The Aristotelian tradition and medieval alchemy eventually gave rise to modern chemistry

European and Asian philosophers

Alchemists

Phlogistonists

Modern chemists

The Macromolecules of Life

- **Carbohydrates (sugar)**
- **Lipids (membranes)**
- **Nucleic acids (DNA, RNA, Gene)**
- **Polypeptides (proteins, enzymes, lectins etc.)**

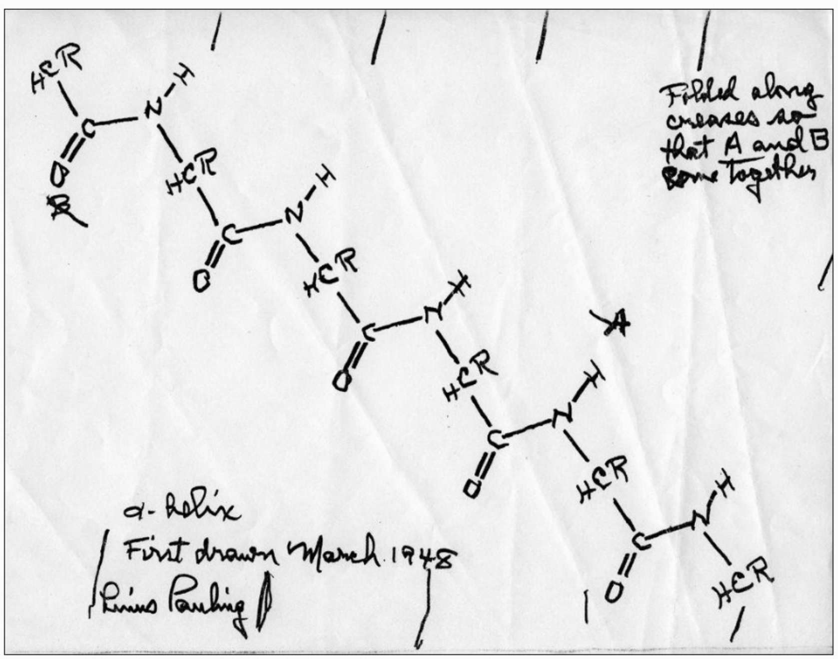
Bragg, Kendrew, and Perutz and the structure of proteins

Polypeptide chain configurations in crystalline proteins

By Sir Lawrence Bragg, F.R.S., J. C. Kendrew and M. F. Perutz
Cavendish Laboratory, University of Cambridge

(*Received* 31 *March* 1950)

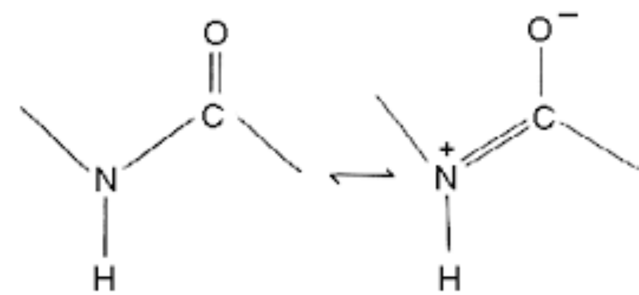
Proceedings of Royal Society, A 205, 321-357, 1950



Bragg, Kendrew, and Perutz, in Cambridge, based on X-ray diffraction published a paper describing a number of helical structures of polypeptide chains obtained in their search for an alpha-keratin structure --"

Pauling showed the proposed structures to be wrong

"From my point of view, all of these structures were wrong, because they did not involve planarity around the nitrogen atom. I thought that it was likely, however, that in the course of time they would learn enough chemistry to see what peptide group had a planar structure, and would discover the alpha helix, so Professor Corey and I decided to publish a short description of the alpha helix and the gamma helix."



Resonance forms

Pauling on Bragg, Kendrew, and Perutz protein structure, *Protein Science*, *2*, 1060-1063, **1993**.

