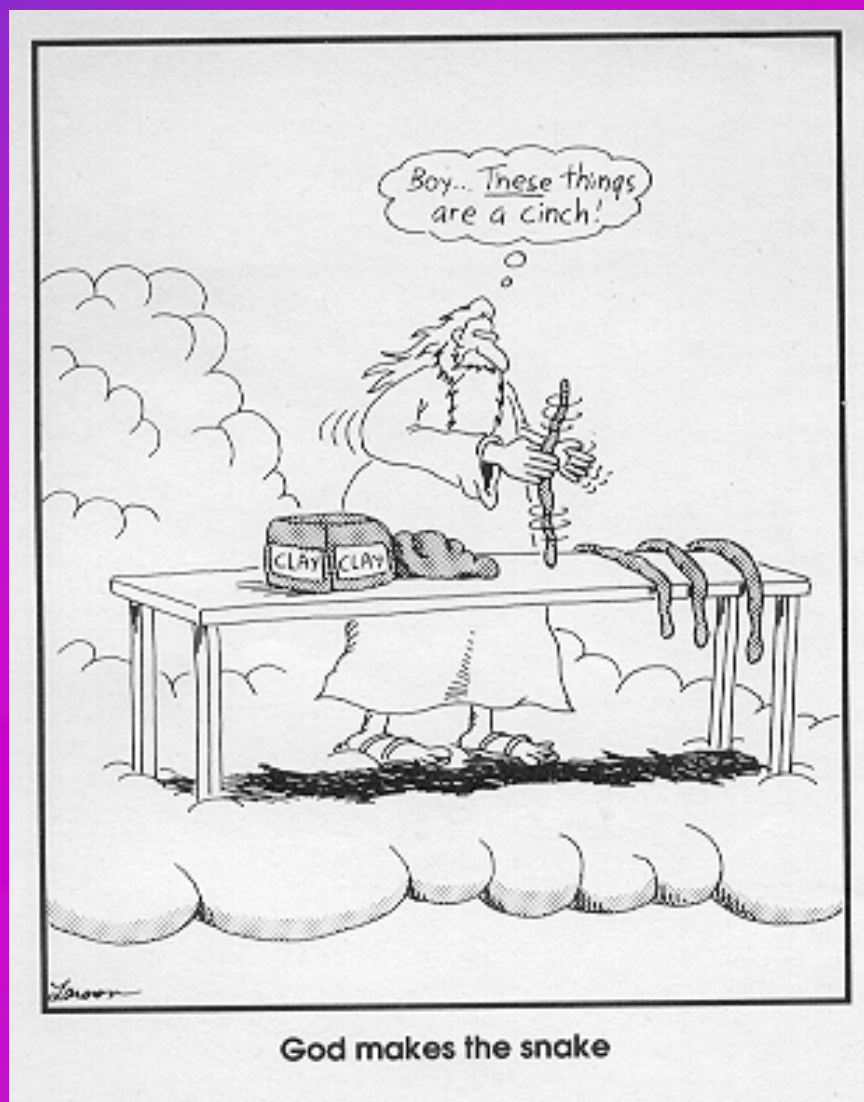


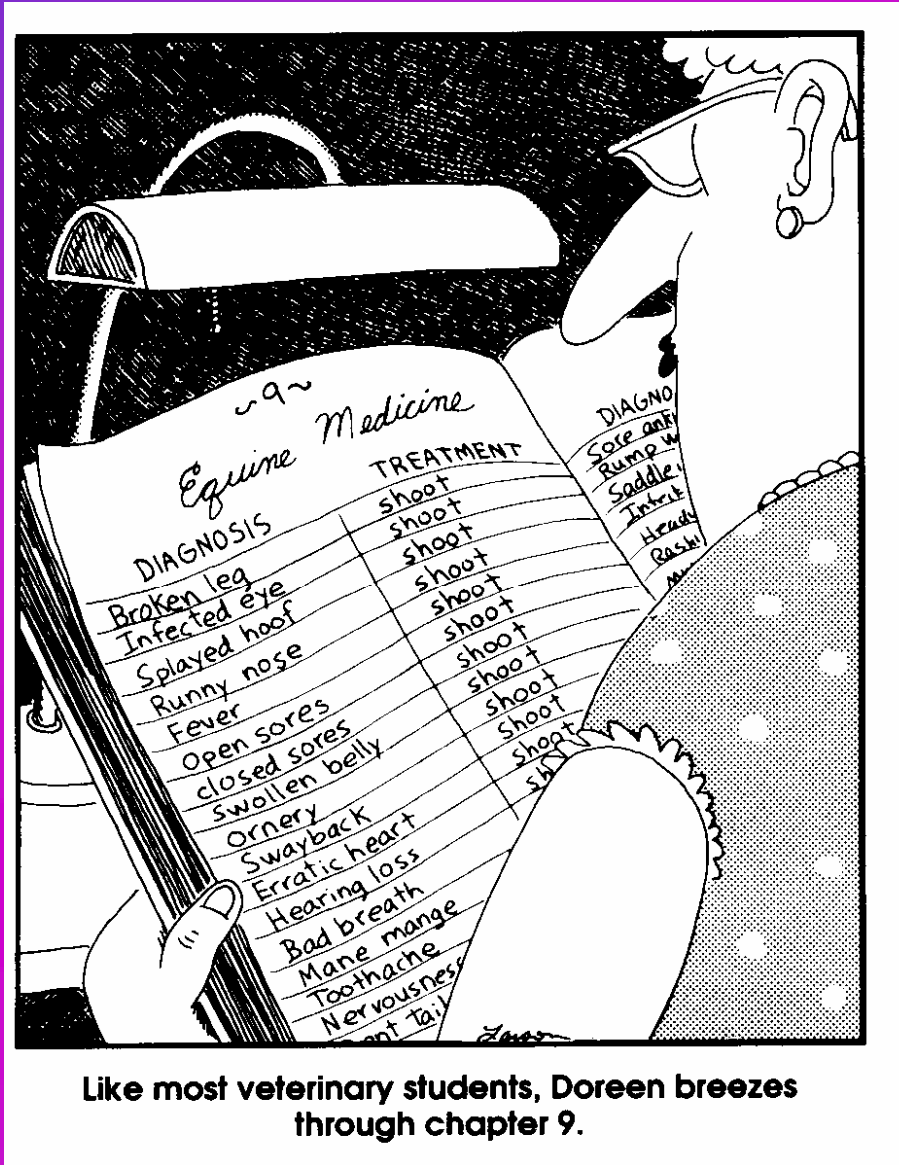
Contents

- **Introduction: biology and medicine, two separated compartments**
- **What we need to know:**
 - boring basics in DNA/RNA structure and overview of particular aspects of molecular biology techniques
 - How DNA is organized and differs in every individual
- **Restriction analysis in cardiovascular diseases**
 - Mutations in Factor V
 - Mutations in Factor II
 - Mutations in MTHFR gene
- **Breast cancer and BRCA1 and 2 genes**
 - Breast cancer in the industrialized countries
 - Breast cancer genes
 - sequence in selected areas
 - p53 and breast cancer
- **Pharmacogenomics: finding the right drug for a patient**
 - ADR: an emerging problem
 - structure of cytochromes
 - Example 1: TPMT-enzyme and the metabolism of azathioprimines
 - Example 2: Clozapine in the treatment of psychiatric diseases
 - CYP3A4 and the metabolism of anti-coagulant drugs

In the beginning...

