Sage - Spring 2023

Welcome to

Session 5 of

"Genes for Very Smart but Ignorant People"

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Course Outline

1. *Gregor Mendel: How a monk came to discover the rules of inheritance*

2. *Genes and chromosomes - the fly in the ointment (continued)*

3. *Microbiologists discover that most genes are made of DNA*

5. *How two amateurs beat the A team to solve the structure of DNA*

6. *The genetic code. Again an obscure team of players beats the pros.*

~~6. How genes are controlled. The French connection.~~

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Grand Summary

Let me remind you of the major take-home lessons that I've presented so far.

Genes come in pairs

Genes are located on chromosomes

Genes specify the structure of proteins

Polymers R us

I'll introduce one more pithy lesson today:

"Complementary, my dear Watson"

While you consider that, let's move on…

Besides specifying the structure of proteins, genes have one more compelling characteristic:

They are passed on accurately from one generation to the next.

How do they do that?

The answer to that question came in 1953 from a pair of eccentric and brilliant scientists

James Watson and Francis Crick

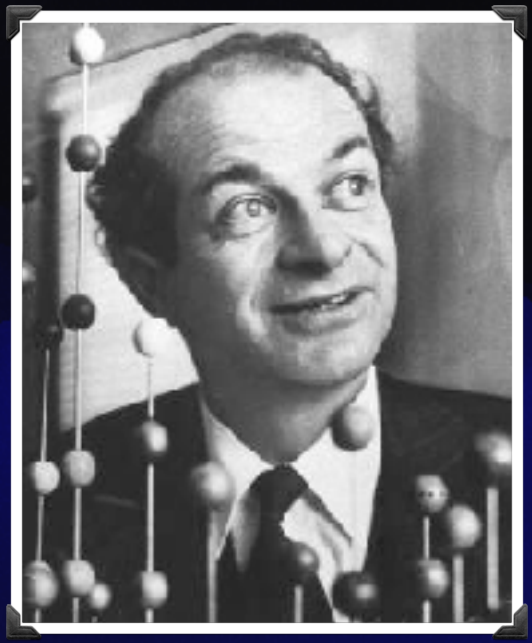
The story of the elucidation of the structure of DNA is the story of a race, but one that was decidedly unfair.

On one side was a team of two amateurs working at Cambridge University in England.

James D. Watson
1928 -

Francis Crick
1916 - 2004

Matched against them was the greatest chemist of the 20th century, Linus Pauling, from the California Institute of Technology.



Linus Pauling (1901-1994)

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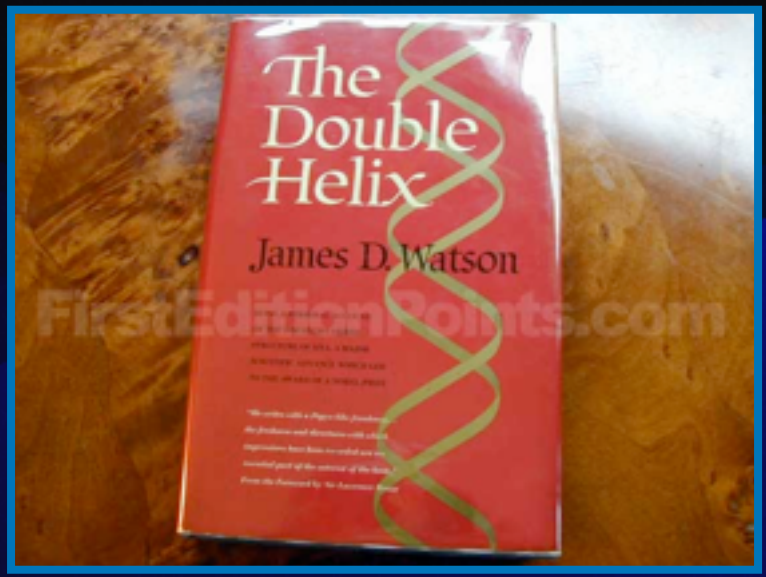
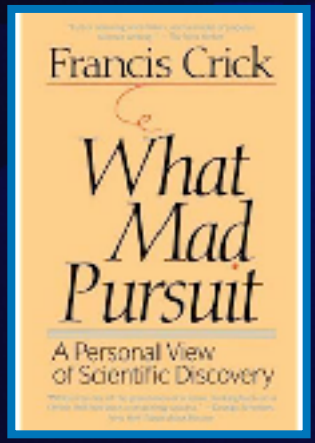
We all know who won. They conquered because they were smart, single minded, extraordinarily lucky, were in the right place at the right time, and because they cut some ethical corners.

Their story, at least a biased version of it, is told in the remarkable memoir written by Jim Watson (first published in 1968).



Crick also published a less popular book on the same subject.



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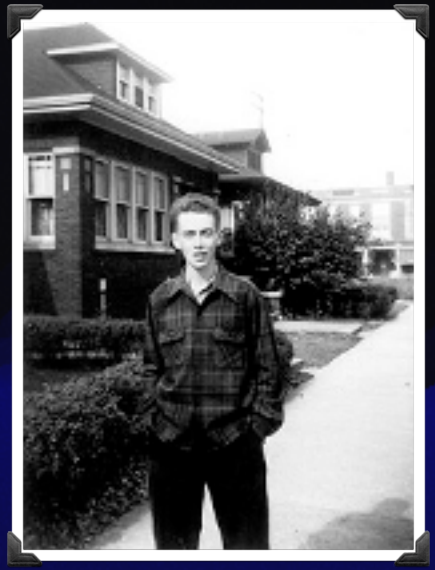
James Watson, the younger member of the team, is (he's 94, still alive) an American who began his scientific career as an undergraduate at the University of Chicago with an interest in ornithology and an aversion to physics and chemistry courses.



Watson as a Chicago teenager. He entered University when he only was 15.

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In his junior year, Watson read a short book by the physicist Erwin Schrödinger called "What is Life". The book and Avery's papers on DNA, convinced Watson to "pursue the gene". He enrolled at Indiana University to work with Hermann Muller.