Perutz's reaction to Pauling's publication

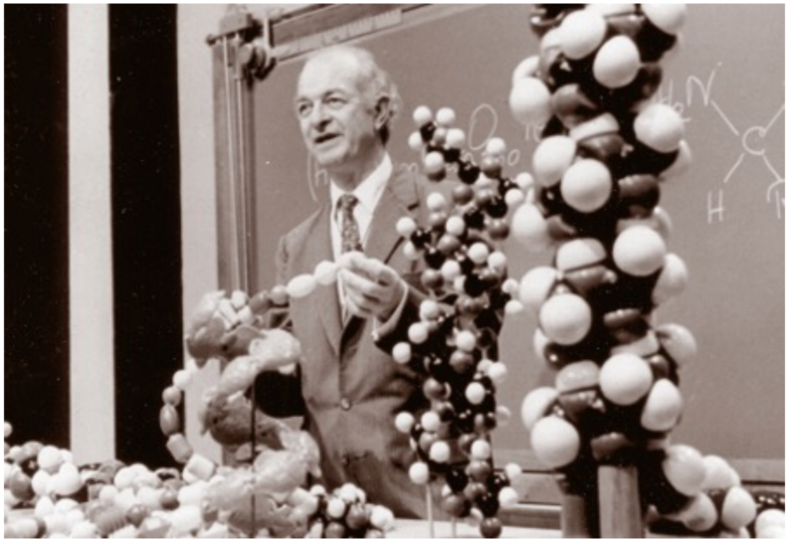
"I was thunderstruck by Pauling and Corey's paper. In contrast to Kendrew's and my helices, theirs was free of strain; all the amide groups were planar, and every carboxyl group formed a perfect hydrogen bond with an amino group four residues further along the chain. The structure looked dead right. How could I have missed it? Why had I not kept the amide groups planar? Why had I stuck blindly to Astbury's 5.1 angstrom repeat? On the other hand, how could Pauling and Corey's helix be right, however nice it looked, if it had the wrong repeat? My mind was in a turmoil. I cycled home to lunch and ate it oblivious of my children's chatter and unresponsive to my wife's inquiries as to what the matter was with me today."

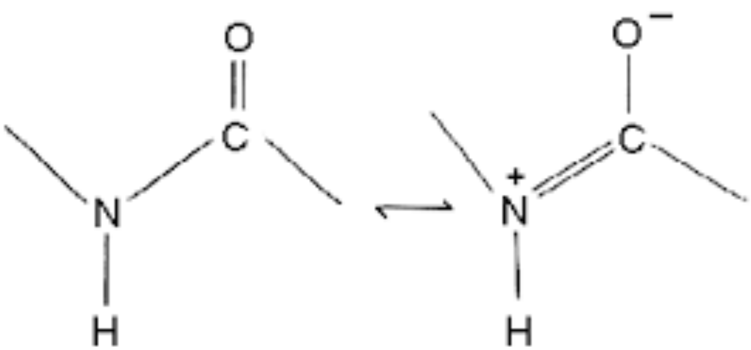
"*Brilliant Blunders: From Darwin to Einstein*"