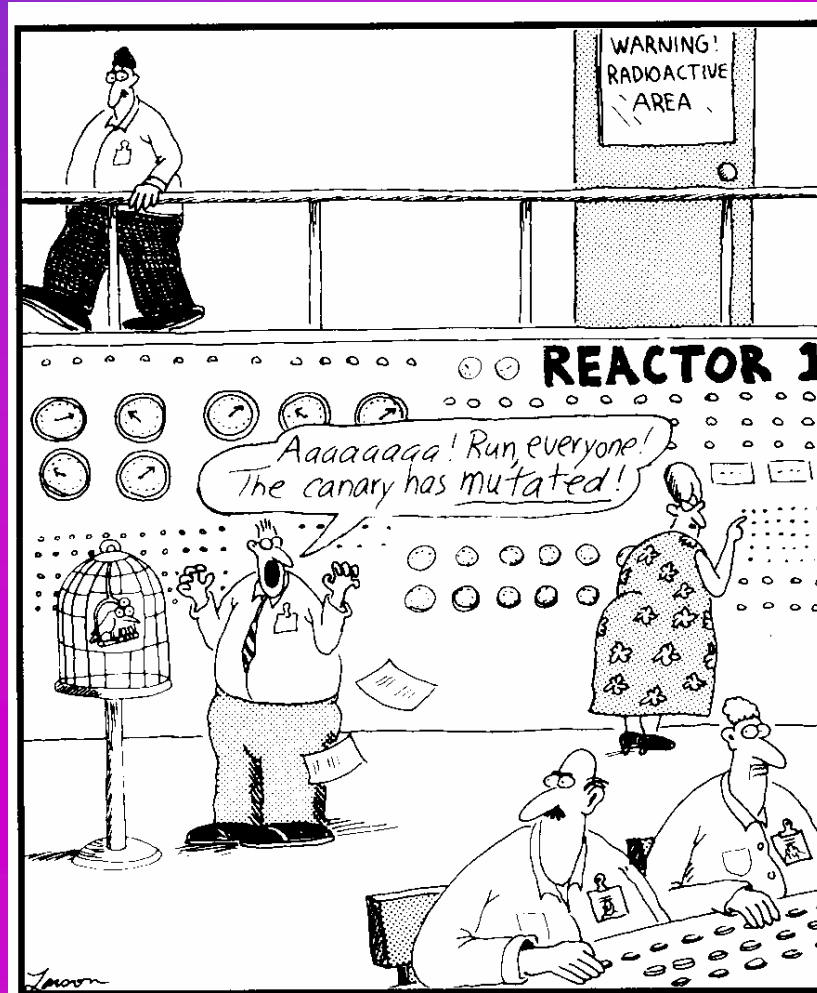


We will talk about diagnosis and



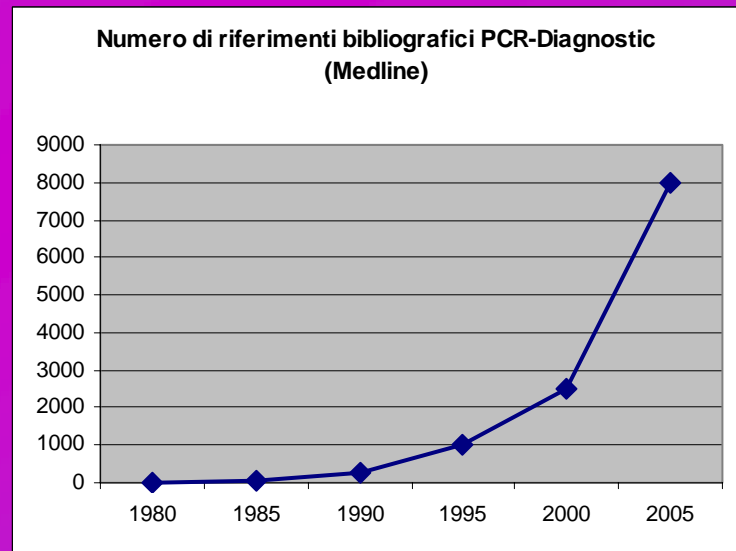
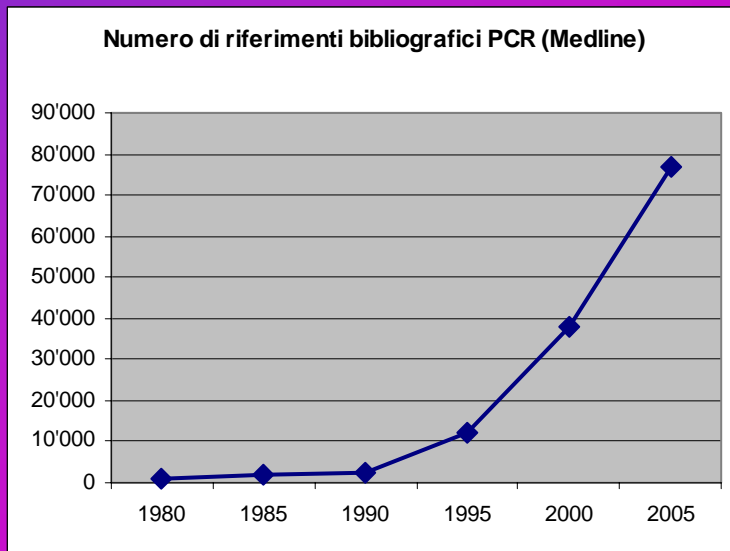
Like most veterinary students, Doreen breezes through chapter 9.