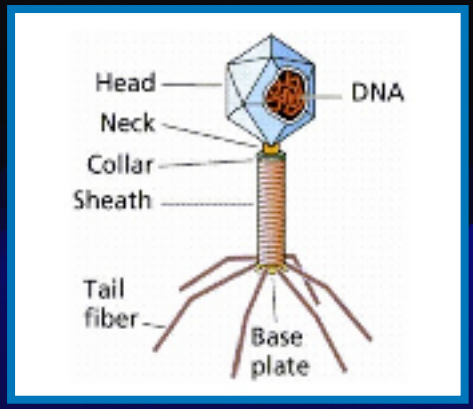
Erwin Schrödinger, German physicist.

But Muller's work on Genetics didn't inspire Watson. He regarded it as too slow and old fashioned. He wanted a quicker way. He turned to Salvatore Luria, who worked with bacteriophage. He was Luria's first graduate student.

Salvador Edward Luria, an Italian who fled Mussolini's Italy. Nobel Prize winner, 1969.

Bacteriophage are essentially genes covered by a protein coat.

A virus, it injects its DNA into bacteria, and produce millions of offspring. Crosses can be analyzed within hours, rather than weeks (as with fruit flies)



A bacteriophage. It injects its DNA into bacteria and reproduces therein, killing the bacteria.

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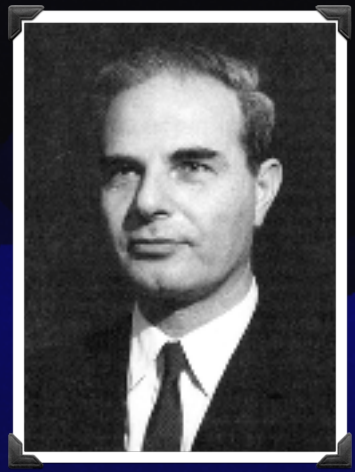
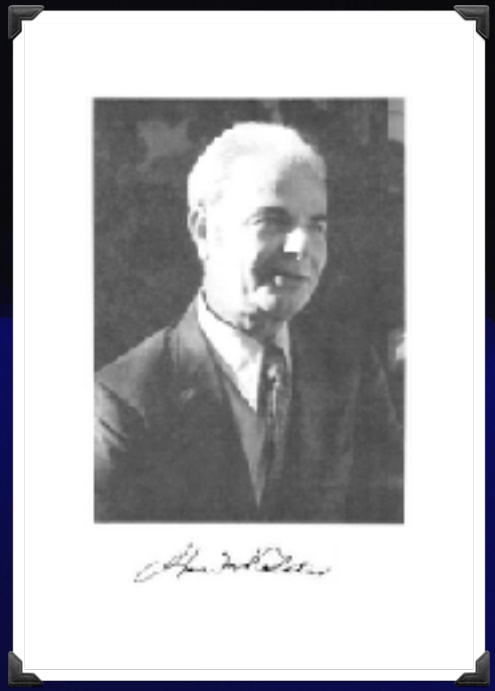
Watson got his doctorate working on "phage", but for Watson even studying bacteriophage wasn't a direct enough route to determine the nature of the gene.

Armed with a PhD, he sailed to Copenhagen to work with Herman Kalckar.



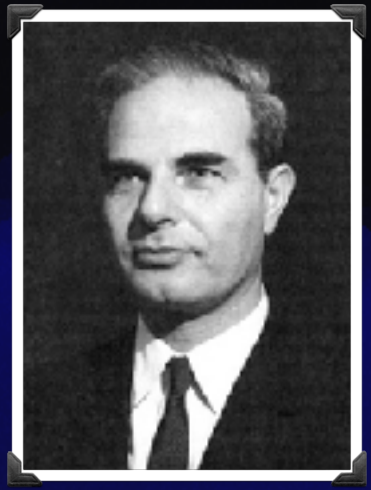
Herman Kalckar, Danish biochemist, who Watson went to work with after his doctorate.

Kalckar was a biochemist. But Watson found that he wasn't really working on the structure of DNA directly, only its subunits.



Herman Kalckar (1908-1991)

They didn't get along. Watson said "... it was impossible to understand him."



Herman Kalckar

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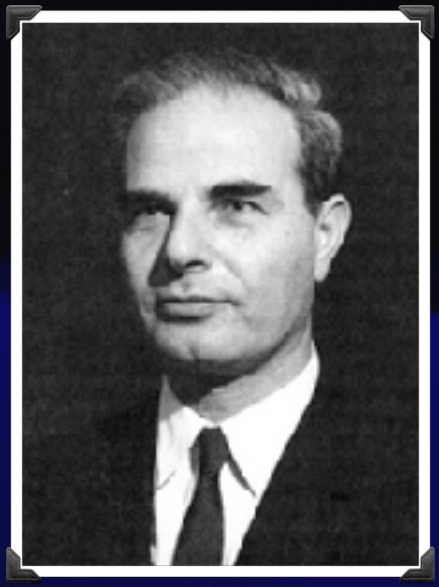
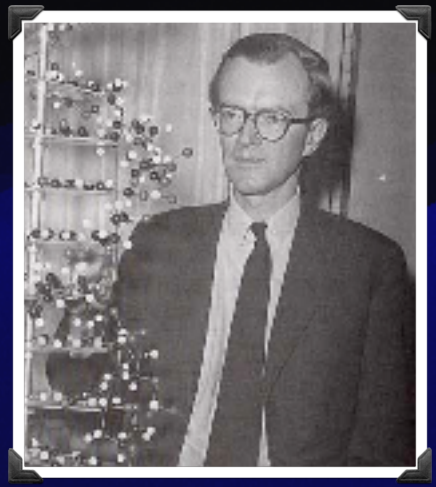
"… Kalckar was … known for his peculiar way of talking, which some hearers found unintelligible. … Boos, his former associate, referred to this speech mode as a "language" he called "Kalckarian": a language that Kalckar occasionally used to avoid conversations he found uninteresting."



