A BRIEF GUIDE TO GENETICS

The Early Days

- **Charles Darwin**

- "On the Origin of Species" - 1859

The Early Years

- **Gregor Mendel**

- German speaking scientist & Augustinian friar
- Worked with peas

The Early Years

Trait	Common or Dominant Form	Uncommon or Recessive Form
Seed colour	Yellow	Green
Seed shape	Round	Wrinkled
Seed coat colour	Grey	White
Pod colour	Green	Yellow
Pod shape	Inflated	Constricted
Plant height	Tall	Short
Flower position	Along stem	At tip of stem

The Early Years

- **Gregor Mendel**

- German speaking scientist & Augustinian friar
- Worked with peas
- Found seven characteristics of pea plants
- Noted Recessive & Dominant Traits

- Published a paper in 1866 stating that invisible factors (what we would now call genes) provide visible traits in predictable ways

The Inter-War Period

- The world was recovering from a devastating war and economic depression
- In 1937, Julian Huxley developed the Theory of Eugenics which had been first proposed in the 1800s
- Bright young men with a physics or chemistry background worked on military hardware projects
- Manhattan Project

The Inter-War Period

- **Erwin Schrodinger**

- Austrian Physicist

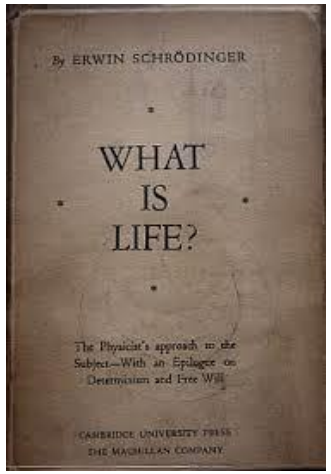
- Won the Nobel Prize for Physics in 1933
- Developed the thought theory known as Schrodinger's Cat in 1935
- Worked in Oxford during World War II
- Turned his thinking to biology:
  - What makes us human?
  - How is information transmitted from one generation to another?
  - Is there a **code**?

The Inter-War Period

- **Erwin Schrodinger**

- Austrian Physicist

- In 1944 published



- The ideas in this book formed the heart of the “new biology” to come

DNA

DNA or deoxyribonucleic acid

was becoming known as the “stupid molecule”

because it was apparent everywhere

but didn’t seem to be doing anything!

DNA

DNA was shown to comprise nucleotides

- Four bases
  - Adenine - A
  - Thymine - T
  - Guanine - G
  - Cytosine - C
- Ribose
- A phosphate group
- A=T and G=C

- Adenine & Guanine are classified as Purines
- Thymine & Cytosine are classified as Pyrimidines

DNA

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In 1944, DNA from two different strains of pneumococcus were mixed together, and the new strain's DNA proved the existence of Schrodinger's **code**

So what's RNA?

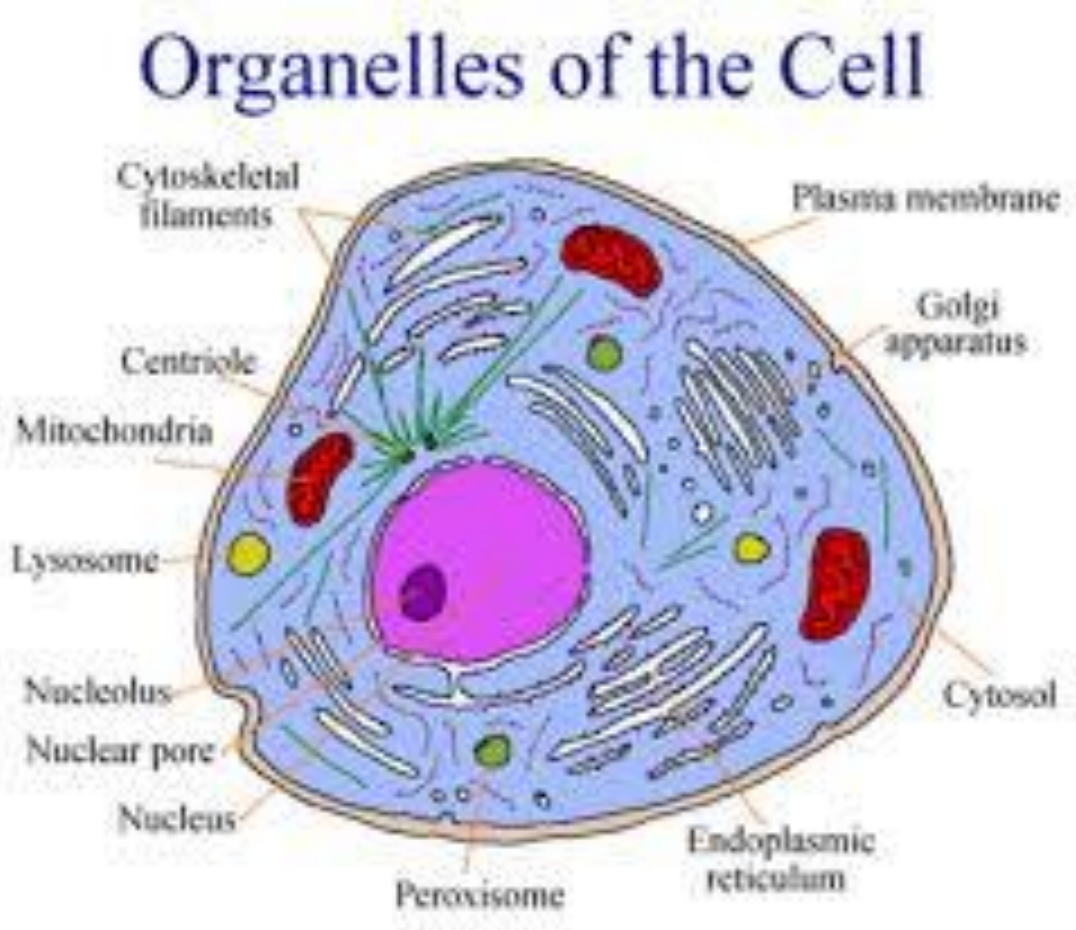
- RNA is ribonucleic acid
- RNA is similar to DNA but with structural difference; it is single stranded
- Uracil is the pyrimidine instead of Thymine
- Uracil pairs with Adenine (U+A)
- More unstable than DNA