Applied research in molecular biology



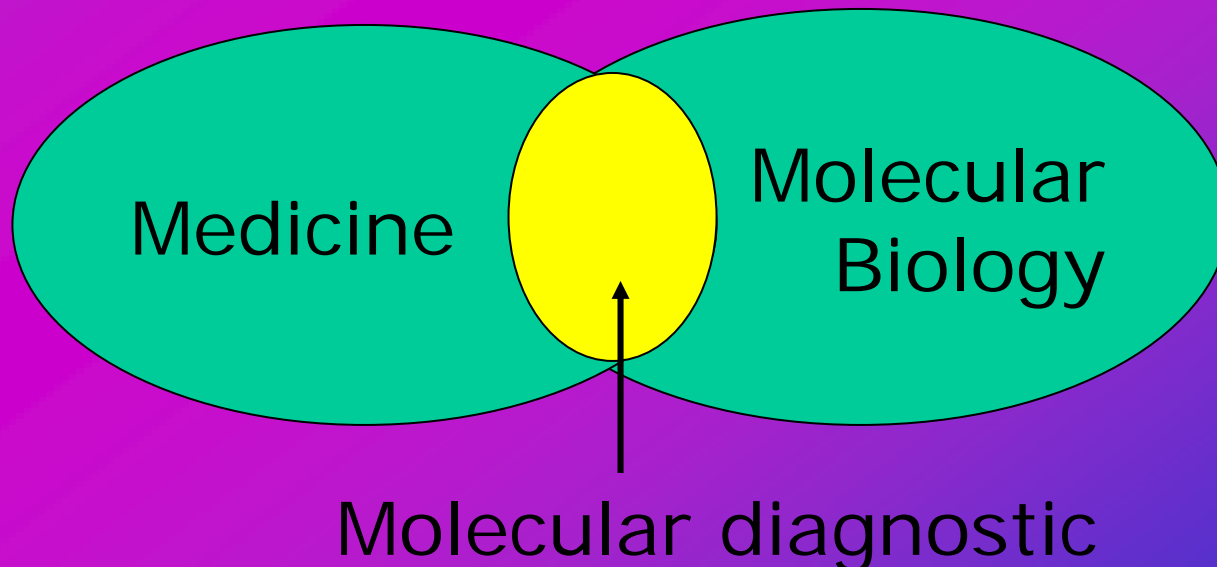
Inside a nuclear power plant

Diagnostic is following research (watch the scales)



But more important...

Try to establish a bridge between medicine and molecular biology, where the competence of both will benefit the patient.

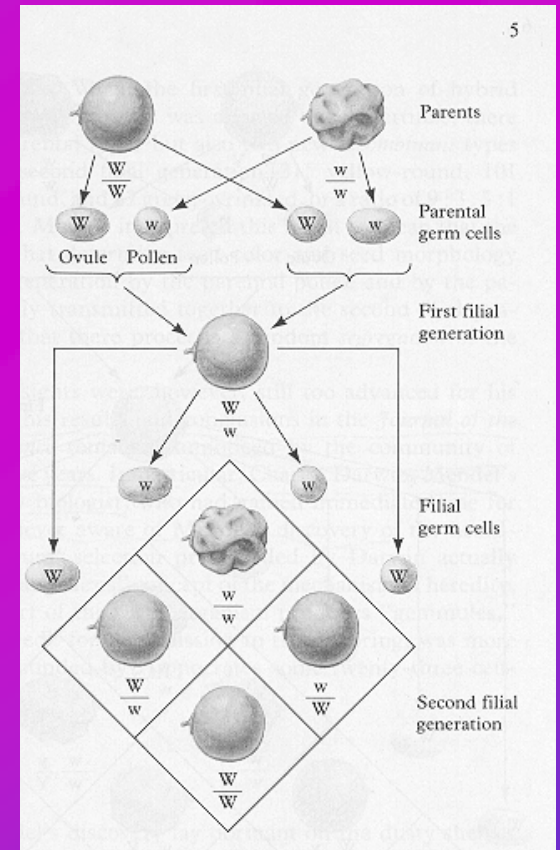
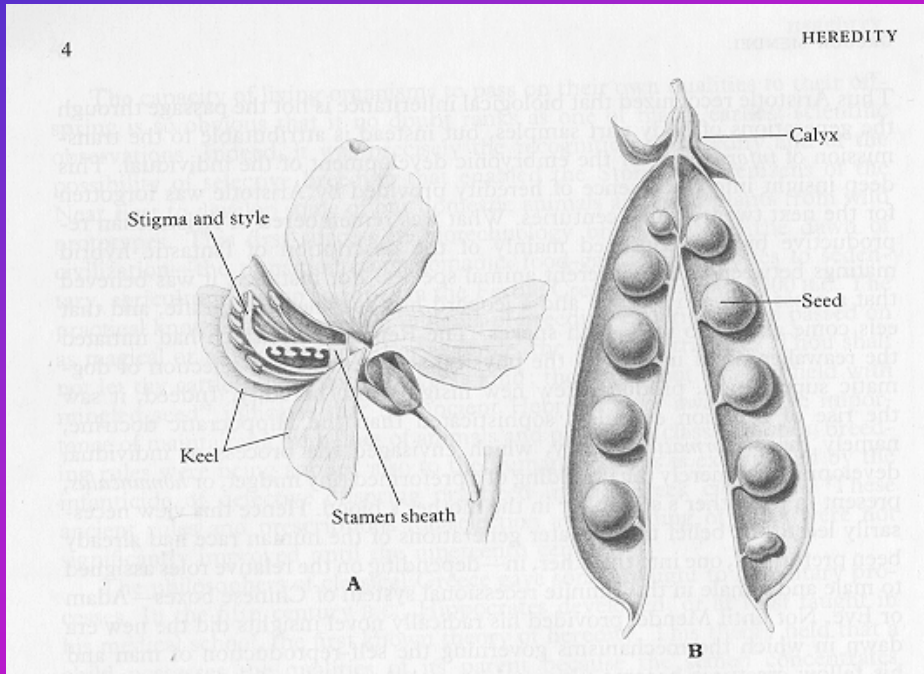


Mendel: the father of genetics

For his "Experiments on plant hybrids" Mendel cultivated the common garden peas in a way as to exactly control their descent.



Crossing the peas forever

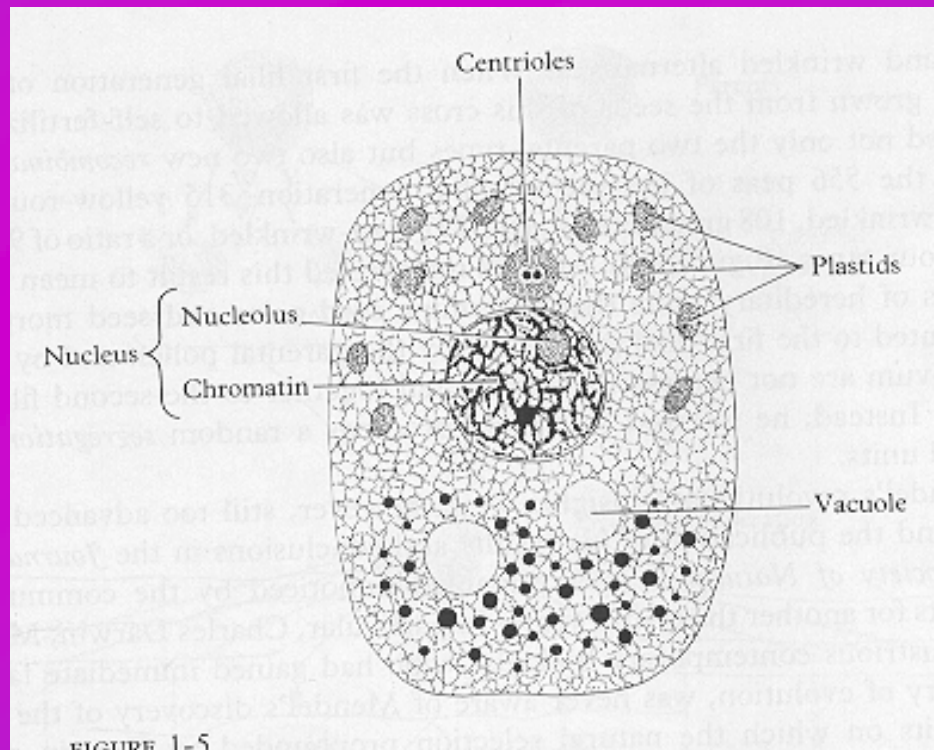


1. By cross-fertilizing round-shaped with wrinkled seed he obtained all round seeds at the F1
2. By self-fertilizing these resulting seeds he found that the second generation seeds were of two type: round and wrinkled having a ratio of ca. 3:1.