Herman Kalckar

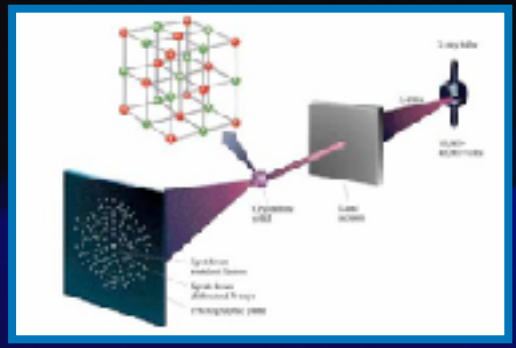
Things were looking bleak. But at a meeting in Naples, Watson heard a talk given by Maurice Wilkins, a New Zealand born physicist and molecular biologist.



Maurice Wilkins (1916-2004)

Wilkins was analyzing DNA by a technique called X-ray crystallography.

Here at last seemed the route to understanding the chemical structure of the gene.



X-ray crystallography

X-ray Crystallography

X-ray crystallography is a method of determining the arrangement of atoms within a crystal. A beam of X-rays strikes a crystal. The atoms bend the rays, and they bounce off into many directions. From the angles and intensities of these deflected rays, a crystallographer can produce a three-dimensional picture of the position of the atoms within the crystal.

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Watson immediately decided that he would solve the structure of DNA using X-ray crystallography. There were, however, a few small obstacles in his path.

First, he knew virtually nothing about X-ray crystallography.

Second, he couldn't get a position in Wilkins' laboratory.

Third, the X-ray laboratory that he did succeed in joining, the Cavendish, wasn't working on DNA.

Fourth, Wilkins' lab was in disarray, torn apart by a dispute between Wilkins and his nominal assistant, Rosiland Franklin.

Rosiland Franklin

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Fifth, Watson's fellowship was for studying with Kalckar in Denmark. The X-ray crystallography lab that he wanted to work in was in Cambridge, England. Would his funds be transferrable?

The Cambridge Laboratory

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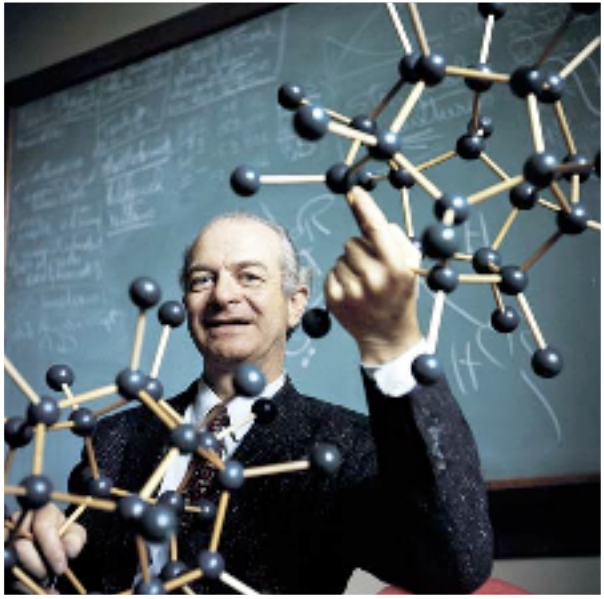
Last, but by no means least, an ominous competitor loomed.

The great chemist Linus Pauling, was turning his attention to solving the structure of DNA.



Linus Pauling

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Lawrence Bragg was the Head of the Cavendish Laboratories at the time.

He, and his father William, had invented X-ray crystallography.

Lawrence and William shared the Nobel Prize (at 25, Lawrence remains the youngest winner)

William and Lawrence Bragg

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Lawrence ("Willie" to his friends), used X-ray crystallography to determine the structure of more and more complex molecules.

After WWII, they were working on the most complex of them all, PROTEINS.

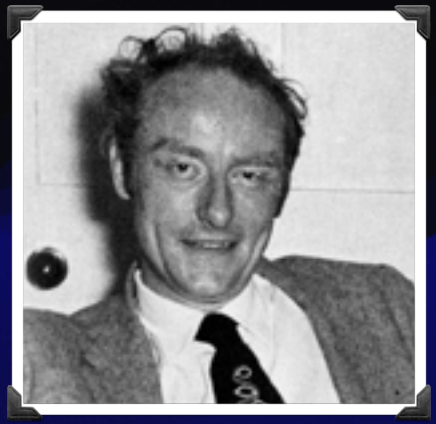
Hemoglobin, one of the proteins being studied at Cambridge

Watson arrived at the Cavendish Labs in the fall of 1951.

"From my first day in the lab I knew I would not leave Cambridge for a long time. Departing would be idiocy, for I had immediately discovered the fun of talking to Francis Crick."

Crick and Watson in Cambridge

Crick was 35, 12 years older than Watson, yet still a graduate student.
Trained in physics and mathematics, during WWII he helped design acoustic and magnetic mines



Francis Crick in 1954

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After the war, he didn't know what to do. He read Schrödinger's book, and decided to investigate the "border between the living and the nonliving".

He joined the Cavendish Laboratories as a graduate student.

Francis Crick next to an X-ray tube

Crick, son of a shoe factory owner, was a character.
He had a thunderous voice and a booming laugh.
He was brilliant and articulate, knew it, and wanted everyone else to know it.

Francis Crick

Watson begins his book, "The Double Helix" with this sentence:

"I have never seen Francis Crick in a modest mood."

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He often dropped in, uninvited on colleagues' labs, persuaded them to tell him what they were doing, and invariably made some suggestions that implied that what they had been up to for years was worthless. He was unpopular, although often right.

Watson and Crick shared an office. They complemented each other. Crick knew little about biology or genetics; Watson didn't understand X-ray crystallography or have much facility with mathematics.

Crick and Watson

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Watson was supposed to be working with John Kendrew (a future Nobel Prize winner), but proved inept at laboratory work and incapable of doing the math required to analyze the data from X-ray crystallography.

John Kendrew with his model of myoglobin, the first protein whose structure was "solved".

