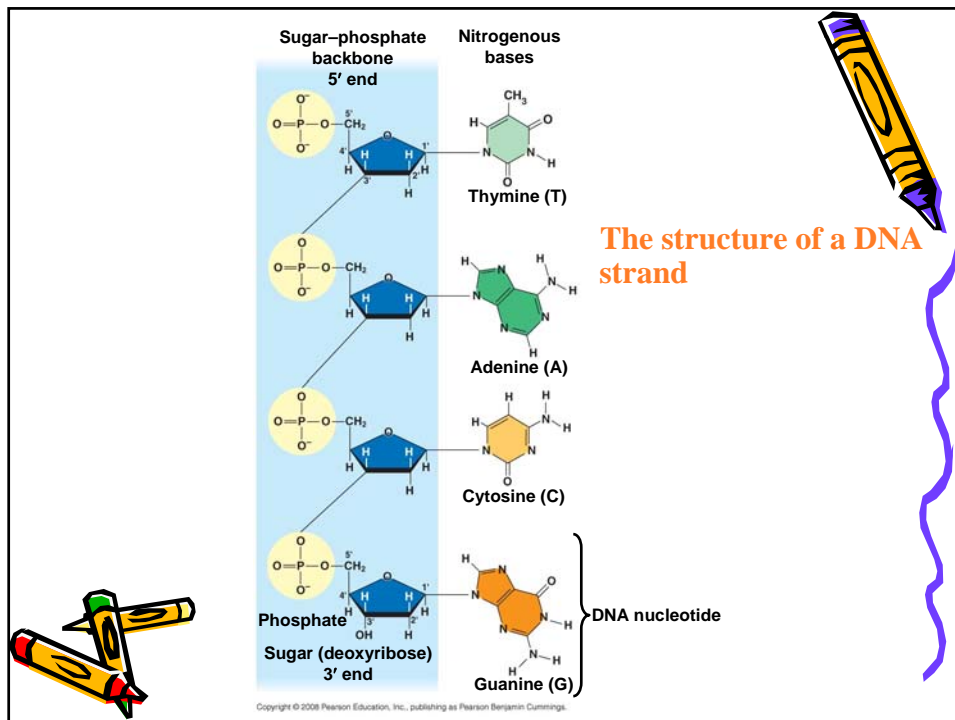
## Hidden Scientists Behind DNA Double Helix

- Erwin Chargaff (Columbia, 1950)



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## Building a Structural Model of DNA: *Scientific Inquiry*

- After most biologists became convinced that DNA was the genetic material, the challenge was to determine how its **structure** accounts for its role
- **Rosalind Franklin** were using a technique called **X-ray crystallography** to study molecular structure
- Franklin produced a picture of the DNA molecule using this technique

# Rosalind Franklin: X-ray diffraction



**Rosalind Franklin: The Dark Lady of DNA.** By Brenda Maddox  
, HarperCollins Publishers,  
New York, 2002, xix + 380 pages, \$29.95.

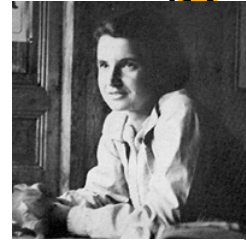
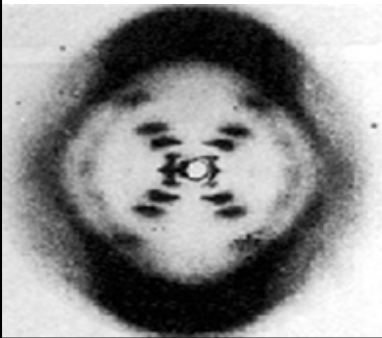
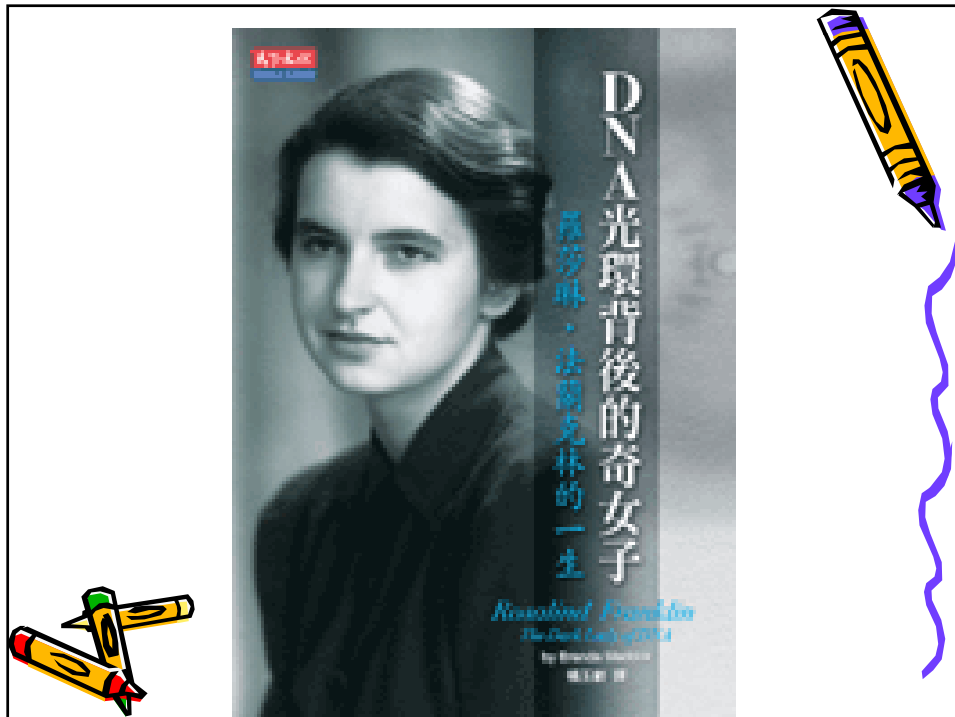