So what's RNA?

There are three types of RNA

- mRNA or "messenger" RNA which carries out the action of genes
- tRNA or "transfer" RNA which carries amino acids around during "translaton"
- rRNA or "ribosomal" RNA which is present in the ribosomes and is essential for protein synthesis in all living organisms

Cell structure

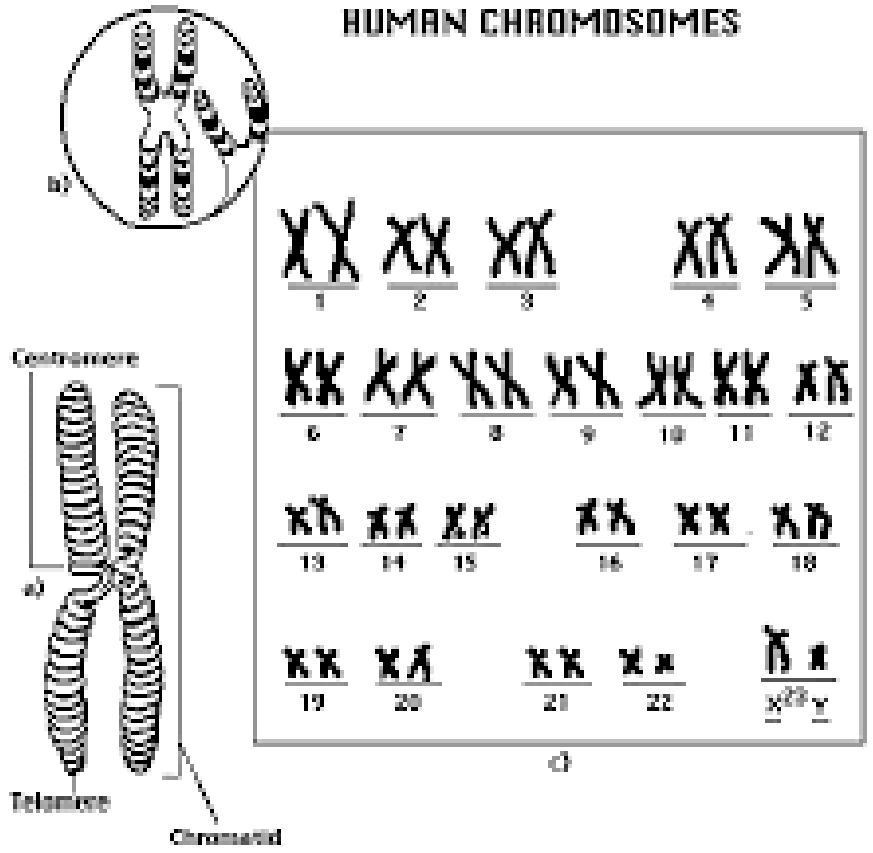


Cell structure

- **Nucleus** : Contains chromosomes
- **Chromosomes**
  - Composed of chromatin & histone proteins
  - Strands of DNA that carries genes & other information
  - 46 chromosomes in humans
  - 22 pairs of autosomes (matching pairs)
  - 2 sex chromosomes (X & Y)

The human chromosomes

- 46 chromosomes arranged in 22 matching pairs and the X/Y



How do cells divide?