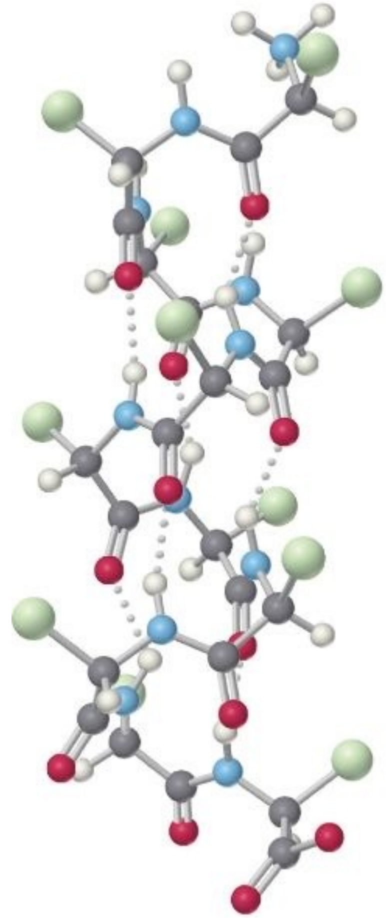
Pauling and Corey papers Series in PNAS

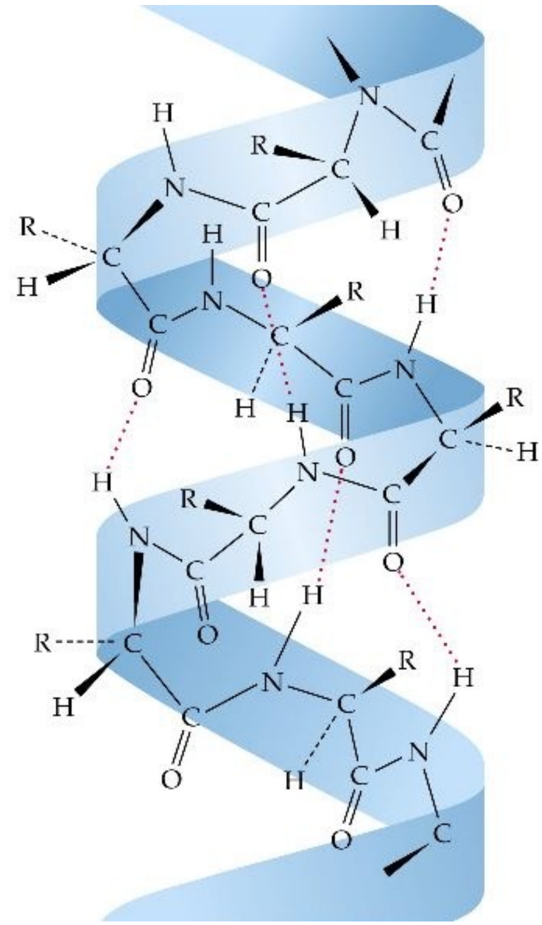
1. Pauling, L., Corey, R.B. and Branson H. R. **The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain.** PNAS, **37**, 205-211, (1951).
2. Pauling, L. & Corey, R. B. **Atomic Coordinates and Structure Factors for Two Helical Configurations of Polypeptide Chains**. PNAS, **37**, 235-240, (1951).
3. Pauling, L. & Corey, R. B. **The Structure of Synthetic Polypeptides**. PNAS, **37**, 241-250, (1951).
4. Pauling, L. & Corey, R. B. **The Pleated Sheet, A New Layer Configuration of Polypeptide Chains**. PNAS, **37**, 251-256, (1951).
5. Pauling, L. & Corey, R. B. **The Structure of Feather Rachis Keratin.** PNAS, **37**, 256-261, (1951).
6. Pauling, L. & Corey, R. B. **The Structure of Hair, Muscle, and Related Proteins**. PNAS, **37**, 261-271, (1951).
7. Pauling, L. & Corey, R. B. **The Structure of Fibrous Proteins of the Collagen-Gelatin Group**. PNAS, **37**, 272-281, (1951).
8. Pauling, L. & Corey, R. B. **The Polypeptide-Chain Configuration in Hemoglobin and Other Globular Proteins**. PNAS, **37**, 282-285, (1951).

Pauling and α-helix of proteins





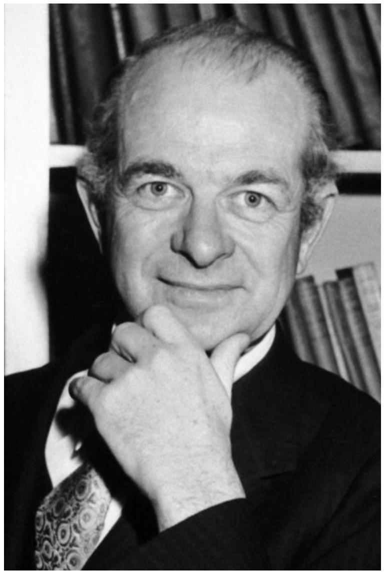




- Pioneered **model building** well before the days of computers
- Understood structural features – bond lengths, hydrogen bond, resonance

Why did Pauling and Corey succeed where others failed?

- Understanding the importance of hydrogen bonds
- Taking into account the planar peptide bond
- Better knowledge of covalent bond lengths and angles (chemical intuition)
- They were NOT crystallographers, and did not consider only models with integer number of residues per turn!