Instead, Watson and Crick talked incessantly. They became obsessed with learning the structure of DNA, which they regarded as the stuff of genes.

W&C with their model of DNA

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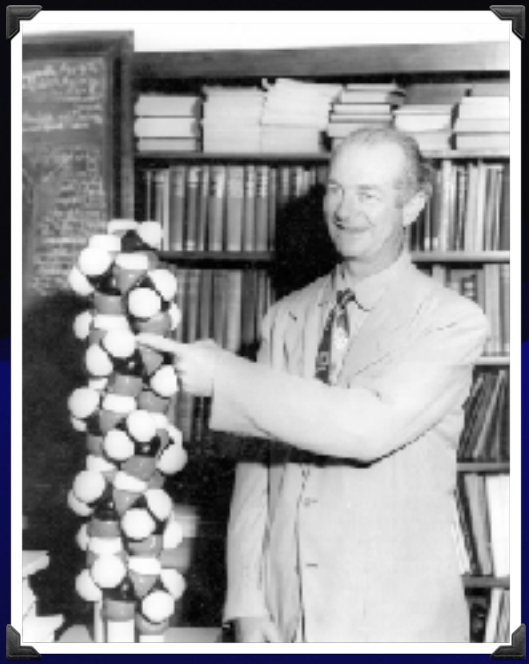
The problem was that no one at Cambridge was working on DNA.

Neither Watson nor Crick had the technical expertise to gather their own data.

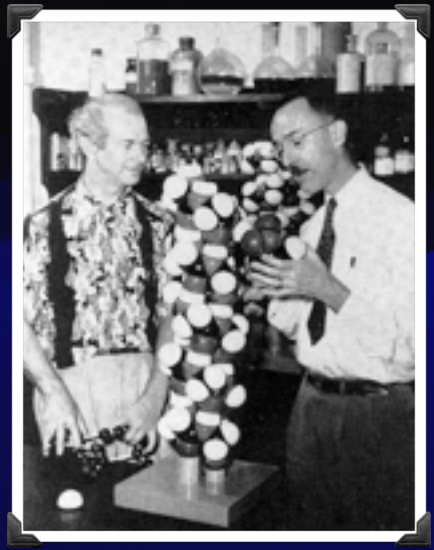
They settled on borrowing a technique from Linus Pauling, their chief rival.



Linus Pauling with his model of the alpha helix

In 1951, Pauling and his collaborator, Robert Corey, published a series of seven papers on the structure of proteins.

While proteins are complex, non-repetitive structures, they do share some repeating parts.



Pauling and Robert Corey

Pauling and Corey predicted that some of these repetitive units would be found when the first proteins structures were figured out.

His main tools were paper models, and a deep knowledge of the way that atoms interacted with each other.

He used a minimum of data.

Myoglobin, a protein with the helical structures first predicted by Corey and Pauling.

Bragg was mortified when these papers came out. He had finished second behind Pauling.

But Watson and Crick realized that they could take Pauling's approach to solving the structure of DNA.

Pauling with his model of the alpha helix.

They had little choice.

And they could take advantage of the fact that Maurice Wilkins was generating some X-ray crystallography data for DNA at King's College in London.

Maurice Wilkins working with a camera for capturing X-ray crystallography data

But, as mentioned, the lab was in disarray. Rosalind Franklin, a talented X-ray crystallographer had been recently hired.

She was under the impression that she would be in charge of a unit studying DNA.

Rosalind Franklin (1920 - 1958)

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When she arrived, she found that Maurice Wilkins was already at work on DNA, and thought that Franklin would be his assistant.

They began a monumental battle. Ultimately, they decided to carve up the project.

They hardly spoke.

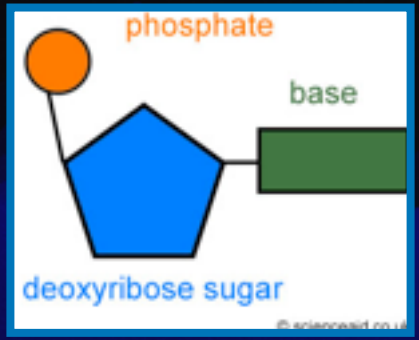
Franklin, ?, and Wilkins at a meeting

Meanwhile, Watson and Crick began playing with metal models of nucleotides, trying to fit them together into a sensible structure.

The metal parts that Watson and Crick used to construct their models of DNA

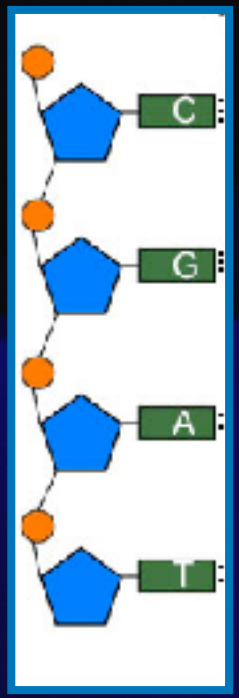
*Watson and Crick knew that DNA is a **polymer**. It consists of four monomers strung together in long chains.*

It's not a simple polymer, because it carries more than one kind of monomer



*A deoxyribonucleotide, a **monomer** of DNA.*

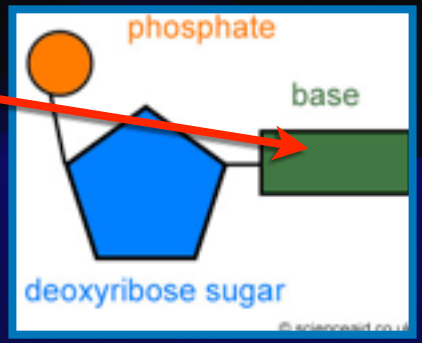
These monomers are connected together.



A DNA polymer, consisting of many monomers linked together.

Each monomer is identical, except for the base.

There are four different bases:
A, C, G, and T, each with a slightly different structure.