Basically two forms of cell division

- Mitosis
- Meiosis

Mitosis

- Essentially asexual reproduction
- Normal process of cell division
- Cell copies its genetic material & divides
- Daughter cells carry same genetic material as parent cells save for random mutations

1940s & 50s

- **Maurice Wilkins**

- During the war, he worked on isotope separation for the Manhattan Project
- King's College, London in 1946
- X-ray crystallography
- "A" form of DNA
- Only managed to produce "fuzzy" images of a cross-shaped pattern indicating a helical structure

1940s & 50s

- **Maurice Wilkins**

- Had some degree of collaboration with **Crick** & **Watson**
- Recruited **Rosalind Franklin** to join him in 1951

- Rosalind finally got a clear “B” form
- Died of ovarian cancer in 1958

1940s & 50s

- **Francis Crick**

- Physicist
- Worked with Admiralty Research Laboratories during the war
- Mine design
- Fascinated by living/non-living differences
- Decided to work in molecular biology
- Moved to the Cavendish Laboratory in Cambridge

1940s & 50s

- **James Watson**

- Brilliant American who had a PhD in Biochemistry by the age of 22
- Post-doc work in Copenhagen
- Moved to the Cavendish Laboratory in Cambridge where he met **Crick**

1950s

- **London**

- **Cambridge**

1950s

London

- Wilkins didn't collaborate with Franklin
- Wilkins always dismissed Crick & Watson because they didn't really do anything
- Franklin worked with Ray Gosling and eventually developed the "B", helical X-ray crystallography photograph

Cambridge

- Crick & Watson were regarded as very bright, very intellectual scientific butterflies!
- They did have an intellectual common ground
- They tried to imagine what DNA would look like, build models and critique them
- They talked a lot but also listened

1950s

Lots of pieces of information

but

no real understanding of how everything worked

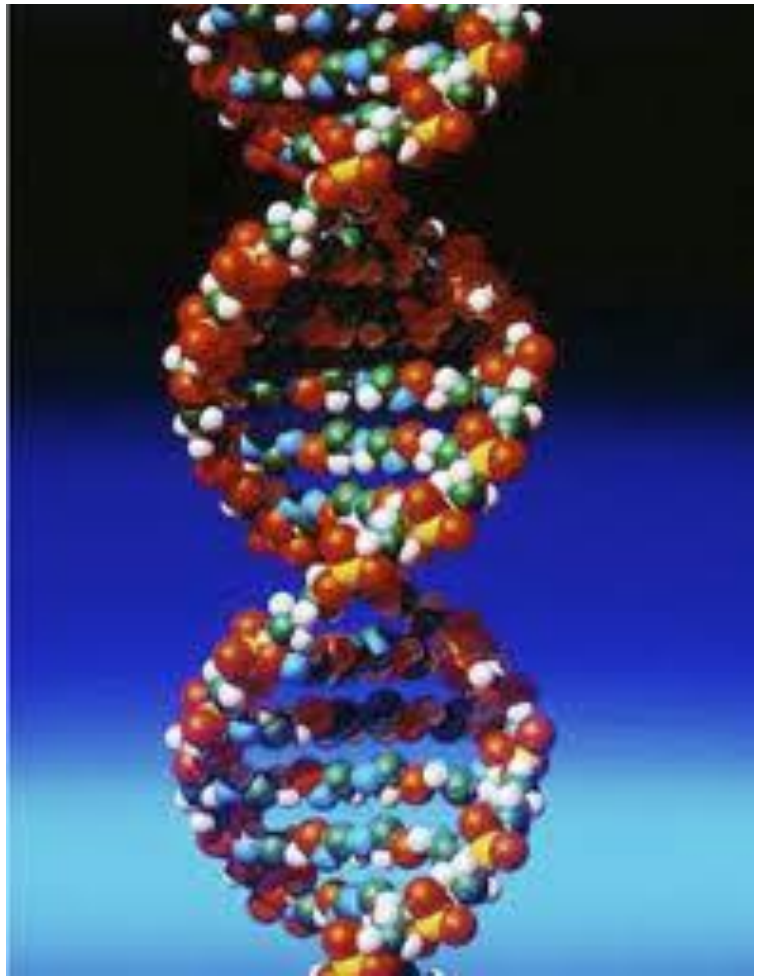
1950s

- Crick & Watson heard that **John Griffiths** thought that the DNA bases might stack
- They heard that **Linus Pauling** in USA was also working on the structure of DNA
- Watson had seen Franklin's "B" form pictures and deduced that DNA must have a helical structure
- They debated whether the phosphates of the bases were on the inner or outer edge of the helix
- Tried with the phosphate on the outside and the rest was history!