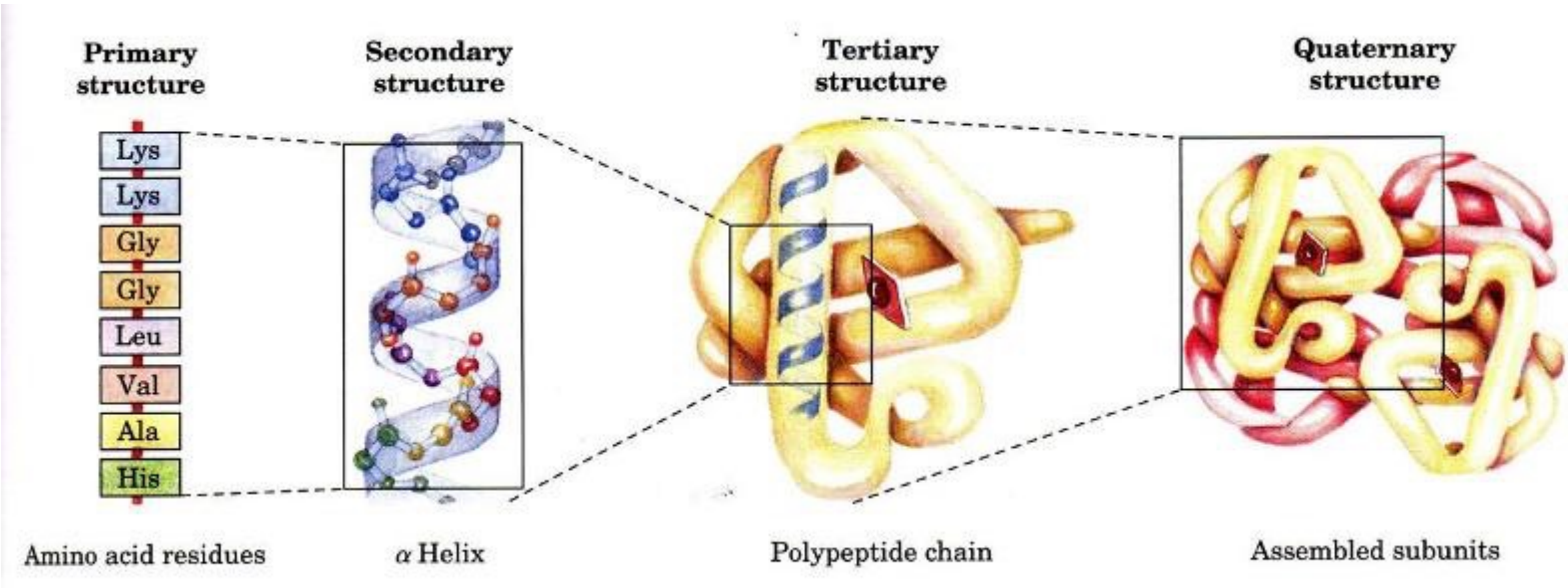
Linus C. Pauling

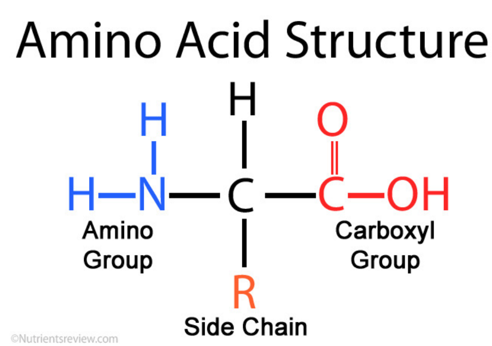
Nobel Prize in Chemistry 1954
Nobel Peace Prize 1962

The Nobel Prize in Chemistry was awarded "for his research into the nature of the chemical bond and its application to the **elucidation of the structure of complex substances**."

During the 1930s Linus Pauling was among the pioneers who used quantum mechanics to understand and describe chemical bonding. Linus Pauling worked in a broad range of areas within chemistry. **In 1951 he published the structure of the alpha helix, which is an important basic component of many proteins.**