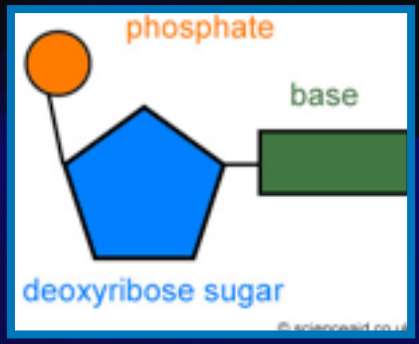


A deoxyribonucleotide, a monomer of DNA.

It's common to call each monomer, a "base".

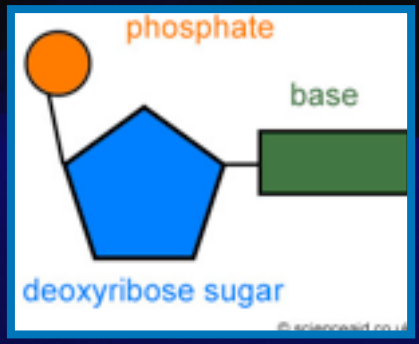
Its real name is "nucleotide", or "deoxyribonucleotide".

(We'll use all these names, but remember, a base is actually only a small part of each nucleotide).



A deoxyribonucleotide, a monomer of DNA.

These facts were known to Watson and Crick before they embarked on their mission to determine the structure of DNA



A deoxyribonucleotide, a monomer of DNA.

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OK. Back to our story. Soon W&C succeeded in building a structure that seemed to incorporate all the facts that were known about DNA.

They invited Wilkins, Franklin, and others to see it. They drove down from London.

It was met by contempt by all the visitors.

Model of DNA

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Disaster!

Watson and Crick had come up with a structure that was entirely wrong.

There were ramifications.

Bragg forbid Watson to work on DNA.

Watson ignored him.

Willie Bragg, Head of the Cavendish Laboratories

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Shortly thereafter, Erwin Chargaff visited Cambridge.

He presented a seminar.

A classically trained biochemist, he knew more about the chemistry of DNA than anybody else in the world. He had lunch with Watson and Crick.

Erwin Chargaff, Professor of Biochemistry at Columbia University

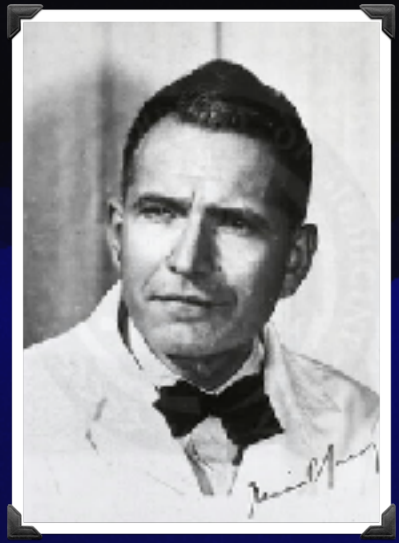
Chargaff was not impressed:

*"So far as I could make out, they wanted, **unencumbered by any knowledge of the chemistry involved**, to fit DNA into a helix. The main reason seemed to be Pauling's alpha-helix model of a protein....I told them all I knew. If they had heard before about the pairing rules, they concealed it. **But as they did not seem to know much about anything**, I was not unduly surprised."*

Erwin Chargaff, Professor of Biochemistry at Columbia University

The pairing rules that they weren't aware of were simply that in any sample of DNA, the A and T monomers were found in the same amounts, as were the G and C monomers.

He later said, "They impressed me with their extreme ignorance".



Erwin Chargaff, Professor of Biochemistry at Columbia University

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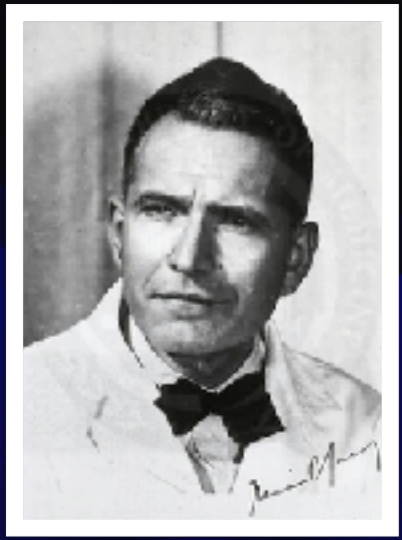
They felt his disdain, and barely were aware of what he told them.

But another event, or more importance, was looming on the horizon.



Erwin Chargaff, Professor of Biochemistry at Columbia University

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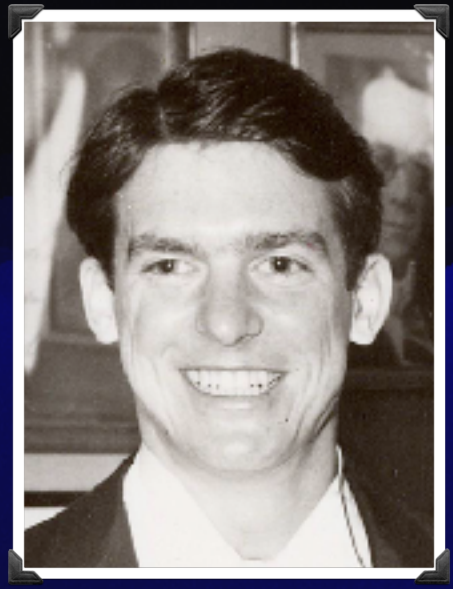
Peter Pauling, Linus' son, who was sharing an office with Watson and Crick, reported that his father had solved the structure of DNA.

Watson and Crick were depressed, Watson particularly so.

They had been beaten to the prize.



Peter Pauling, a graduate student at Cambridge, Linus' son.

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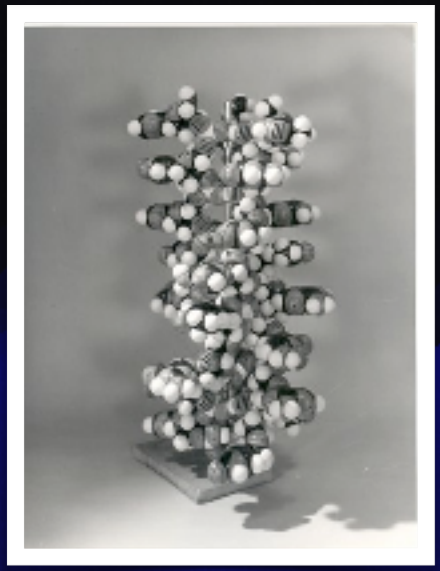
In January, 1953, a manuscript came to Peter from his father describing the structure of DNA.