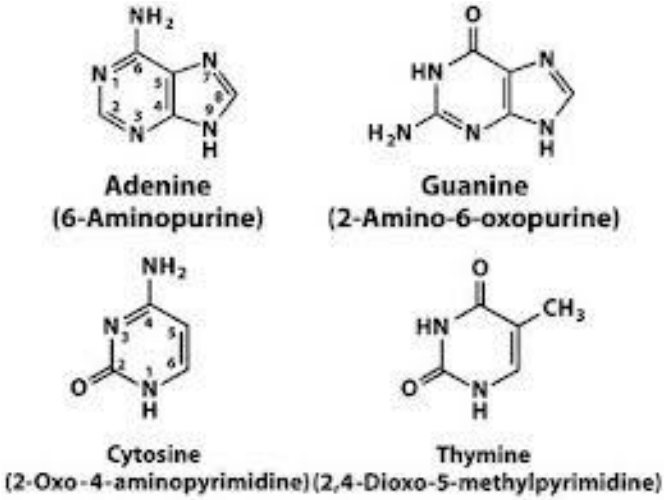
The Eureka Moment

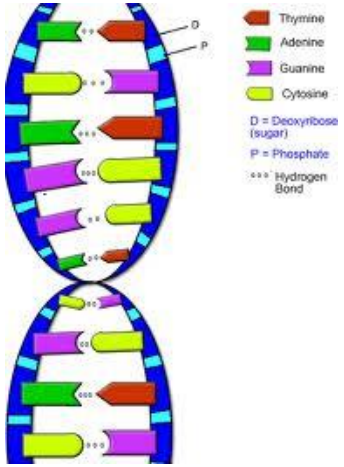
- It took them only four days to produce the model
- They understood how the two strands could separate and be replicated
- They published a rather “understated” paper in Nature, on 25th April 1953
- This was a critical moment in biology for which they were awarded the Nobel prize, together with Wilkins, in 1962

The familiar helix!



Back to DNA



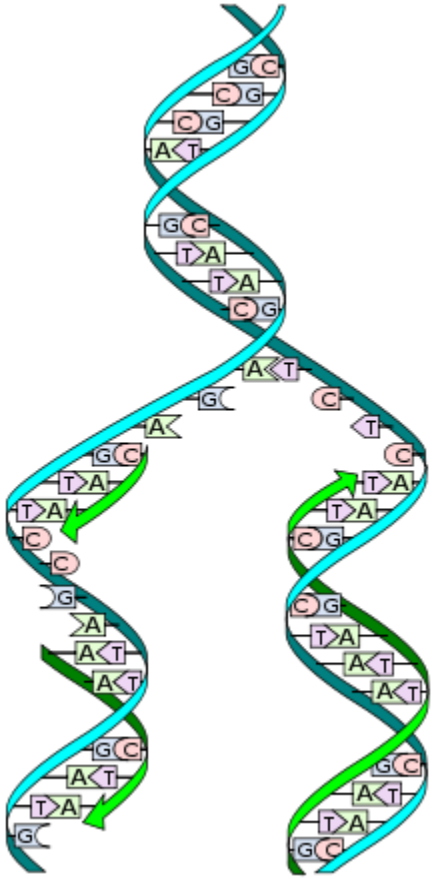


- DNA is deoxyribonucleic acid
- Bases
  - Purines : Adenine & Guanine
  - Pyrimidines : Thymine & Cytosine
- Base pair
  - A pair of complimentary bases or nucleotides
  - Always paired A & T, or C & G
- “Backbone” of helix is sugar & phosphate