Hierarchy of Protein Structure





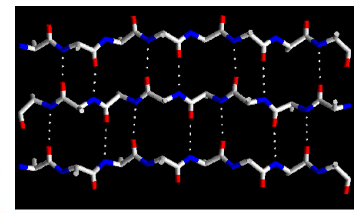
Hierarchy of Protein Structure

Primary 1^o

AKSDQPWFAGLE

Linear chain made of 20 possible amino acids

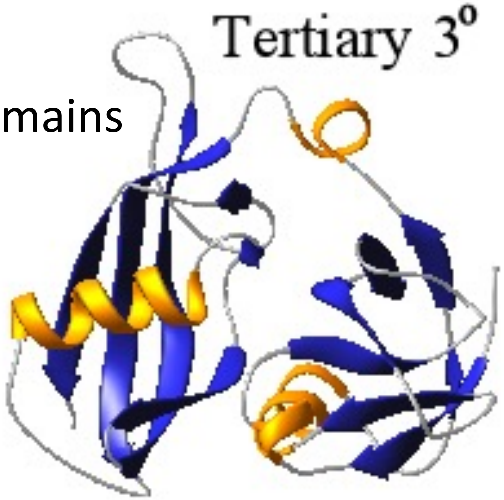
Secondary 2^o



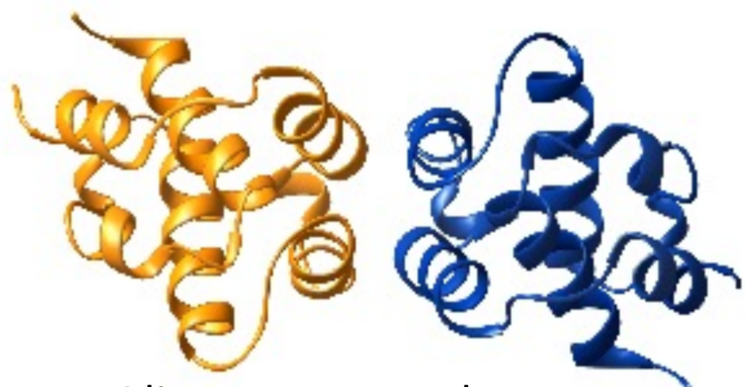
Alpha-helices, beta-sheets, turns

Tertiary 3^o

Motifs, domains

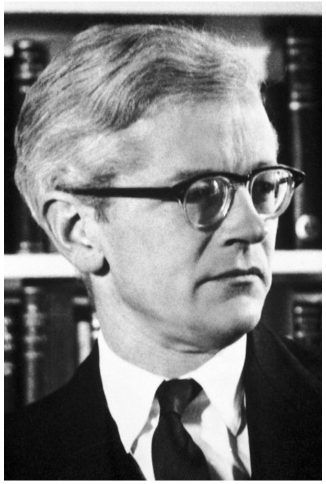


Quaternary 4^o

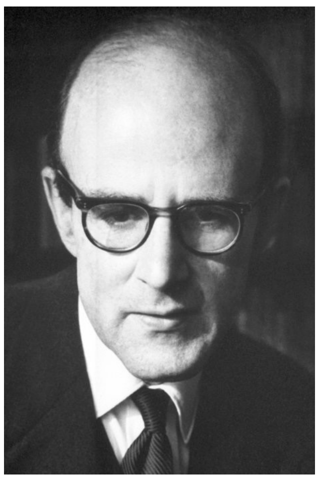


Oligomers, complexes

In the long run X-ray structure determination works better

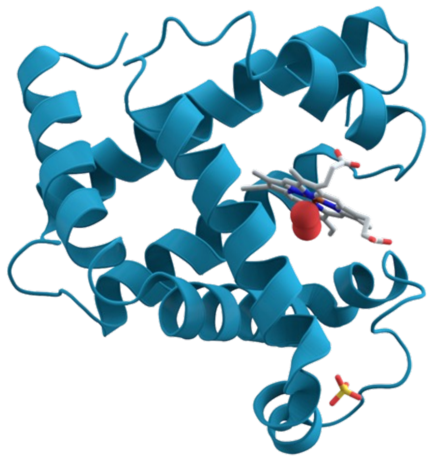


John Cowdery Kendrew

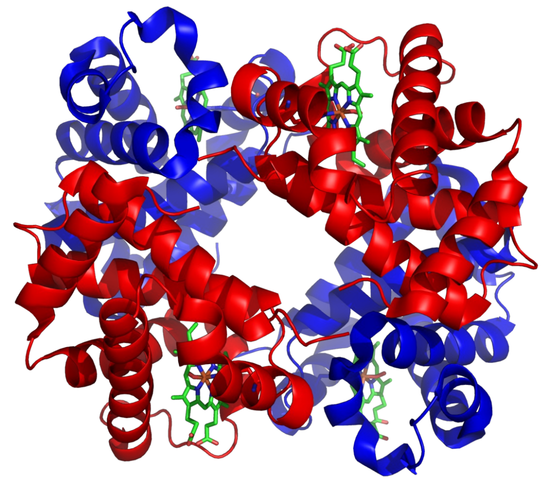


Max Ferdinand Perutz

The Nobel Prize in Chemistry 1962 was awarded jointly to Max Ferdinand Perutz and John Cowdery Kendrew **"for their studies of the structures of globular proteins."**



Myoglobin



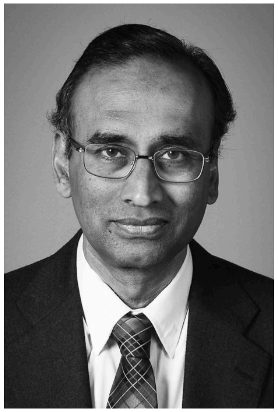
Hemoglobin

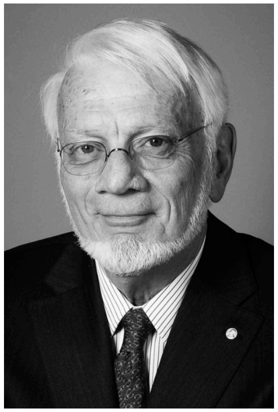
Pioneered the use of X-ray crystallography to solve the structure of macromolecules

Architects of Structural Biology: Bragg, Perutz, Kendrew and Hodgkin, J. M. Thomas, Oxford Uni. Press, 2020

The Nobel Prize in Chemistry 2009

The Nobel Prize in Chemistry 2009 was awarded jointly to Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath "for studies of the structure and function of the ribosome."