A cell in the early 19th century

In 1850 Rudolf Virchow generalized the concept of cell saying that every cell is sprung from another cell

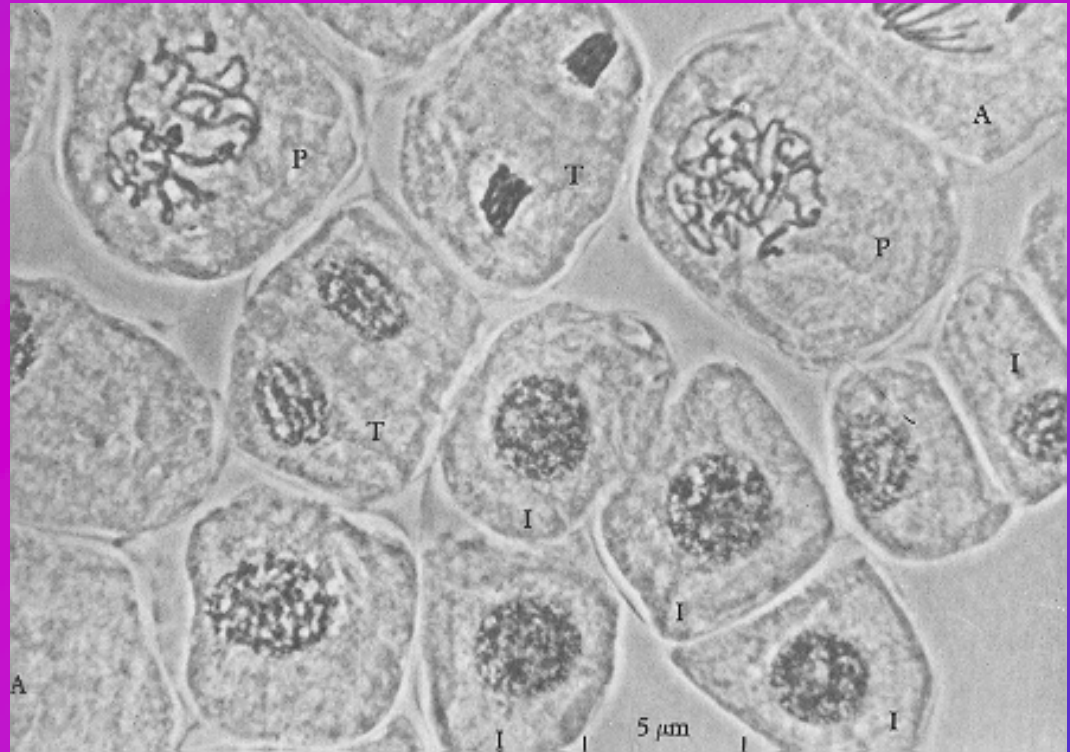
In 1884 by Mendel's death it was discovered that the chromatin of the nucleus is composed of thread-like particles, the chromosomes



Thread-like particles composing the nucleus

In 1880 Wilhelm Roux proposed that chromosomes constitute the hereditary material

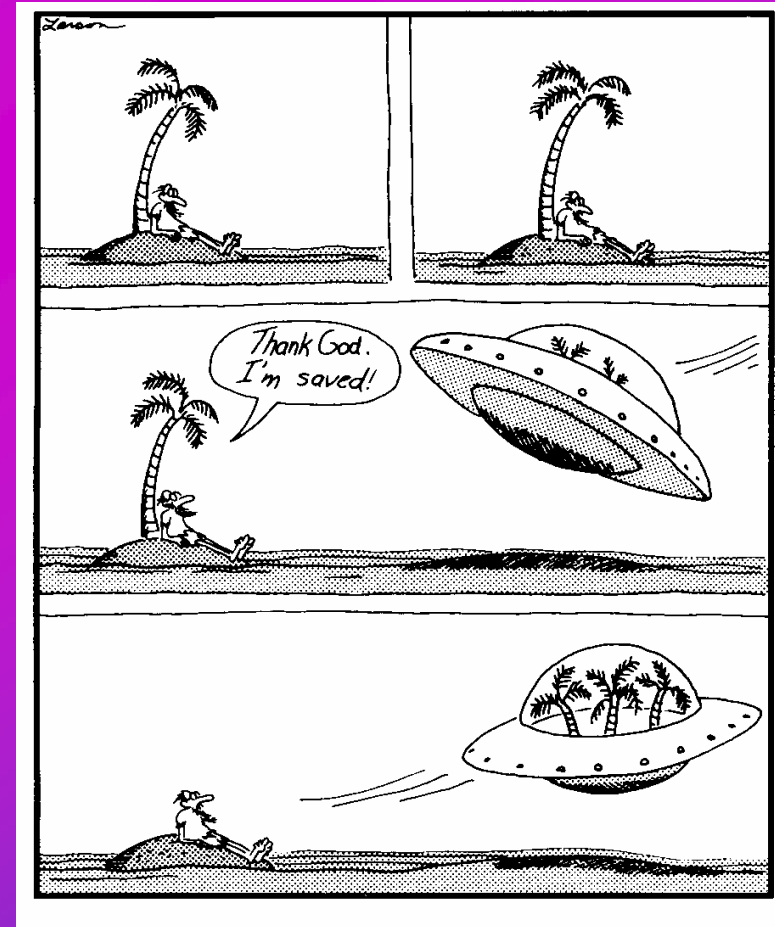
In 1900 Hugo de Vries rediscover the 3:1 distribution of recessive characters...and proposes that "different alleles of the same gene arise by mutation".



The results of De Vries caused enormous excitement and...

A new terminology was introduced.