Photo 51





<http://www.wisniewskis.de/mystery.html>

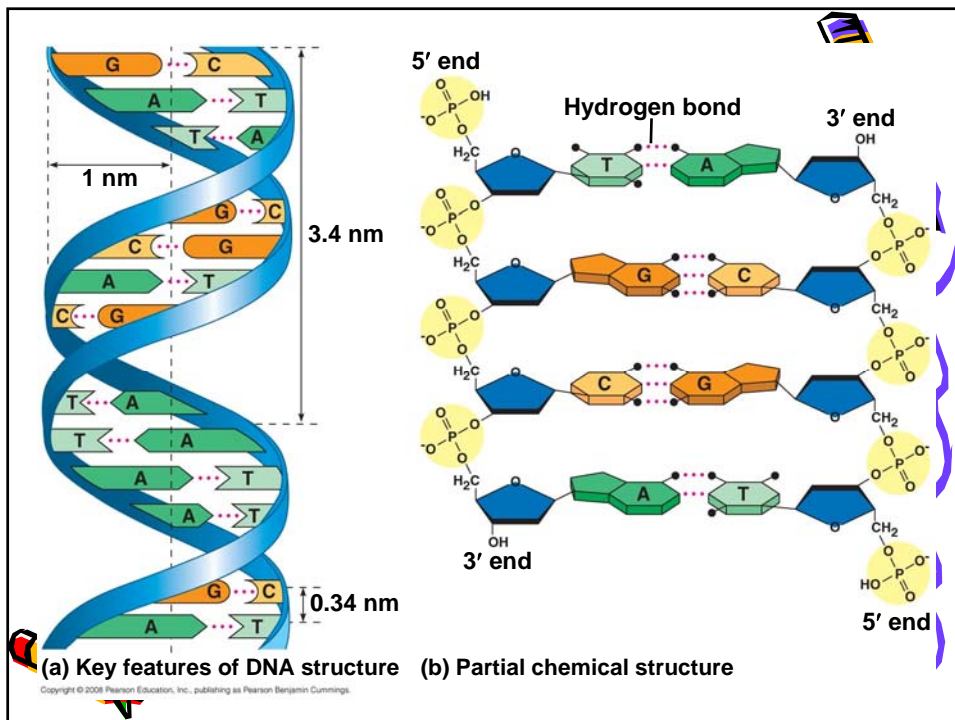
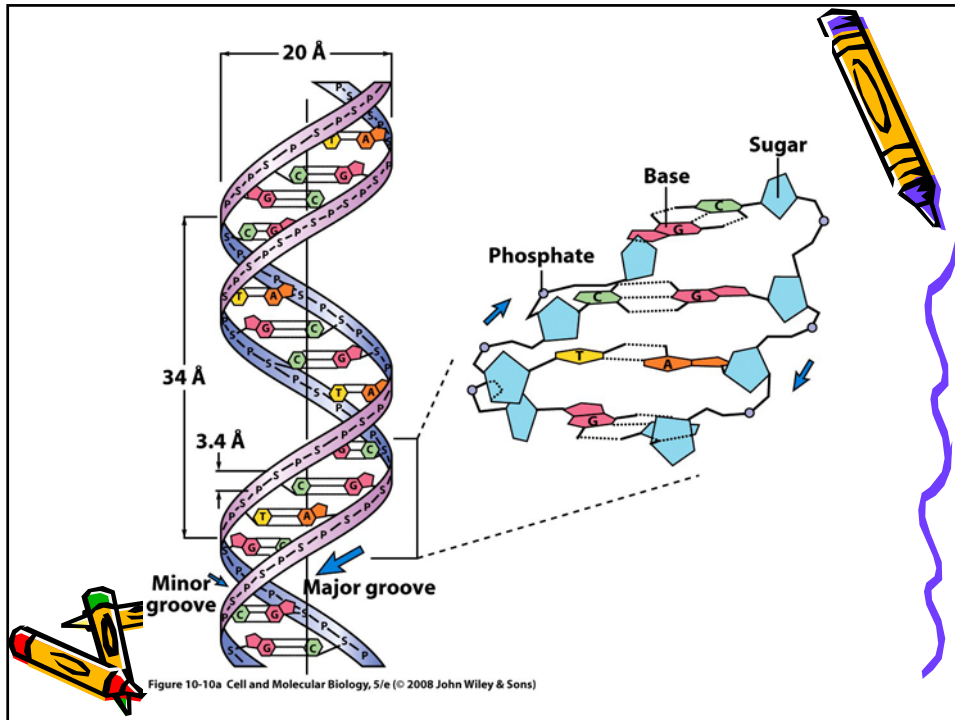





- 
- Franklin's X-ray crystallographic images of DNA enabled Watson to deduce that DNA was **helical**
  - The X-ray images also enabled Watson to deduce the **width of the helix** and the **spacing of the nitrogenous bases**
  - The width suggested that the DNA molecule was made up of two strands, forming a **double helix**
- 


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- 
- X-ray diffraction analysis revealed dimensions (the distance between nucleotides of the stack -  $3.4 \text{ \AA}$  (0.34 nm) between nucleotides in stack; suggested a large structural repeat every  $34 \text{ \AA}$  (3.4 nm).
- 







- Watson and Crick built models of a double helix to conform to the X-rays and chemistry of DNA
- Franklin had concluded that there were two antiparallel sugar-phosphate backbones, with the nitrogenous bases paired in the molecule's interior