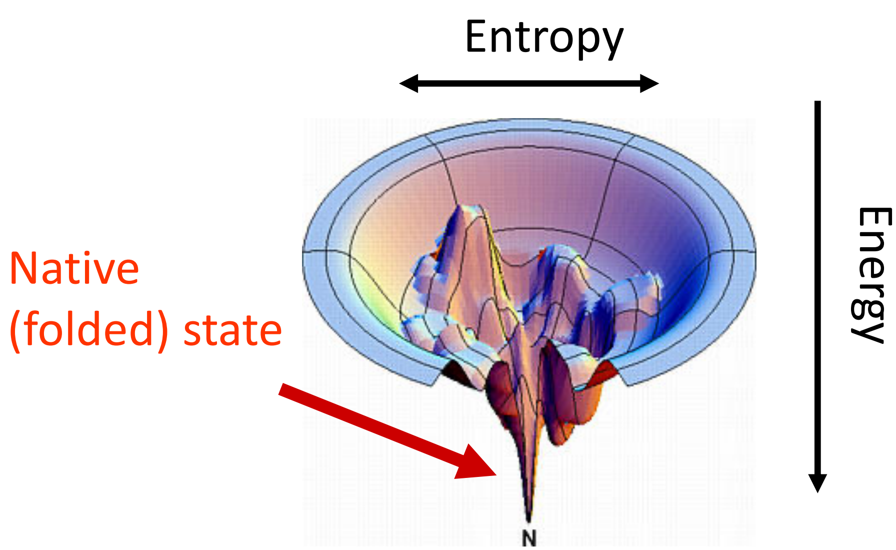


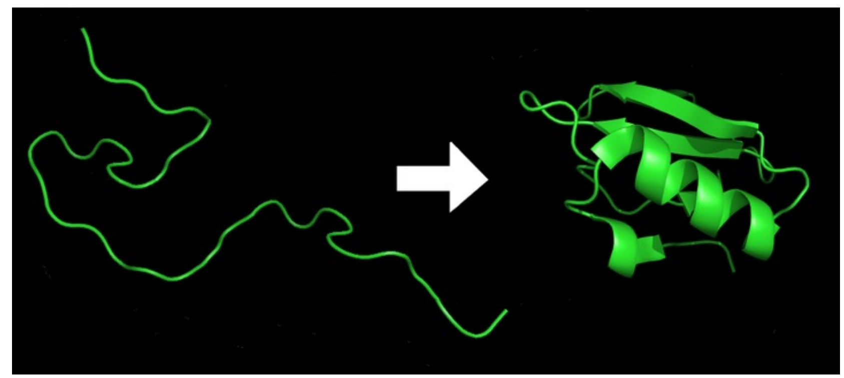


Ribosome is the machinery that synthesizes proteins.

Protein folding - research continues

- Late **1980's** - Wolynes et al. present the "Energy Landscape" or "Folding Funnel" model for protein folding

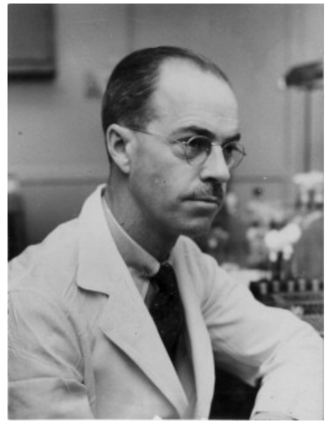




- **2006** – There is still no precise understanding how proteins fold fast (μsec time scale), reliably and accurately to their native structure