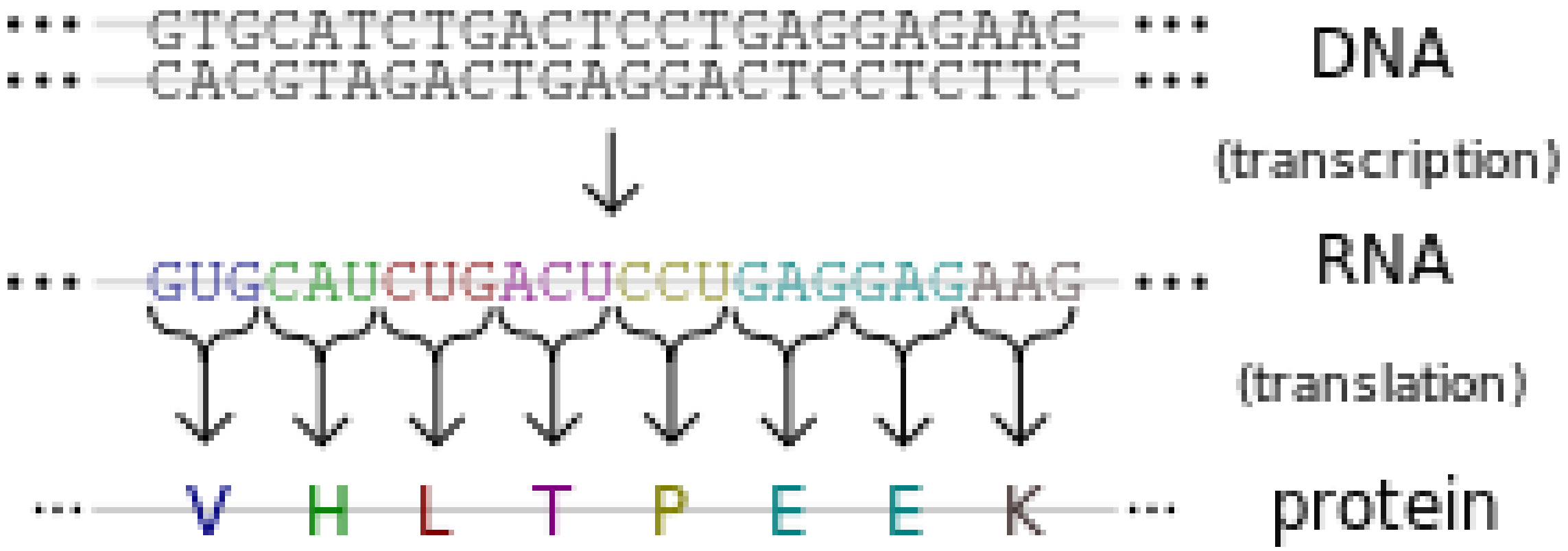
DNA replication

The double helix can split and make a new strand which is an exact copy

This process is known as replication



Transcription & Translation



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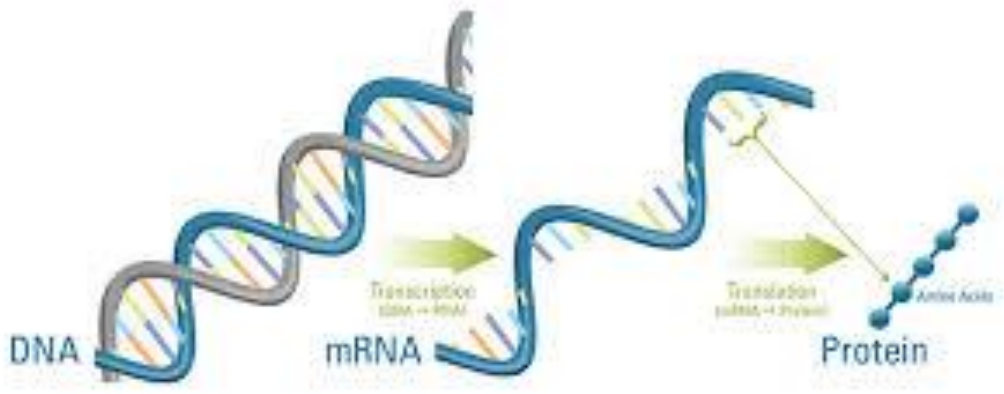


The genetic code (DNA transcribed as mRNA) provides instructions to make these proteins

Transcription & Translation

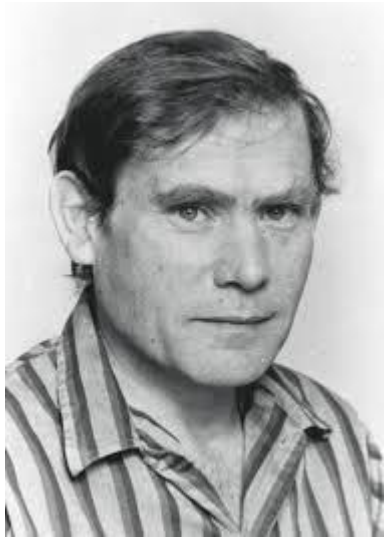
- Remember the three types of RNA?
- mRNA carries out the action of genes, ie transcription
- tRNA carries amino acids around during translation
- rRNA in the ribosomes is essential for protein synthesis

Not quite there yet

- How does DNA become tissue?
- How can only four bases contain enough information to encode complex phenotypes (bone structure, eye colour)?