Watson and Crick read it with trepidation. They immediately realized that Pauling had come up with a model similar to that which they had arrived at.



Pauling's model, consisted of three polymer strands, with the bases on the outside.

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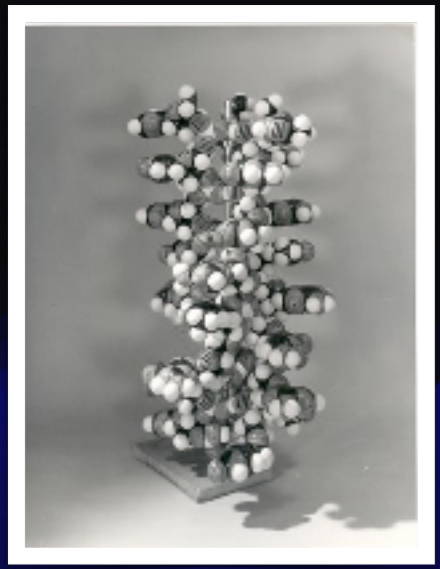
Pauling, the world's greatest chemist, had made a mistake!

His model disobeyed some fundamental laws of chemistry that even a beginner should have been aware of!

Watson and Crick were elated!



The negatively charged phosphates were in the inside. DNA wasn't even an acid according to this model

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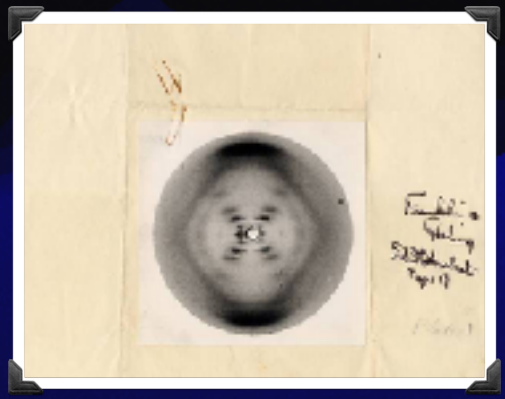
Watson took the train to London to tell Wilkins the good news. He barged in on Franklin and an argument ensued. Wilkins intervened.

On the basis of this newfound camaraderie, Wilkins showed Watson the best X-ray picture that he had of DNA. It was Franklin's.



To even a neophyte like Watson, this picture cried "helix".

But even with Franklin's data, it is unlikely that W&C would have come up with the correct structure of DNA.

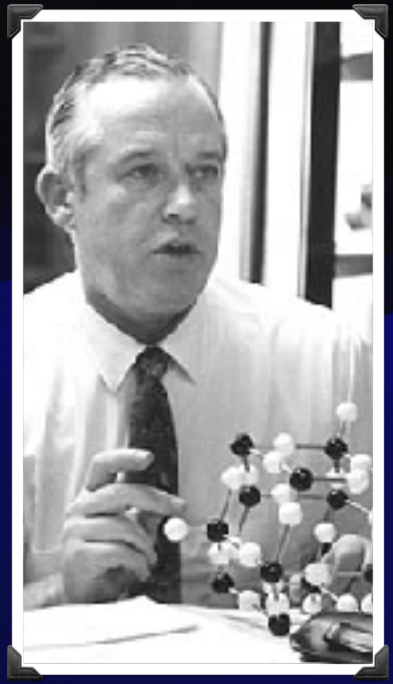
Two other events were crucial.

Rosalind Franklin

First, Bragg gave them permission to work on DNA. He didn't want to be beaten again by Pauling.They got back their metal models.

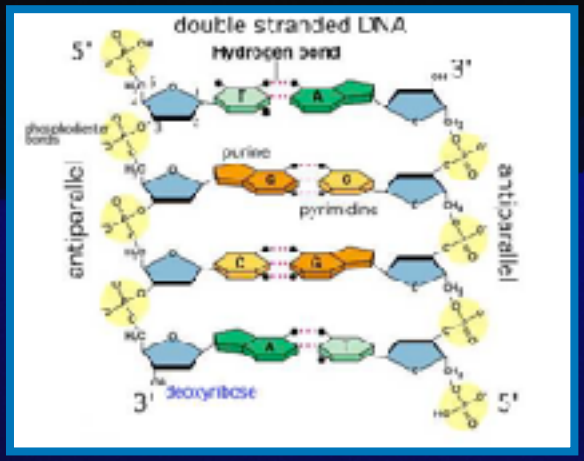
"Willie" Bragg

Second, Jerry Donahue, a chemist on a Fulbright at Cambridge, told Watson that the structure of the monomer models he and Crick were using were incorrect.



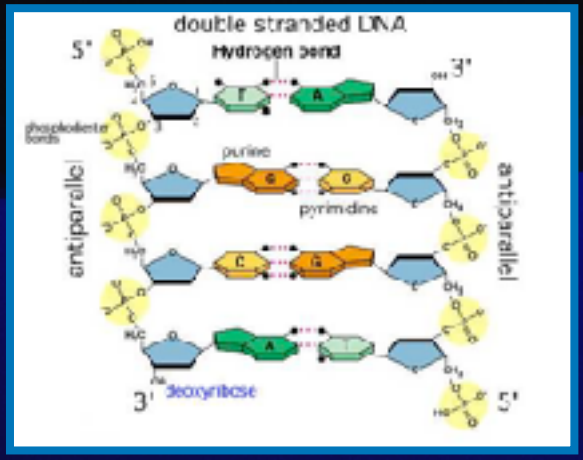
Jerry Donohue
(1920 - 1985)

This last point proved to be key. Armed with this new information, Watson proposed a two stranded model where the bases faced toward the inside of the molecule instead of towards the outside á la Pauling.