DNA is the polymer that transfers the genetic information

Oswald Avery

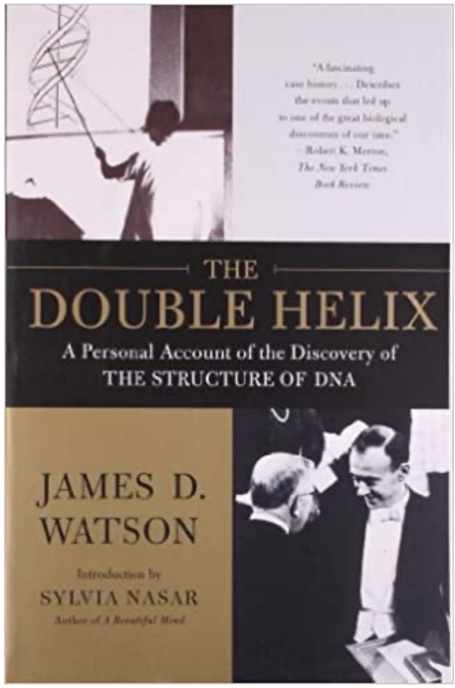


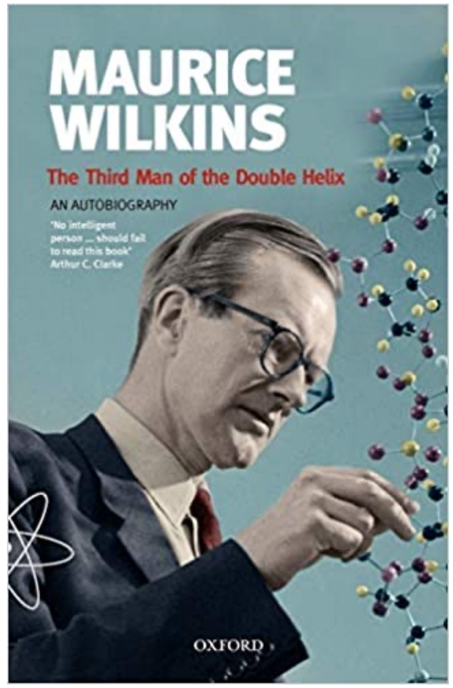
Colin MacLeod

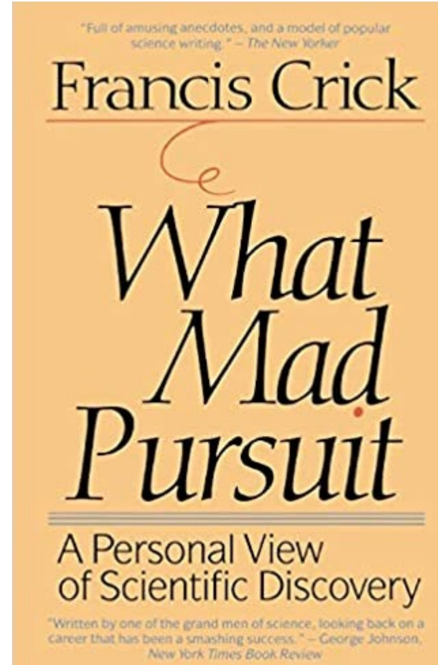
Maclyn McCarty

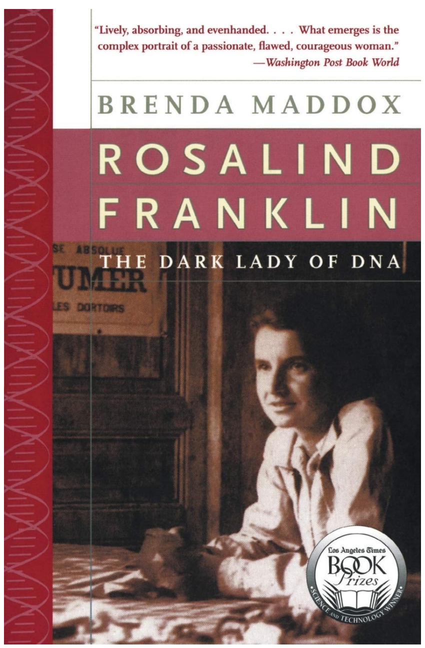
Avery, O.T., MacLeod, C.M., and McCarty, M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation by a desoxyribosenucleic acid fraction isolated from pneumococcus type III.
J. Exp. Med. 79, 137–158, **1944**

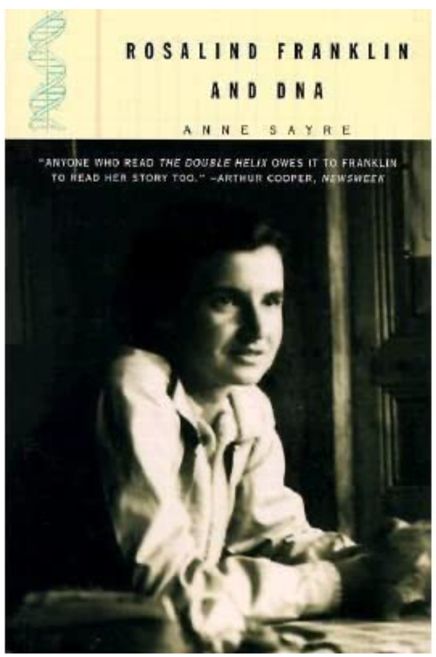
"If the results of the present study on the chemical nature of the transforming principle are confirmed, then nucleic acids must be regarded as possessing biological specificity the chemical basis of which is as yet undetermined."

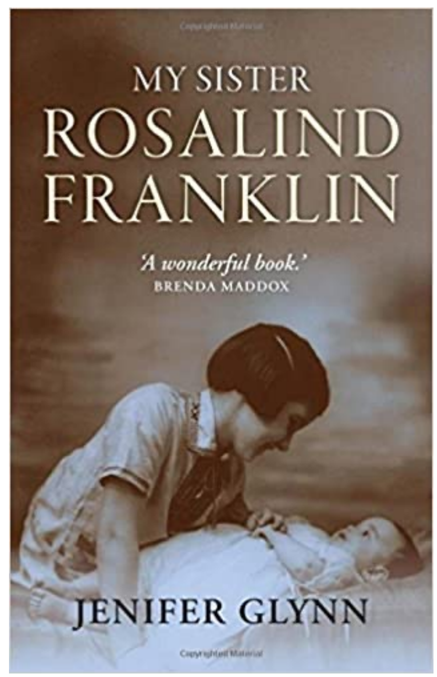

"A fascinating case history . . . Describes the events that led up to one of the great biological discoveries of our time."
—Robert K. Merton, The New York Times Book Review
THE
DOUBLE HELIX
A Personal Account of the Discovery of THE STRUCTURE OF DNA
JAMES D. WATSON
Introduction by
SYLVIA NASAR
Author of A Beautiful Mind