Not quite there yet

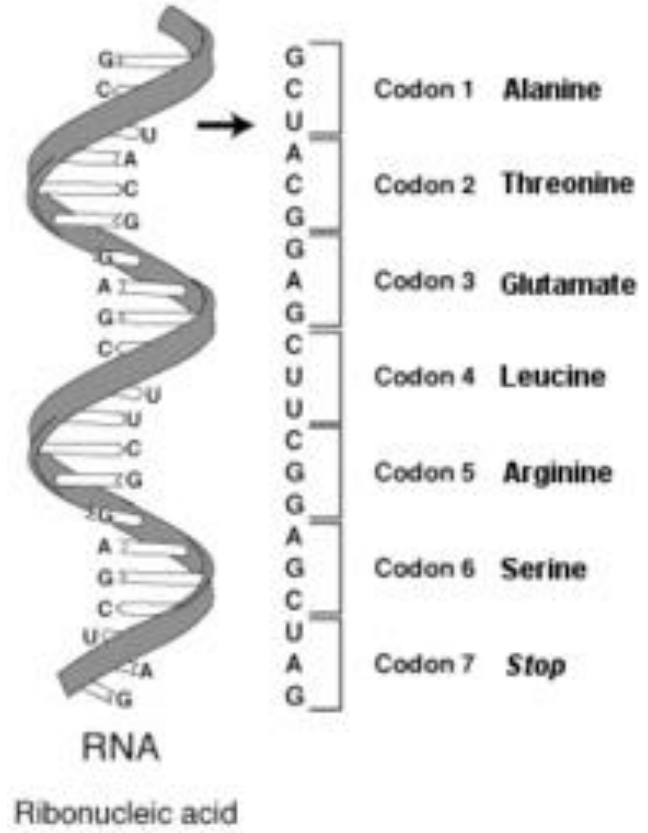
- A South African called **Sydney Brenner** came to UK to do his PhD



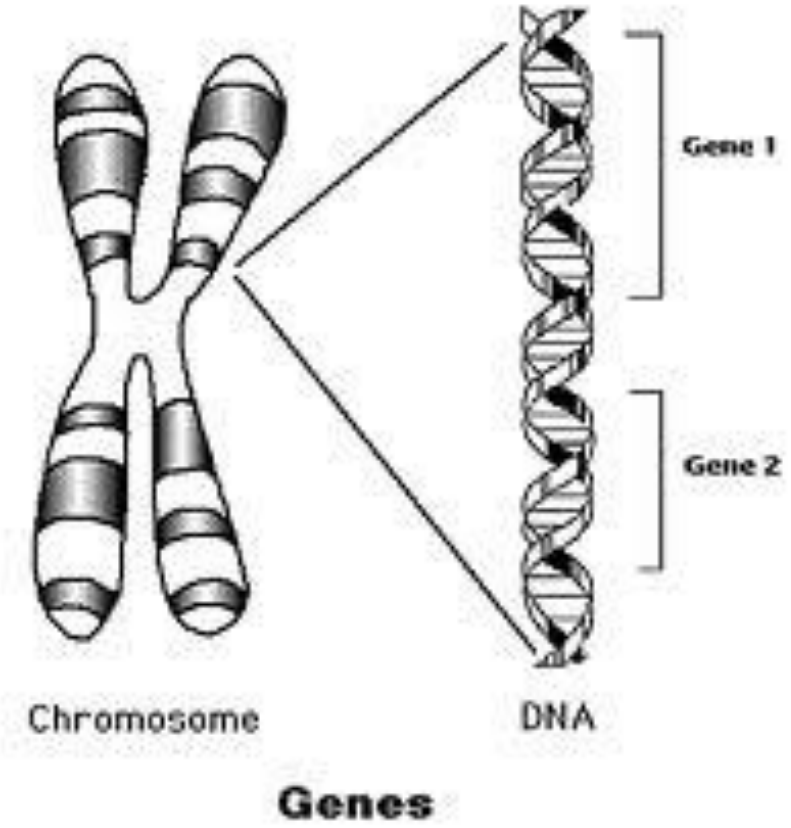
  - Brenner was a highly creative man
  - He started to work collaboratively with **Crick** on what became known as “the coding problem”
  - Together they determined that as DNA had four bases and protein was made up of 20 amino acids, then DNA must be triplet in nature
  - They called this triplet a **codon** and each codon corresponds to an amino acid

A codon

- A **codon** is the combination of three nucleotides in an mRNA that corresponds to an amino acid



So where do genes fit in?