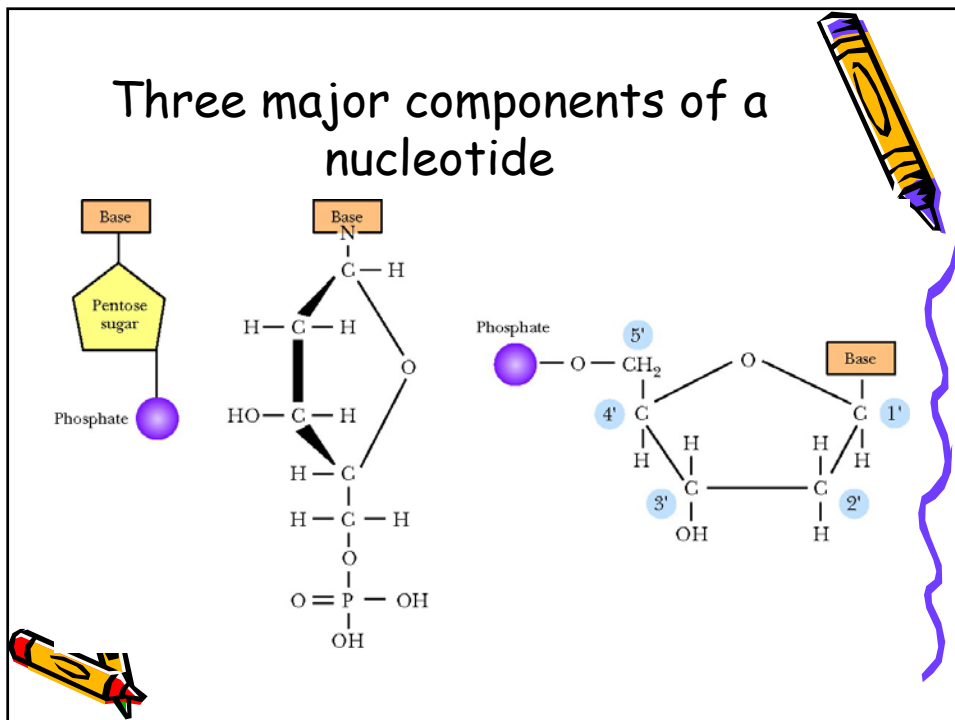
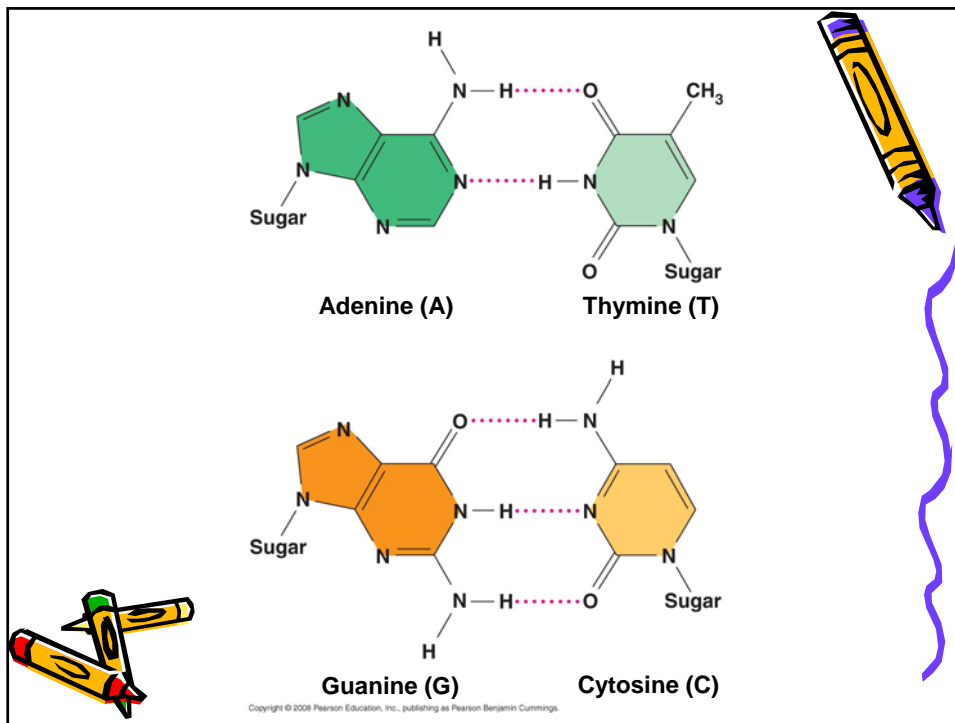
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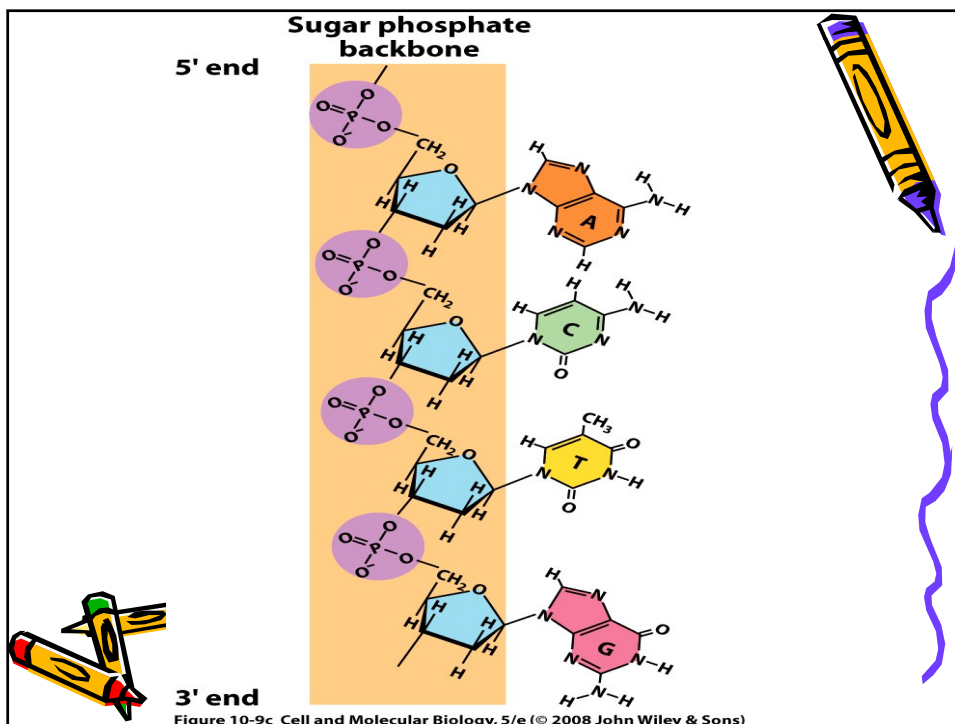
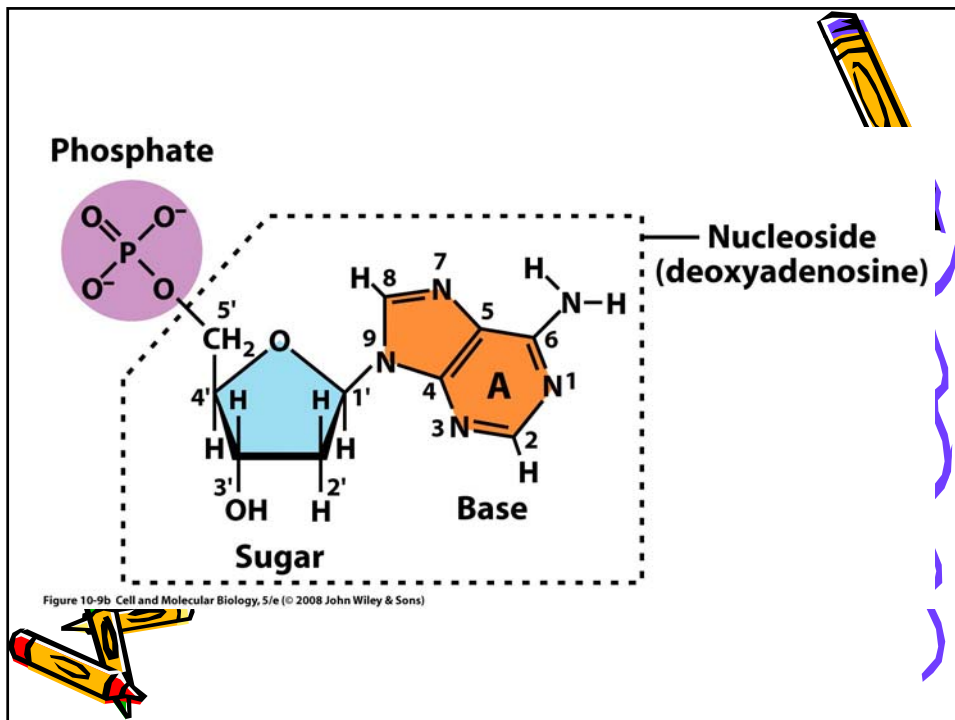