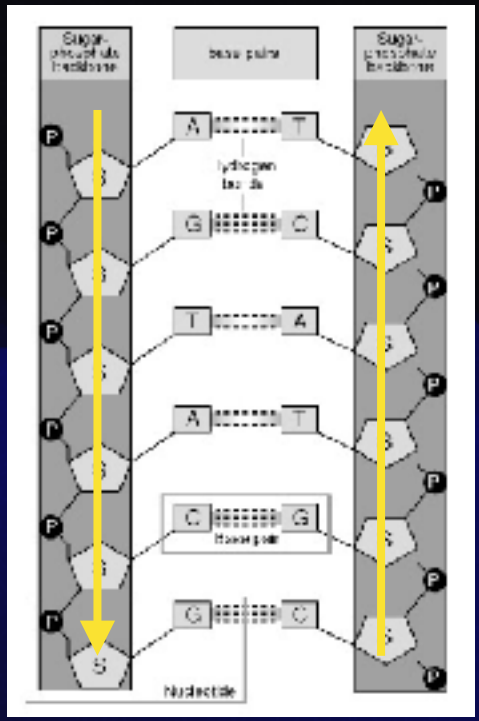


Using the model monomers, Watson matched the C's with the G's, and the A's with the T's.

The model explained why Chargaff's rules held.

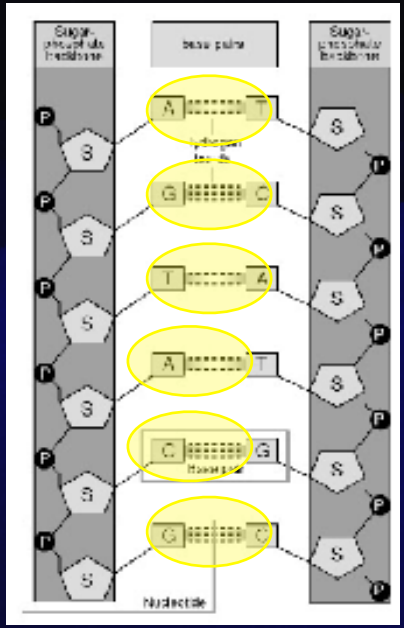


DNA consists of two polymer "chains", each one going in opposite directions.

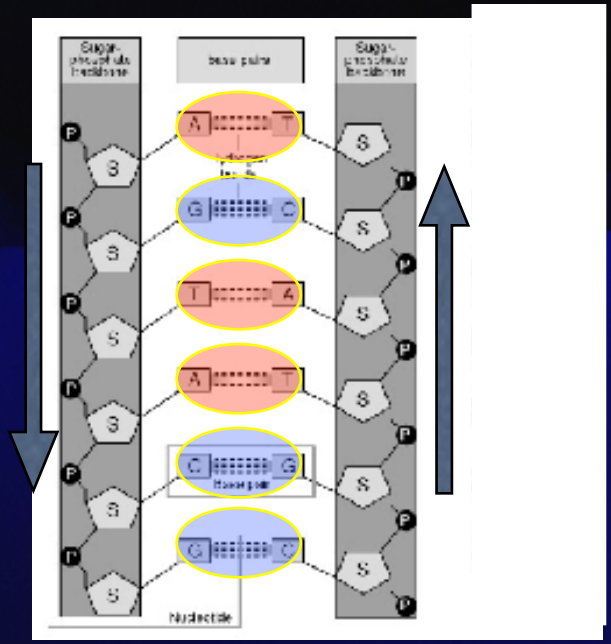


The two chains are held together by bonds between the bases on adjacent chains.

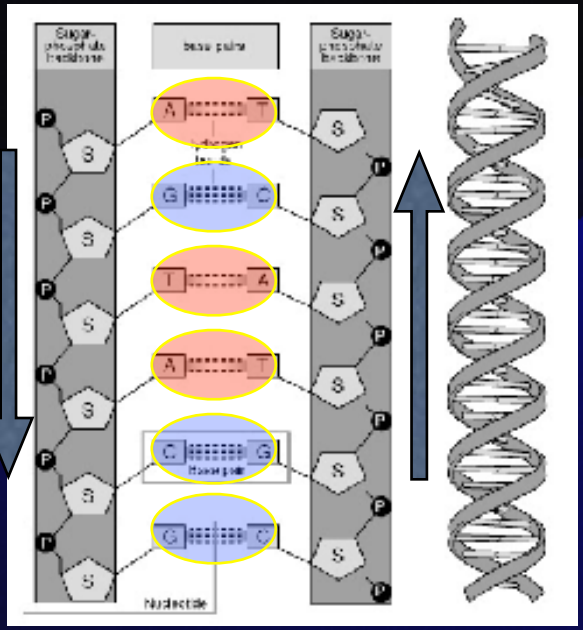
The two chains form one "double-stranded" molecule.



Bonds can only form between A's and T's, or G's and C's

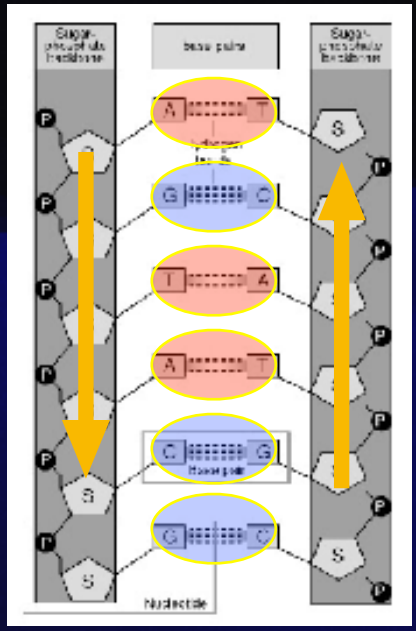


The two chains twist about each other, forming two spring-like structures or a "double helix"

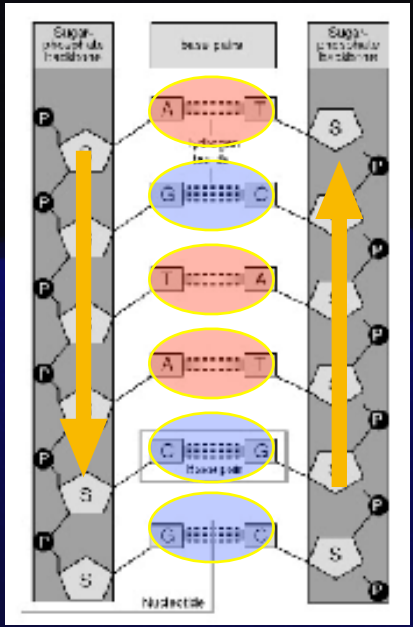


Again, the two chains are complementary to one another.