The discipline was given the name **genetics** and Mendel's hereditary unit became the **gene** two homologous genes were called **alleles** and the sum of total of all an individual's genes became the **genome**

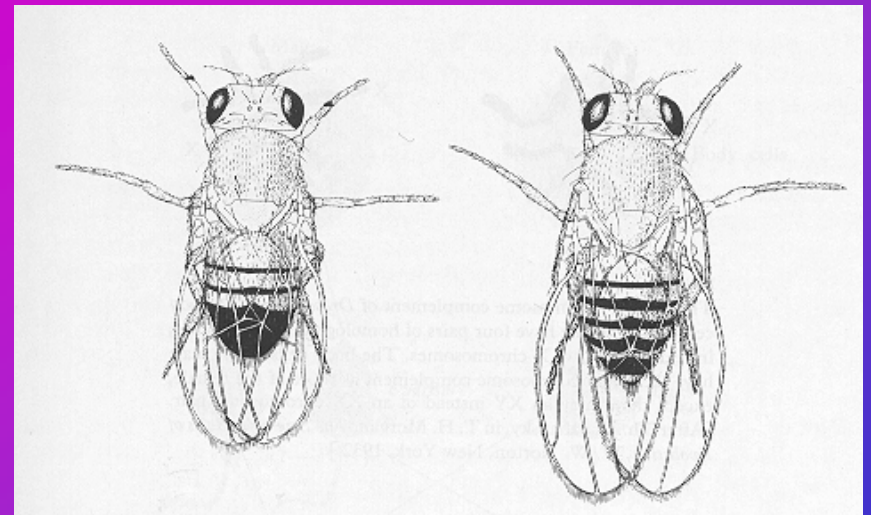
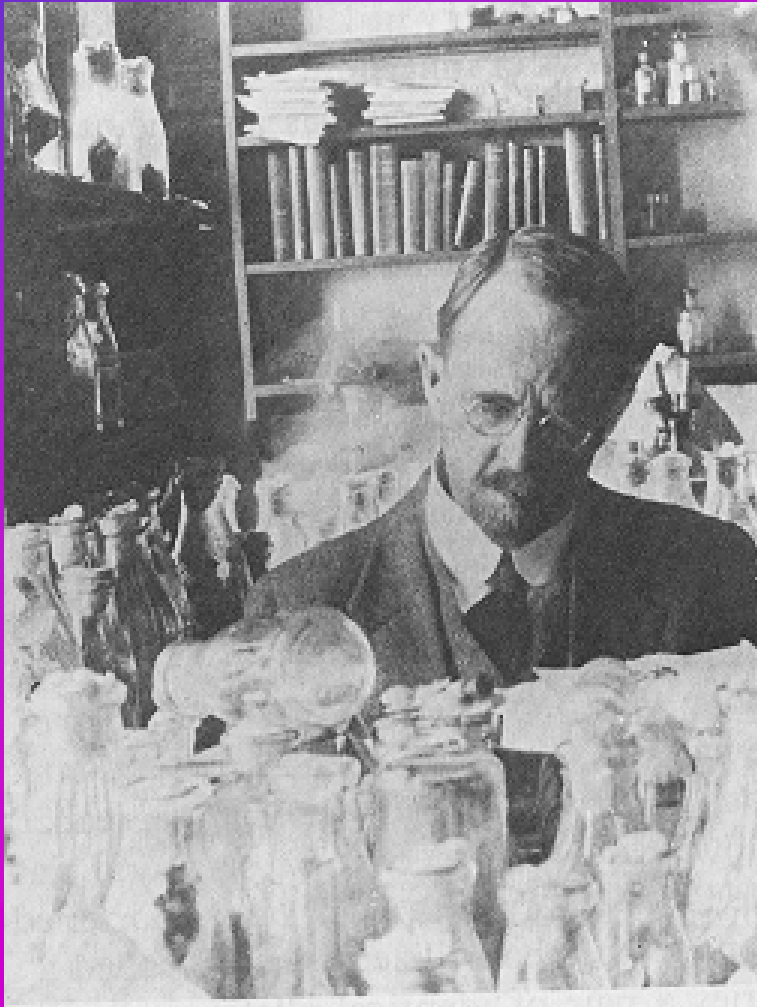


Mr. Morgan and the Drosophilas

1910, Thomas Morgan turn to the study of the genetics of the Drosophilas which are:

- small and simple to rear
- has a time generation of 2 weeks

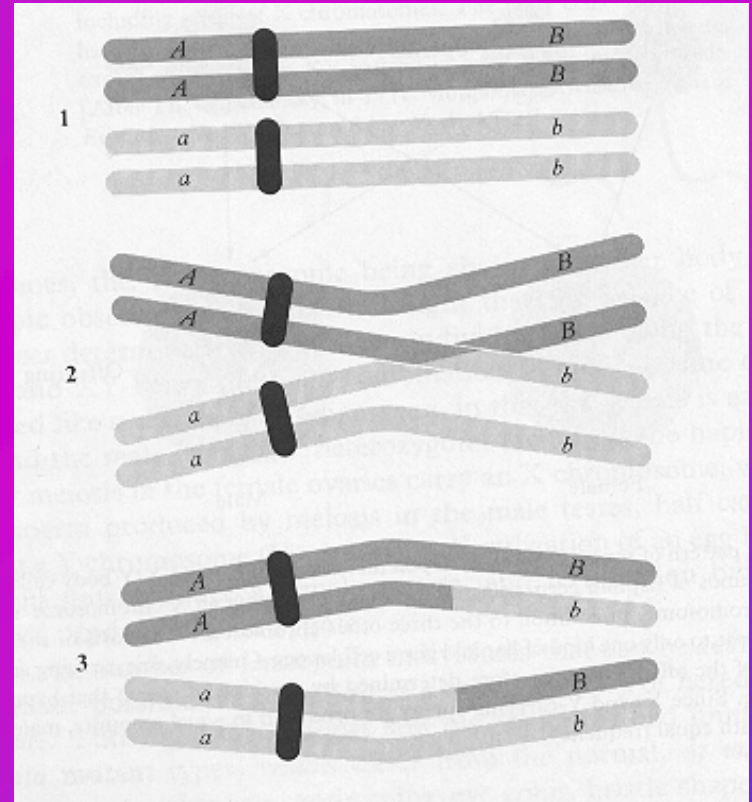
In 5 years he collects more than 85 different Drosophila mutant types.