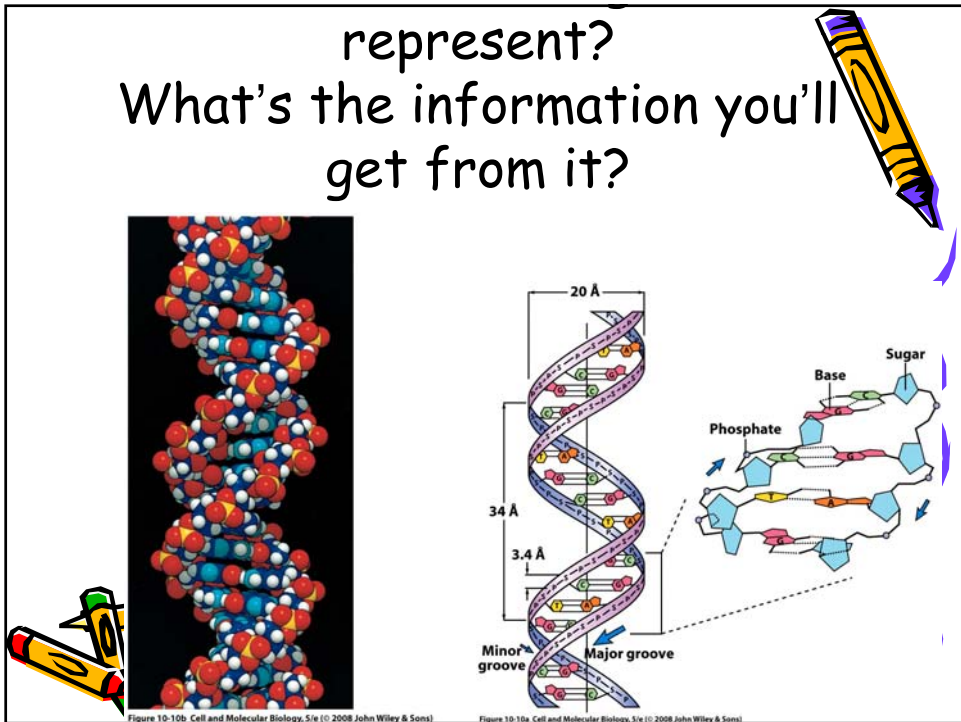
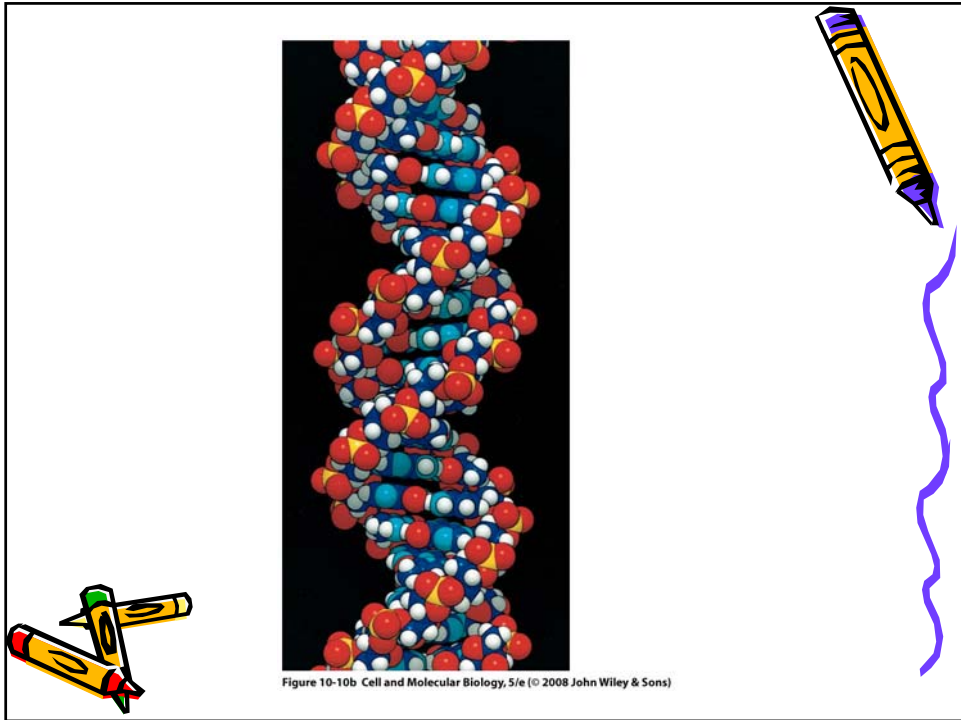
- At first, Watson and Crick thought the bases paired like with like (A with A, and so on), but such pairings did not result in a uniform width
- Instead, pairing a purine with a pyrimidine resulted in a uniform width consistent with the X-ray



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## The Double Helix: Deduced from the data of two research groups

### Watson - Crick Proposal

- 1. Composed of 2 nucleotide chains
- 2. Form a pair of right-handed helices
- 3. Run in opposite directions (**antiparallel**)
- 4. The backbone of each strand is on the outside of the molecule
- 5. Chains held together by H bonds
- 6. The sequence of one chain specifies the other's sequence (**complementarity**)

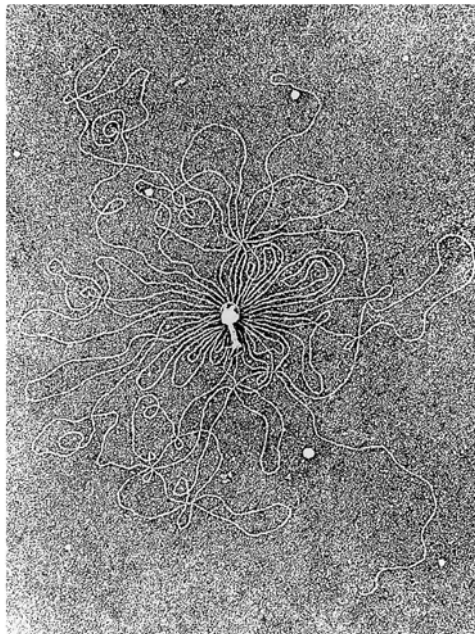
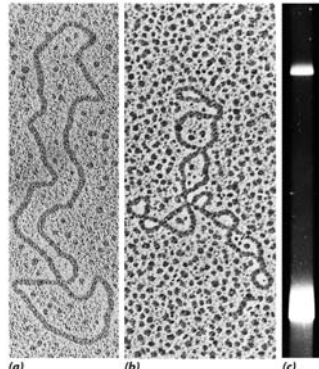