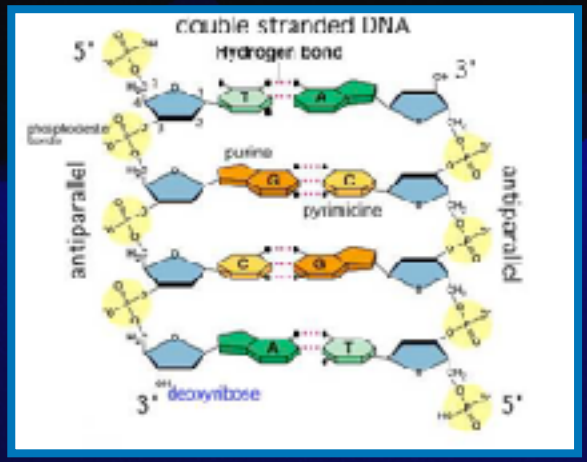
It's elementary.



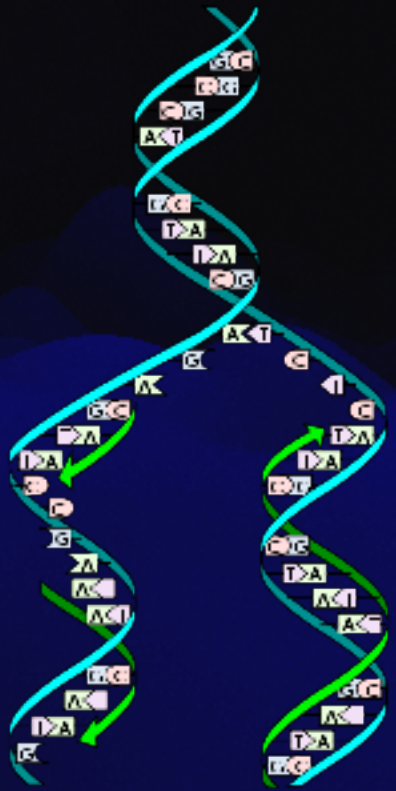
Complementarity means that if you know the sequence of bases on one strand, you also know the other.



Most importantly, the ***complementarity*** *of the bases instantly revealed how DNA might replicate.*



You "simply" separate the two strands, and then make new complementary strands from the two old ones.



The two strands separate…

ATTCCGACTGA
TAAGGCTGACT

They then act as templates for the opposite strand…

ATTCCGACTGA
TAAGGCTGACT

TAAGGCTGACT
ATTCCGACTGA

Four strands where there were two!

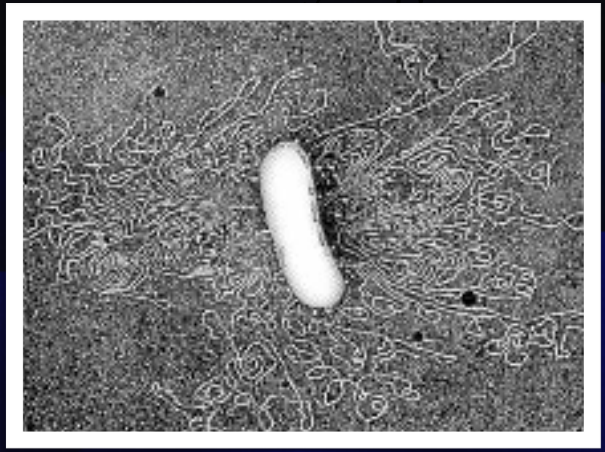
DNA is a very big molecule.

Some other questions you might have about DNA.

How long are DNA chains?

Very, very long!

DNA is a very big molecule.



E. coli

This intestinal bacterium's DNA consists of one molecule, 4,639,221 base pairs long!

Human DNA is much longer. In a human sperm or egg cell, the 23 chromosomes hold over 3,100,000,000 (3.1 billion) pairs of monomers in total.

The biggest chromosome carries about 250,000,000 monomers; the smallest about 48,000,000

Astonishingly, these 3,100,000,000 bases are arranged in a specific sequence.

The "complete" sequence of human DNA was reported in April, 2003.

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The sequence of the DNA molecules in

ed.

DNA is a very big molecule.

Some other questions you might have about DNA.

Where is the human DNA sequence stored?

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In GenBank, a repository for all the DNA sequences in the world.

The collection is very large.

		GenBank	
Release	Date	Bases	Sequences
3	Dec 1989	680338	606
14	Nov 1990	2274029	2427
20	May 1991	3502388	3665
24	Sep 1991	3833270	4135
25	Oct 1991	3960740	4175

...

249	Apr 2022	1266154830918	2375203118
250	Jun 2022	1395628631137	2390017893
251	Aug 2022	1492930734497	2399015786
252	Oct 2022	1582933336851	2405930282
253	Dec 2022	1655941304420	2410015745
254	Feb 2023	1731302248418	2418830635

That's 1,731,302,248,418 or over one trillion, seven hundred billion bases!

The fact that DNA replication (duplication) could be explained so easily, lead to the quick acceptance of Watson and Crick's model.

It explained how DNA was passed from generation to generation.

It was the answer to one of the secrets of life.

The next secret of life?

How is the information in DNA used to direct the processes of cells?

Tune in next week, same time, same station, for the exciting conclusion of this seminar.