Mr. Morgan's deduction



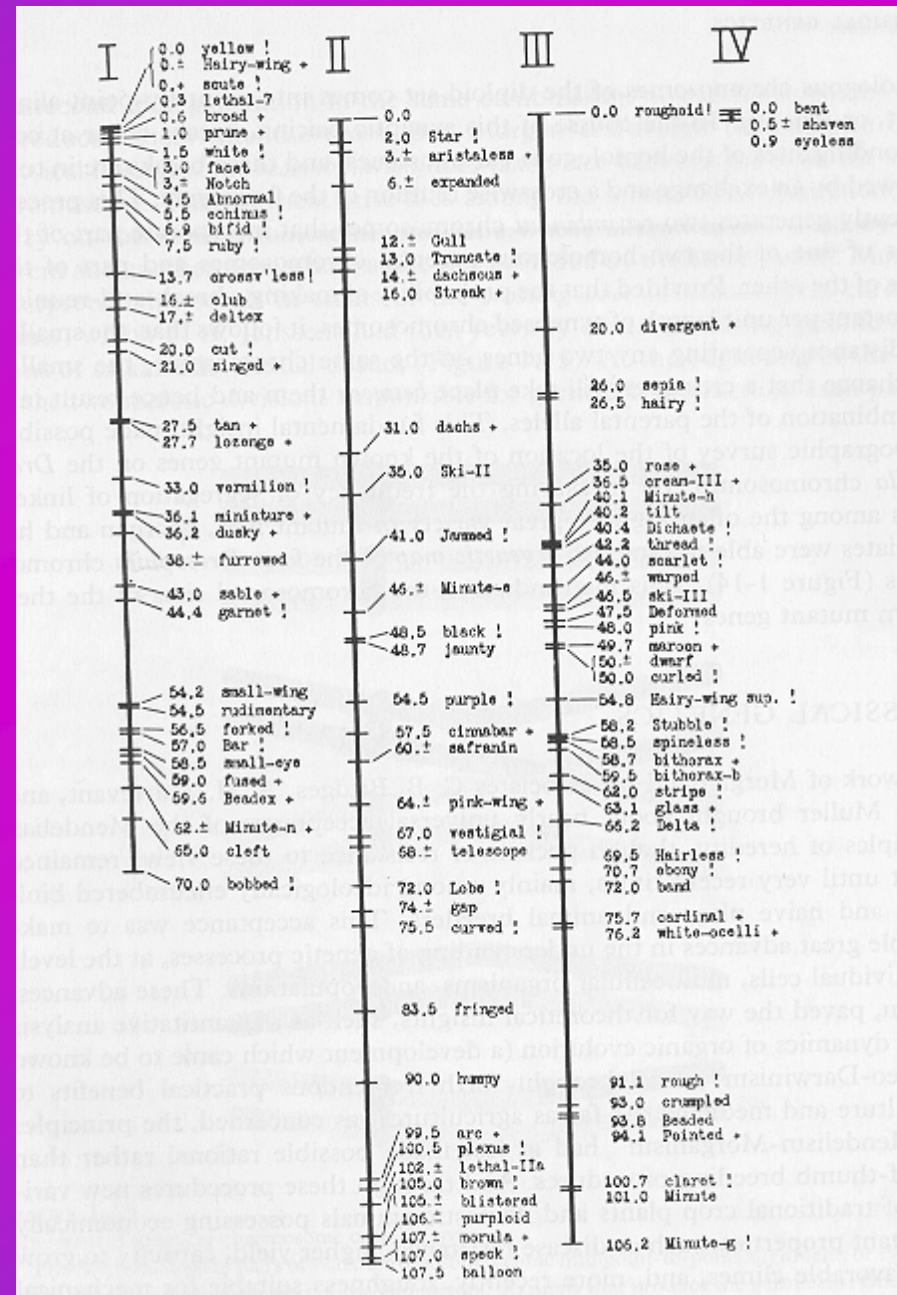
X-rays



In 1927 H.J.Müller showed that X-irradiation of flies greatly raises the frequency of mutations. Morgan discovered that crossing flies with two mutant genes on the same chromosome (linked genes) leads to some degree of recombination and interpreted these results as crossing-over of homologous chromosomes.

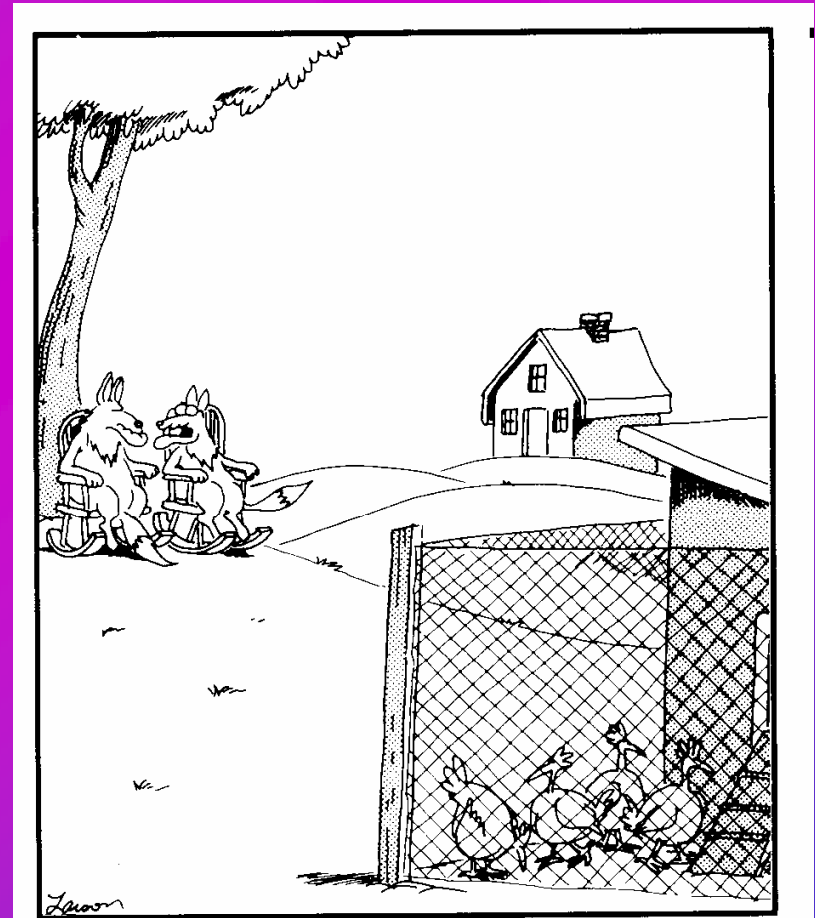
1926: the genetic map of *Drosophila* is charted.

This period of genetic research is generally referred to as **classical genetics** whose fundamental unit is an indivisible and abstract gene.



The birth of molecular genetics

By 1940 a new era was dawning. Most of the people involved wasn't from the domain of biology but trained in physical sciences. Their interest was confined to solve one and only one problem:
the physical bases of genetic information



"Look at us, Hank. . . . I tell you, there was a time when we did more than just watch the henhouse."