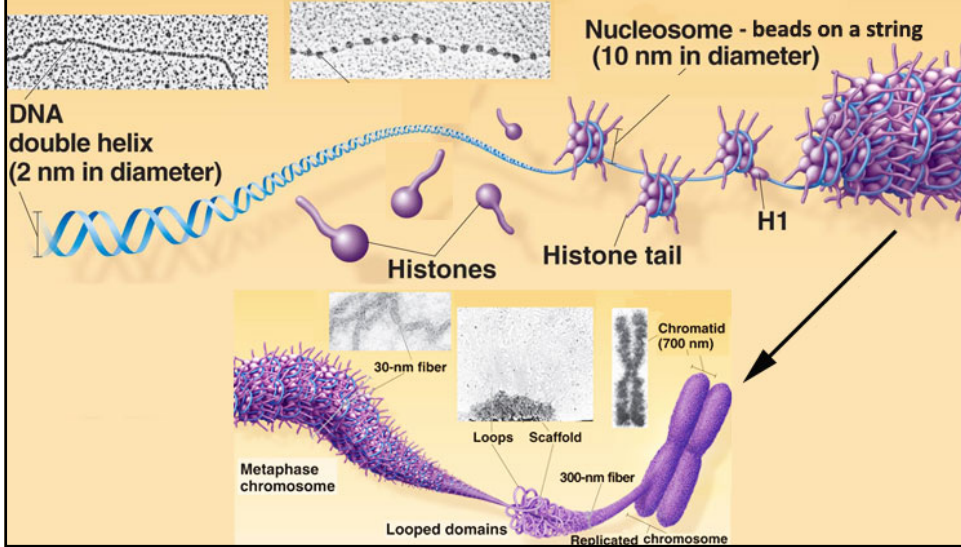
Figure 10-10d Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)



# DNA supercoiling



# The Structure of the Genome



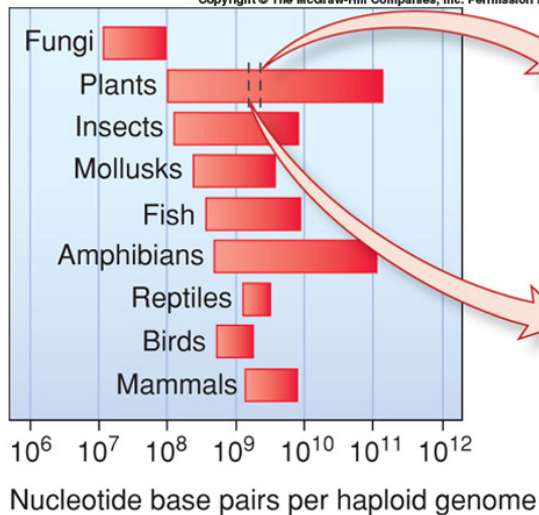


## Features of Genome

- Genome size is not the same as the number of genes
- Relative size of nuclear genome varies dramatically
- In general, increases in the amount of DNA are correlated with increasing cell size, cell complexity and body complexity
- However, major variations are observed between organisms with similar form and function



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(b) *Echinops bannaticus*





(c) *Echinops nanus*



(a) Genome size

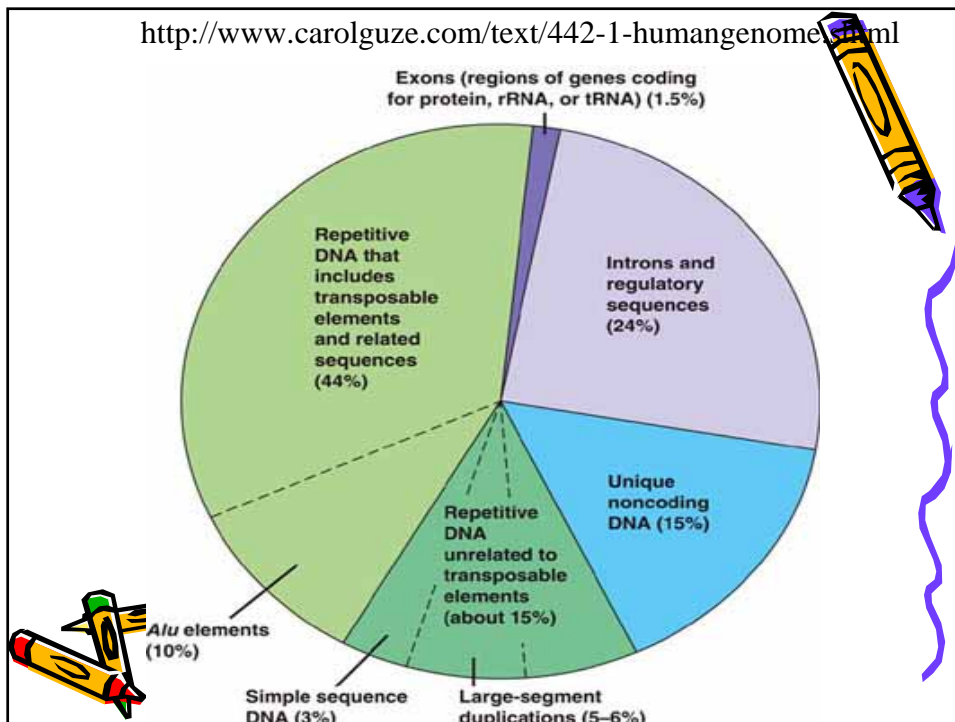
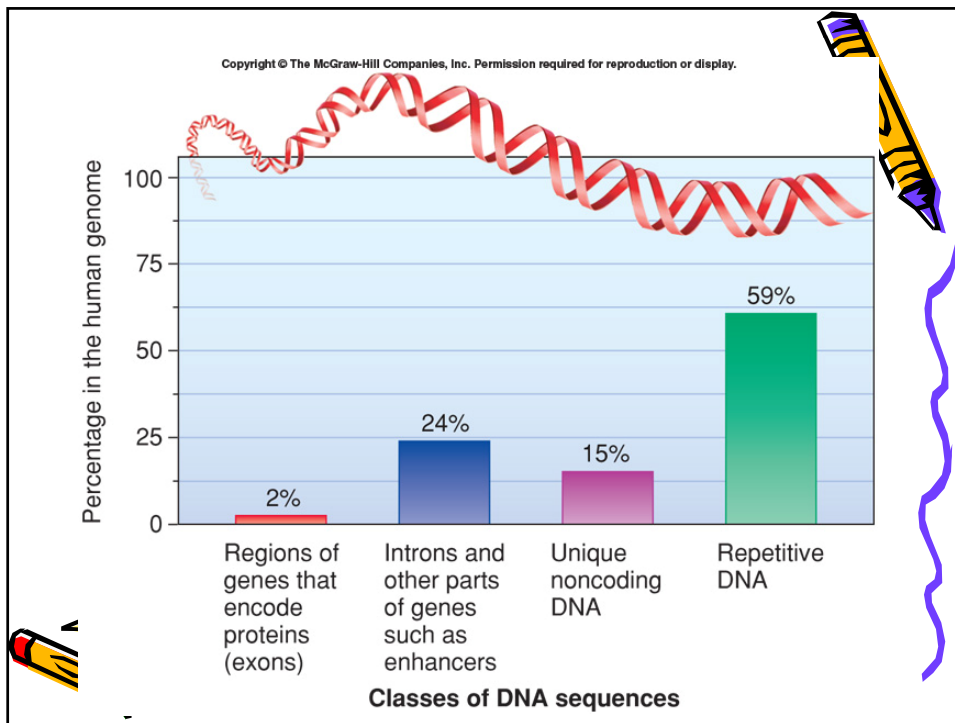
b: The Picture Store/Science Photo Library; c: Michael Beckmann, Institute of Geobotany and Botanical Garden, Halle, Germany