- A gene is the fundamental unit of heredity
- It is a specific section of DNA within a chromosome

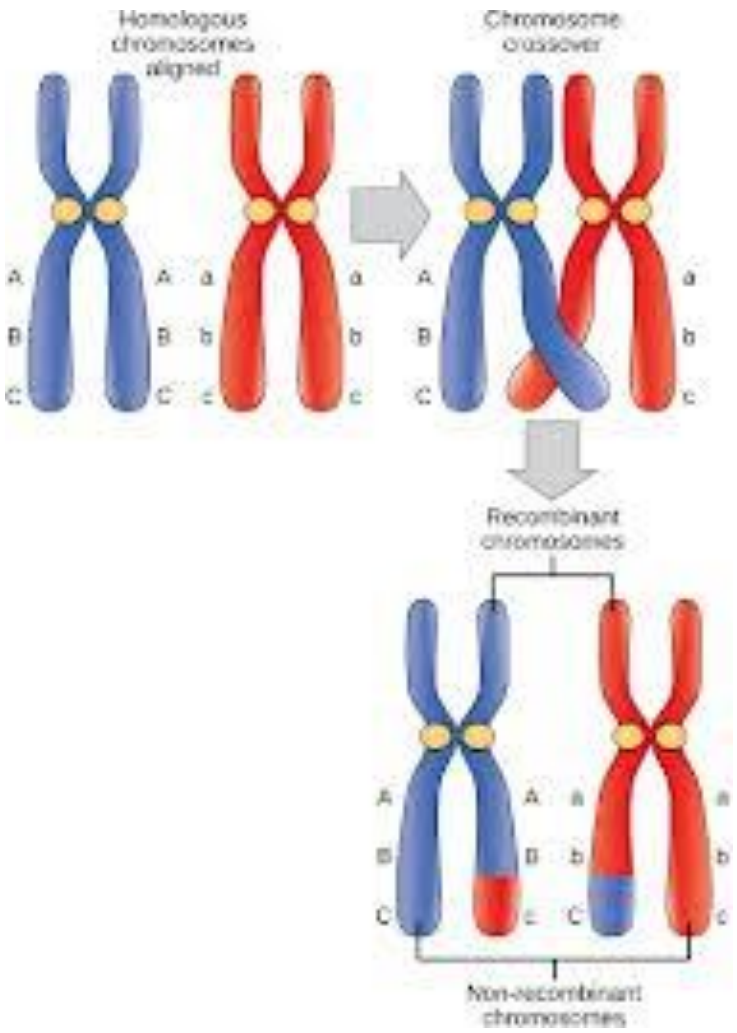
Remember there are two ways that cells divide?

Mitosis or Meiosis

Meiosis

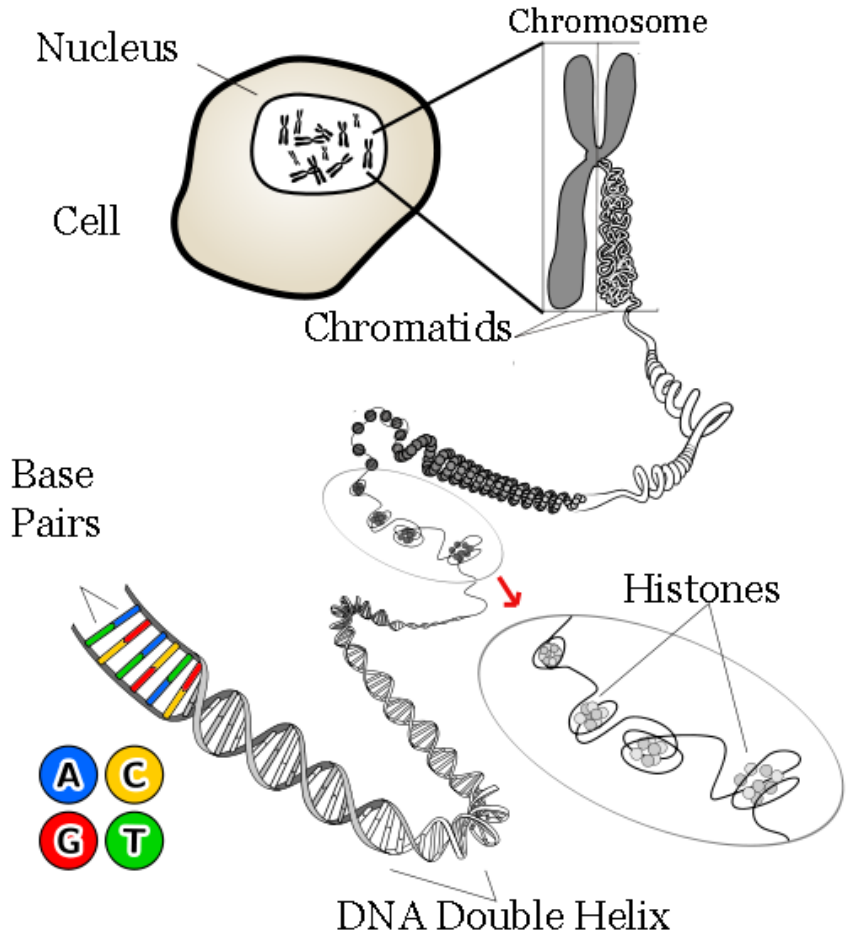
- Sexual reproduction
- Cell division by which germ cells create gametes (haploids)
- Cells have only one set of chromosomes
- Recombination occurs during meiosis

Meiosis – the recombination phase



- Chromosomes inherited from mother & father line up during meiosis
- Chromosomes cross over
- Chromosomes exchange segments of DNA to produce new configuration

How does all this fit into a cell?