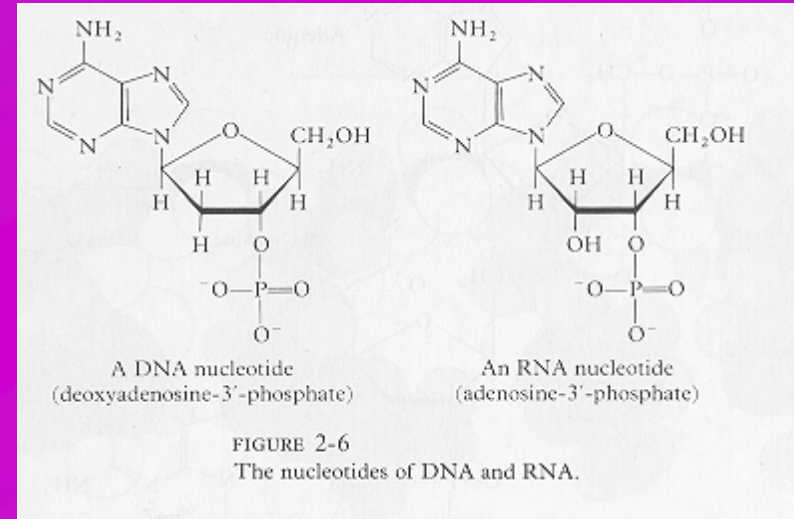
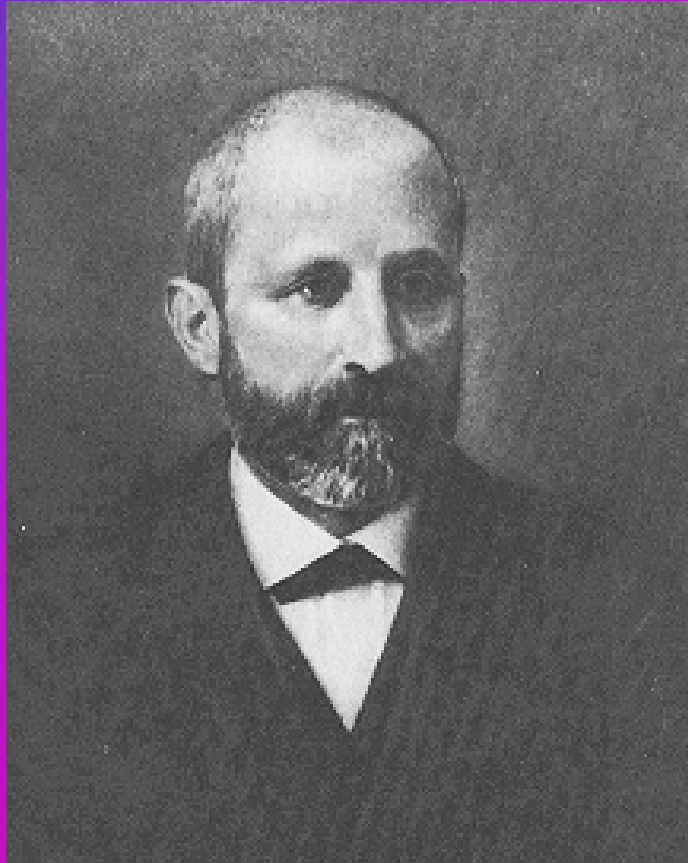
Erwin Schrödinger: Nobel Prize at 32

1945: E. S., a physicist, publishes the book: "What is life?" in which he stated that:

- chromosomes that carry genes are **aperiodic crystals**
- the crystal is a succession of a **small number of isomeric units**
- the nature of the succession constitutes the **hereditary code**



Friedrich Miescher in search of "nuclein"

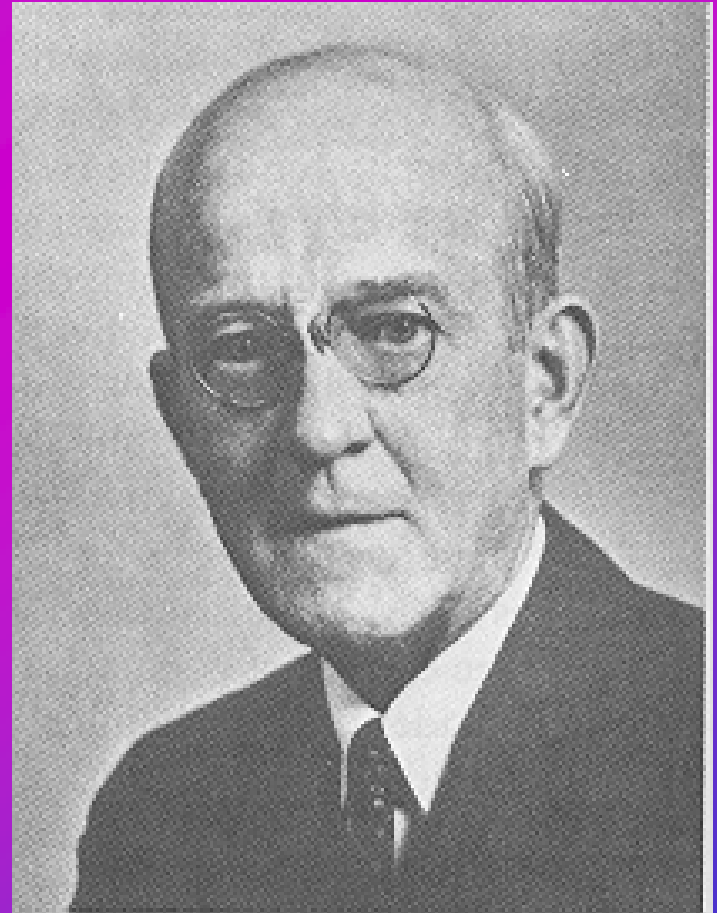


"Nuclei contains an hitherto unknown phosphorous-rich, acid substance."
This novel substance was later rechristened "nucleic acid".

DNA is the carrier of the genetic information (1944)

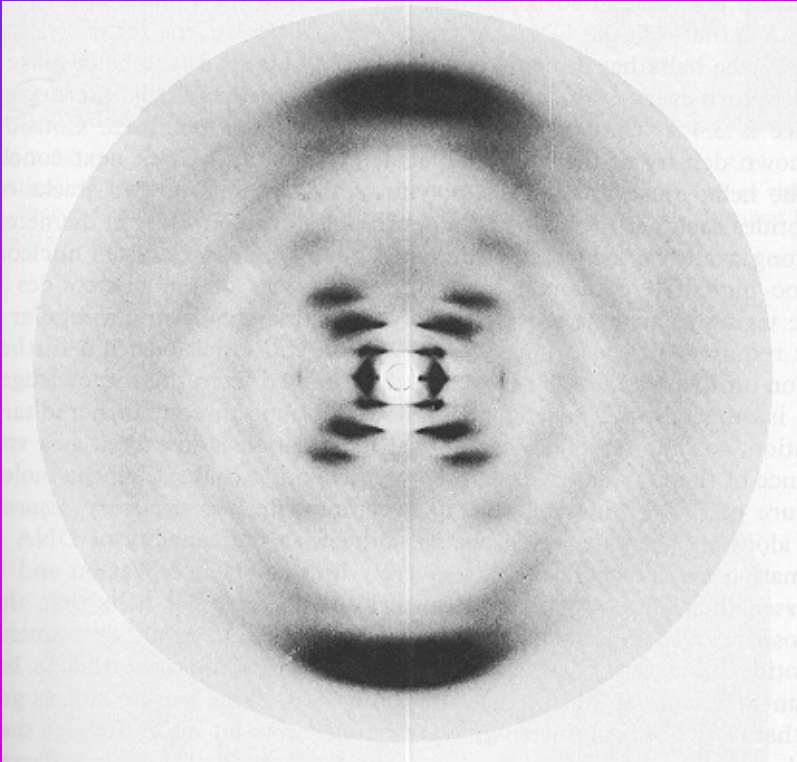
- By fractionation of the transforming principle" in a cell-free extract of S-bacteria Avery was able to remove proteins, lipids, polysaccharides and ribonucleic acid.
- Finally he concluded that the transforming principle is DNA.

...and everybody said: "This cannot be true!"



This is the picture.

(how technology can help solving a problem...)