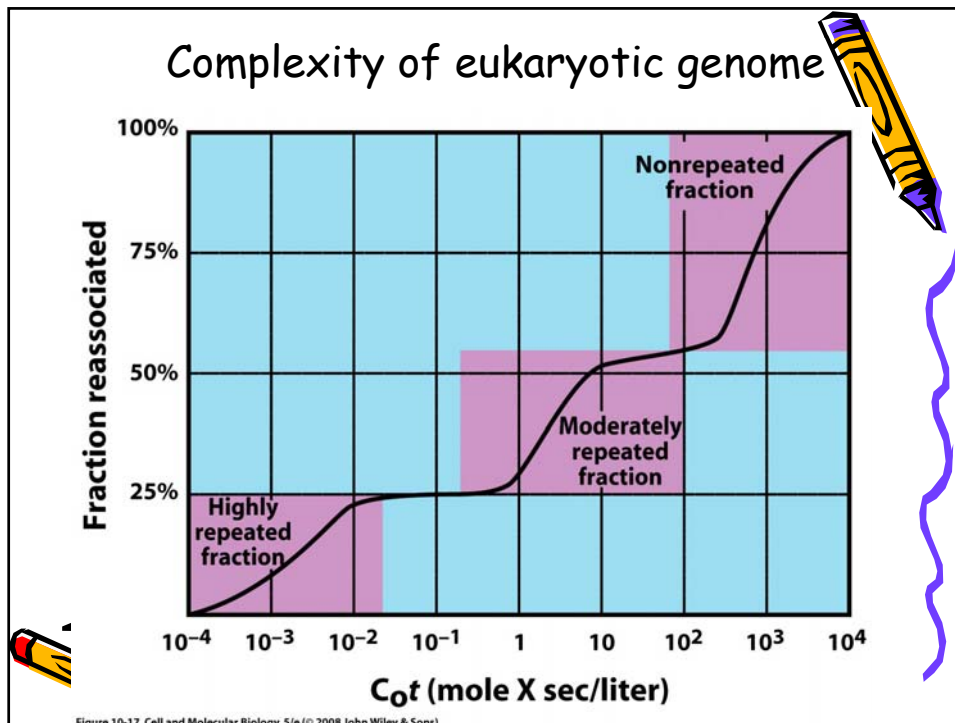


- 
- Eukaryotic genomes have repetitive sequences
    - Many copies of short DNA sequences
  - Moderately repetitive sequences
    - Few hundred to several thousand times
    - rRNA genes, multiple origins of replication, or role in gene transcription and translation
  - Highly repetitive sequences
    - Tens of thousands or millions of times
    - Most have no known function
  - Coding regions are only 2% of our genome
- 

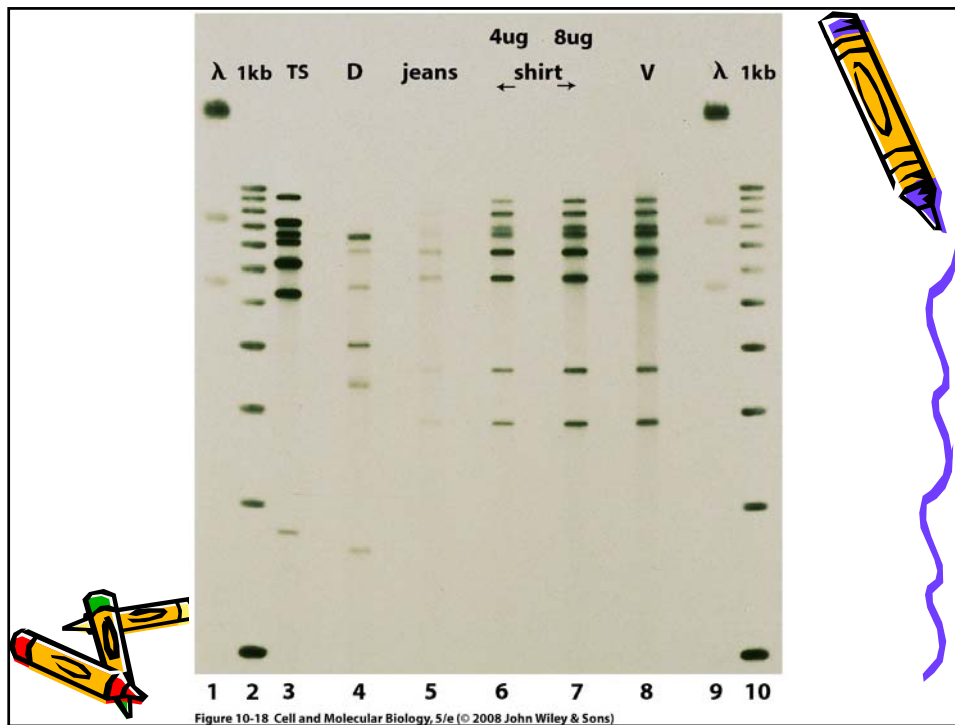
### % of genome

- 
- 98% noncoding
    - Intron DNA – 24%
    - Unique noncoding DNA – 15%
    - Repetitive DNA – 59%
      - Much derived from transposable elements
  - 2% coding regions of genes
- 