The next big leap forward

- **John Sulston**

- **Sydney Brenner** persuaded Sulston to come to Cambridge
- Sulston was another “character”
- Worked on the worm c.elegans
- Counted all the codons in the DNA
- Therefore determined the worm’s **genome**
- Awarded the Nobel Prize in 2002

Lots of genes make up a genome

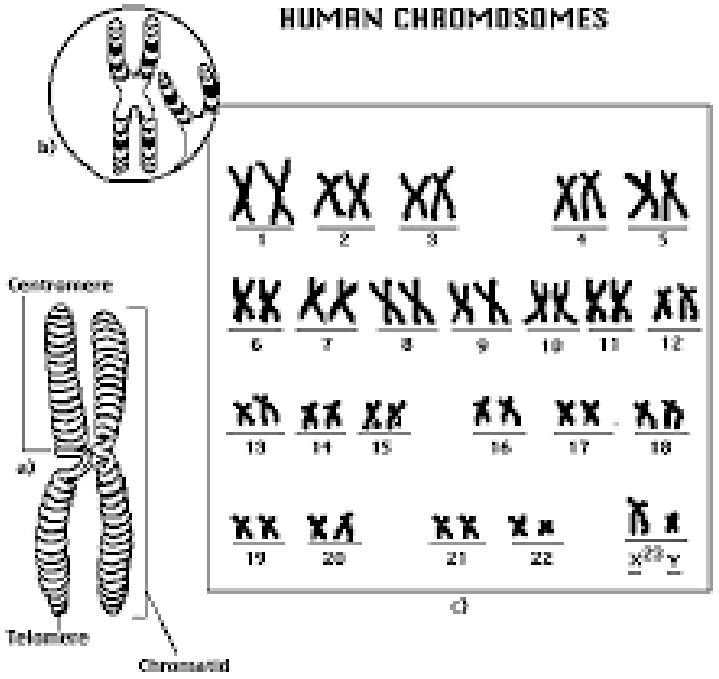
- A gene is specific section of DNA within a chromosome
- A genome is an organism’s full set of chromosomes
- To sequence a genome means determining the sequence of bases in all the DNA of a chromosome and then doing the same for all the chromosomes

The final race

- The race was now on to determine the human genome
- Big debate as to whether the genome could be patented
- All scientists in the field met and agreed the Bermuda Principles
- All data published and in the public domain, and no patents

The challenge ahead

Chromosomes



The sequence of the bases

The human genome

- **Craig Venter**

- American team leader
- Owned a large company called Celera
- Venter saw the commercial potential of the human genome
- Very different attitude from John Sulston's UK team
- Everything became highly competitive

The human genome

- **Craig Venter**

- **John Sulston**

The human genome

- Eventually the politicians became involved

- Agreement in 2000 that there would be free access to all genetic data

The human genome

- **But** – the human genome consists of more than three billion base pairs!
- Just as the physicists and chemists gave new insights into the field of biology, so the application of computer techniques speeded up the sequencing of the genome
- Craig Venter's genome was published in 2007
- James Watson's genome was published in 2008

So how unique are we??

- 99% of human genes
  - are shared with chimpanzees

- 97.5% of human genes
  - are shared with mice

- 50% of human genes
  - are shared with bananas!!

Still much more to learn

- We know that the codes are read from beginning to end
- We know that certain codons start the sequence
- We know that certain codons end the sequence
- But less than 9.5% of human DNA is functional
- The rest is called “junk” DNA

Solving mysteries using DNA

- Generating DNA fingerprints
- Using DNA to match criminals to crimes
- Identifying persons using DNA from family members
  - Paternity testing
  - Aircraft disasters
  - Wartime mass burials

Genetic Makeovers
Fitting new genes into plants and animals

- Genetic modification of crops to feed the ever increasing world population
- Understanding any potential dangers or down-sides
- “Designer” babies
  - Eugenics by any other name
- Designing new antibiotics
- Designing drugs for people with genetic disorders

Recent press releases

- 8th December 2014
  - Pfizer bets on gene therapy as technology comes of age
- 10th December 2014
  - Genomics startup NextCode stakes claim in paediatric disease market
- 11th December 2014
  - Unchecked superbugs could kill 10 million a year, cost $100 trillion
- 22nd December 2014
  - Genomics England and the 100,000 genomes project
  - Three year project; cancer & rare diseases

Where is the ethical & moral conscience in our society?