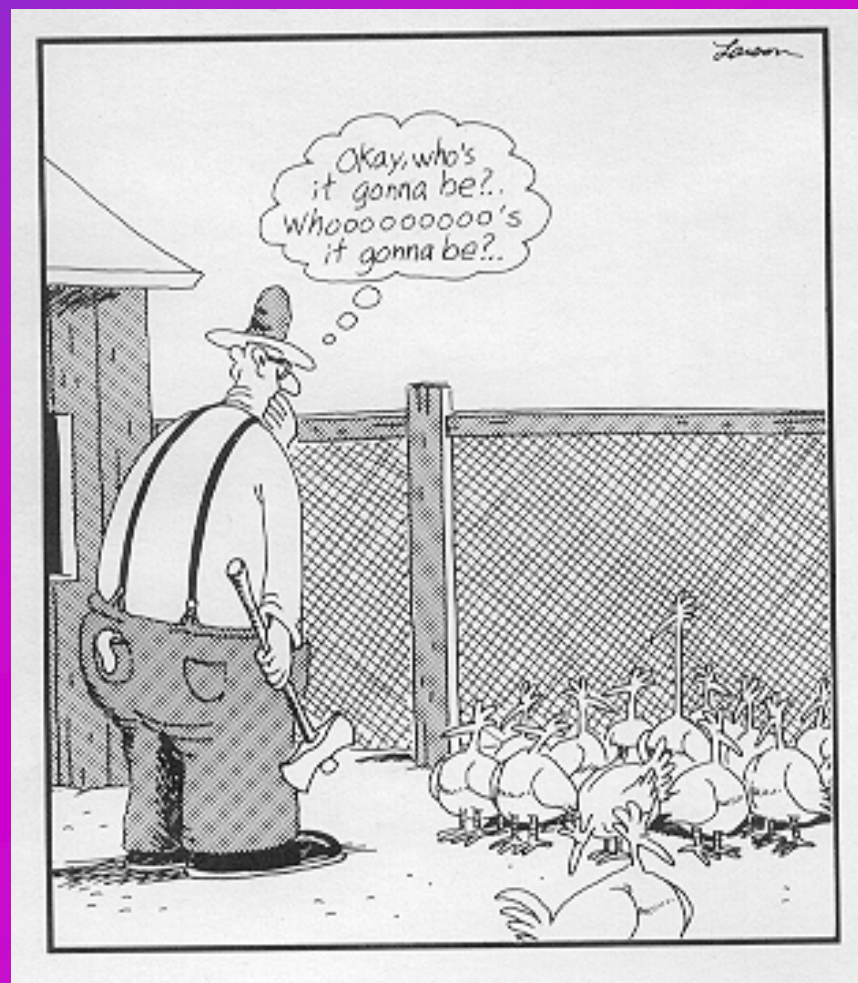
- 1950: in the lab of Wilson circulates this remarkable X-ray picture of crystals of DNA
- this was possible by preparing highly oriented DNA fibers
- new details become evident...

This is one of the three groups that saw the previous X-ray picture...

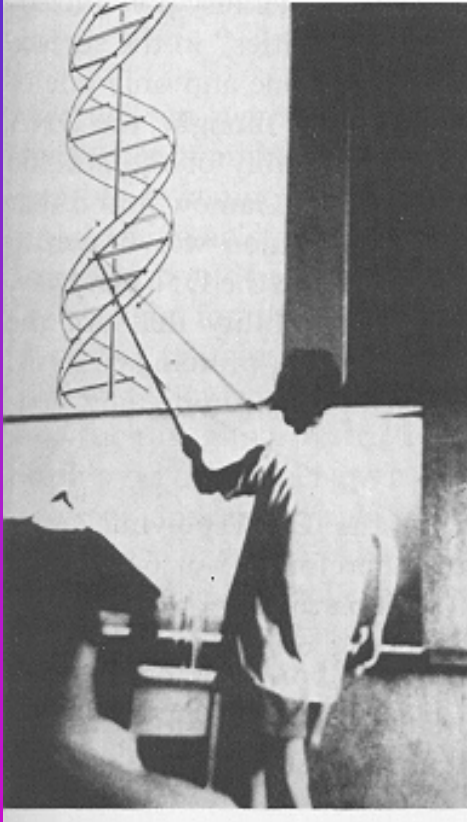


Forget the other two...

Who's gonna beeee....?

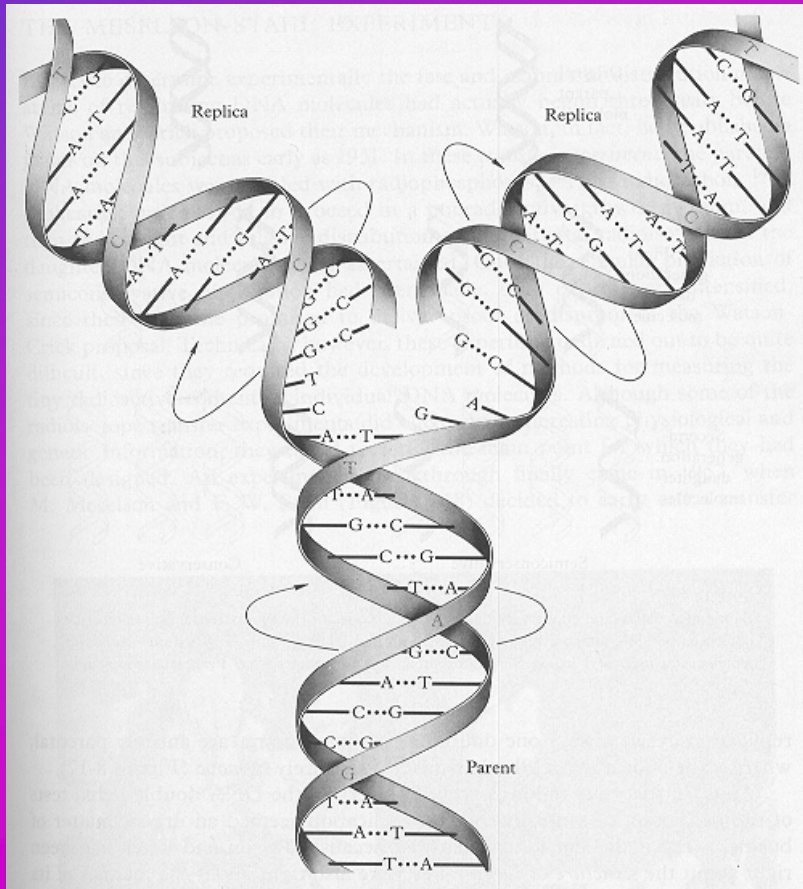


Few weeks later...



1. The DNA polynucleotide chain has the form of a regular helix
2. The helix has a diameter of 20 Å
3. The helix makes one complete turn every 34 Å
4. Since the nucleotide distance is 3.4 Å, a complete turn contains a stack of 10 nucleotides
5. Furthermore, considering its density the helix must contain two polynucleotide chains
6. Since the diameter of the helix is constant at 20 Å and the purine ring is greater than the pyrimidine ring there must exist a sort of complementary relation between the two nucleotide stacks.

And finally...



"...it has not escaped our notice that the specific pairing we have postulated immediately suggest a possible copying mechanism for the genetic material..."

Watson and Crick
Nature, April 1953.

You gave him the Nobel
Prize...