- ### Highly Repeated DNA Sequences
- A. Satellite DNAs
  - B. Minisatellite DNAs
    - Length of a particular minisatellite locus is highly variable (**polymorphic**)
  - C. Microsatellite DNAs



## "Jumping Genes" and the Dynamic Nature of the Genome

- Repeated sequences
- Members of a gene family
- Barbara McClintock (Cold Spring Harbor geneticist, late 1940s; Nobel - 1983)

# 玉米田裡的先知：異類遺傳學家麥克林托克

## A Feeling for the Organism

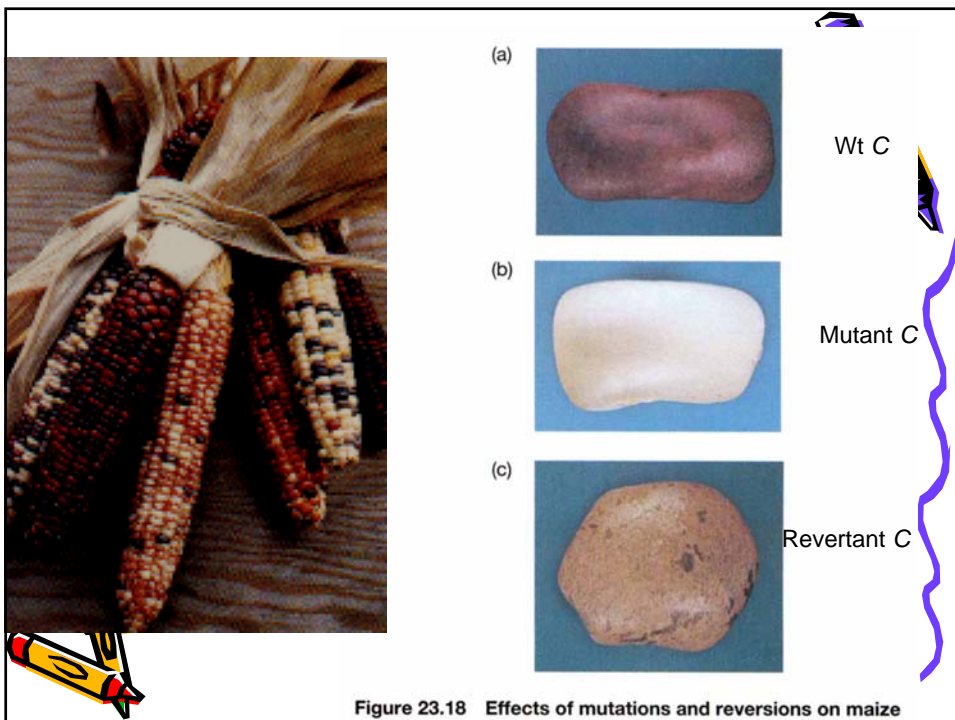


Figure 23.18 Effects of mutations and reversions on maize

## Barbara McClintock

- 1. Found that some mutations were very unstable.
- 2. Concluded that certain genetic elements had moved from one place to an entirely different site, affecting gene expression.
- 3. Called the genetic rearrangement **transposition** and the mobile genetic elements **transposable elements**.



## Transposable elements

- Transposition – short segment of DNA moves from original site to a new site
- Transposable elements (TEs) – DNA segments that move
  - “Jumping genes”
  - Found in all species examined
- First discovered by Barbara McClintock
  - 1983, awarded Nobel Prize



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(a)



(b)

a: © Topham/The Image Works; b: © Jerome Wexler/Visuals Unlimited

## Transposable elements of the Eukaryotic genomes

- 1. At least 45% of DNA in human cell nucleus
- 2. >99% of these transposable elements
- 3. Transposons insert almost randomly
- 4. Can insert themselves within a protein-coding gene
- 5. ~1 in 500 human disease-causing mutations



## The function of transposable elements

- “Junk” DNA with no function?
- Potential as a key element of evolution
- Transposition has had a profound impact on altering the genetic composition
- A good paper: *The Unseen Genome: Gems among the Junk* (Scientific American, Nov. 2003)



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FGGGATAGCCGACGAGCCAGTCTGCTCTAGACAGACGTAGCATATGGGATAGCCGACGAGCCAGTCTGCTCTAGACAGT

PLACES OF HIDE-OUTS: Even the rougher, wilder regions of the hidden genome of such. Certain bits are somewhat useful though, and many genes sit within through the rest of the genome. Some, however, are not. Some are responsible for parts like "junk" DNA. Other genes, however, are not. Some are often invisible and appear in some cells but not others. (The slide appears on the page in reflection of the light striking on the page.)

*Just when scientists thought they had DNA almost figured out, they are discovering in chromosomes two vast, but largely hidden, layers of information that affect inheritance, development and disease*

# The Unseen Genome:

## Gems among the Junk

BY W. WATT GIBBS

FGGGATAGCCGACGAGCCAGTCTGCTCTAGACAGACGTAGCATATGGGATAGCCGACGAGCCAGTCTGCTCTAGACAGT

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2 of 8

## Four Motivators of Genome Project

1. Great benefit from identifying and characterizing genes in model organisms
2. More information to identify and treat human diseases
3. Improved strains of agricultural species
4. Way to establish evolutionary relationships



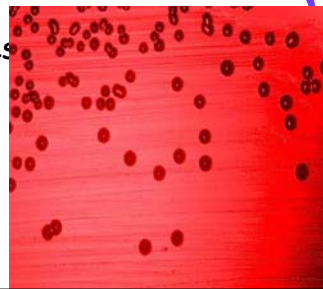
## Human Genome Project

- Officially began October 1, 1990
- Goals
  - Identify all human genes
  - Sequence entire human genome
  - Develop technology for information management
  - Analyze genomes of model organisms
  - Develop legal, ethical and social programs addressing the results



## The first complete sequence of a prokaryotic organism

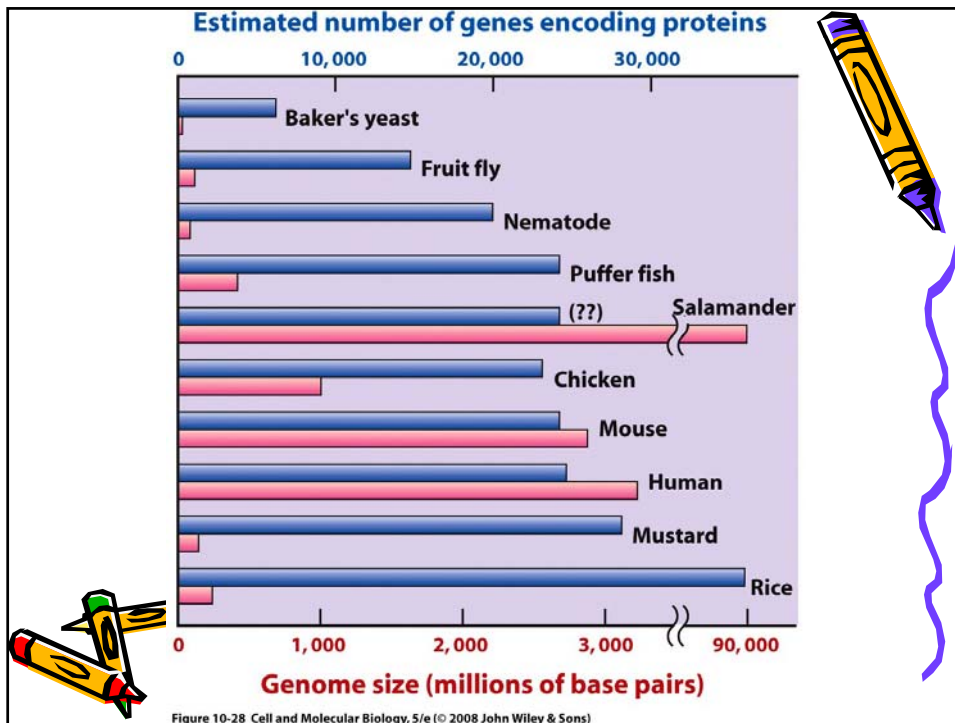
- Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. Science. 1995 Jul 28;269(5223)
- 1,830,140 bp
- Contains 1740 protein-coding genes
- 58 transfer RNA genes tRNA,
- and 18 other RNA genes



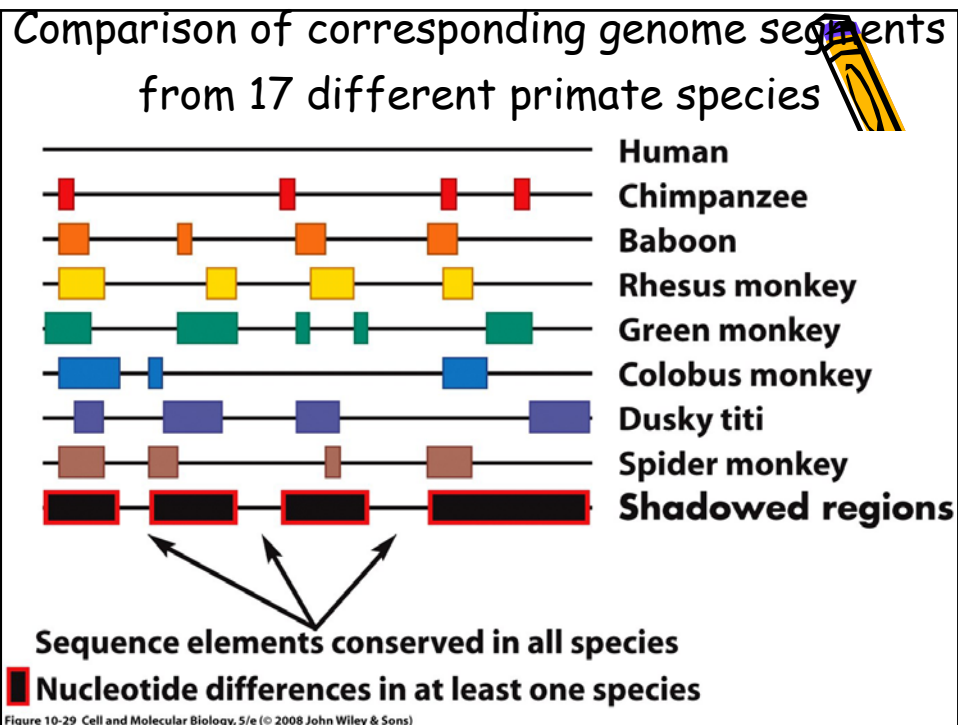
## The Human Genome Project (HGP)

- [http://www.ornl.gov/sci/techresources/Human\\_Genome/home.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml)
- All About The Human Genome Project (HGP) <http://www.genome.gov/10001772>
- <http://www.sanger.ac.uk/HGP/>





**Comparative Genomics:**  
 "If It's Conserved, It Must Be Important"



### What make the difference between human and chimpanzees?

- 2005 - ~4% difference
- Some of the fastest evolving genes encode transcription factors
- Many other difference
- *FOXP2* gene: 2 amino acid differences

Mutations in the *FOXP2* gene having a severe speech & language disorder

## Structural variation

- Change as a result of duplications, deletions, insertions, inversions, and othe

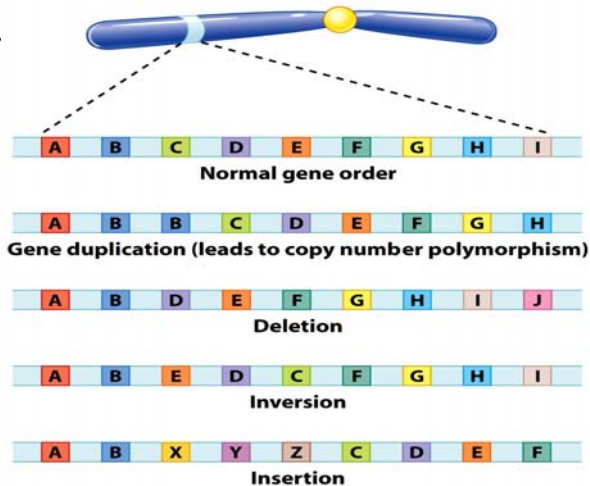
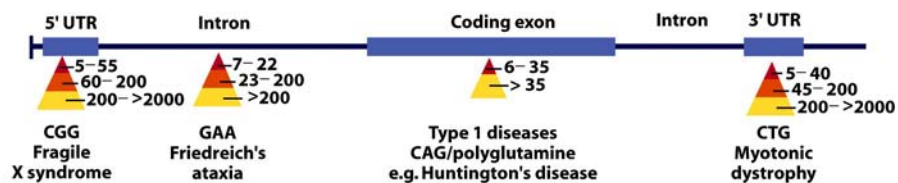


Figure 10-30a Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

## Trinucleotide repeat sequences and human disease



HP Figure 10a-1 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)