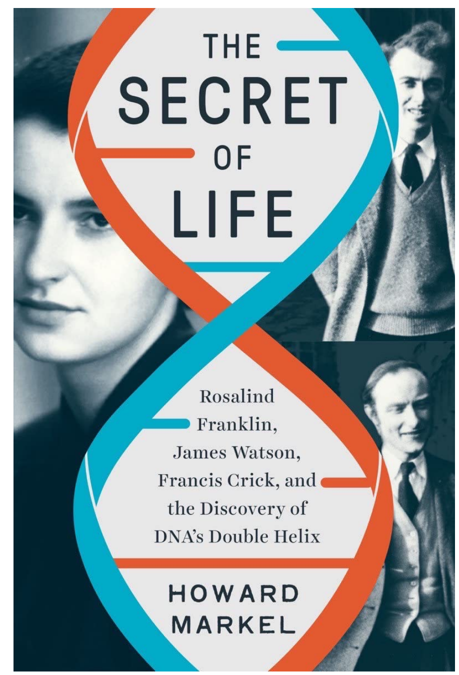

MAURICE WILKINS
The Third Man of the Double Helix
AN AUTOBIOGRAPHY
"No intelligent person ... should fail to read this book"
Arthur C. Clarke
OXFORD


"Full of amusing anecdotes, and a model of popular science writing." – The New Yorker
Francis Crick
What Mad Pursuit
A Personal View of Scientific Discovery
"Written by one of the grand men of science, looking back on a career that has been a smashing success." – George Johnson, New York Times Book Review

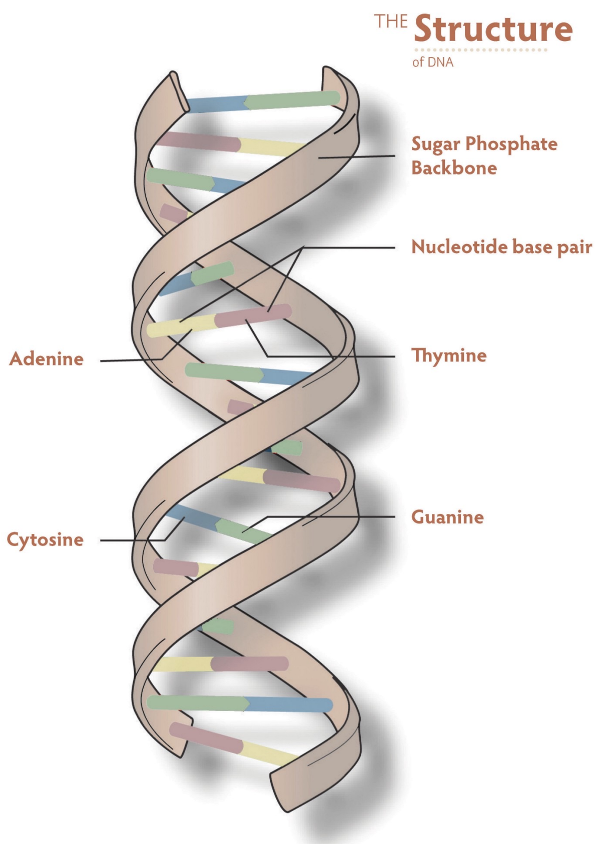

"Lively, absorbing, and evenhanded. . . . What emerges is the complex portrait of a passionate, flawed, courageous woman."
—Washington Post Book World
BRENDA MADDOX
ROSALIND FRANKLIN
THE DARK LADY OF DNA
Los Angeles Times
BOOK Prizes


ROSALIND FRANKLIN AND DNA
ANNE SAYRE
"ANYONE WHO READ THE DOUBLE HELIX OWES IT TO FRANKLIN TO READ HER STORY TOO." –ARTHUR COOPER, NEWSWEEK


MY SISTER
ROSALIND FRANKLIN
'A wonderful book.'
BRENDA MADDOX
JENIFER GLYNN


THE
SECRET
OF
LIFE
Rosalind Franklin, James Watson, Francis Crick, and the Discovery of DNA's Double Helix
HOWARD MARKEL

Casts involved in the structure determination of DNA



E. Chargaff	Columbia Uni
J. Donahue	Caltech, Uni. Southern California
L. Pauling	Caltech
P. Pauling	Cambridge
Lawrence Bragg	Cambridge
J. Watson	Cambridge
F. Crick	Cambridge
John Randal	King's College
M. Wilkins	King's College
R. Franklin	King's College

The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to

Francis H. C. Crick, James D. Watson and Maurice H. F. Wilkins

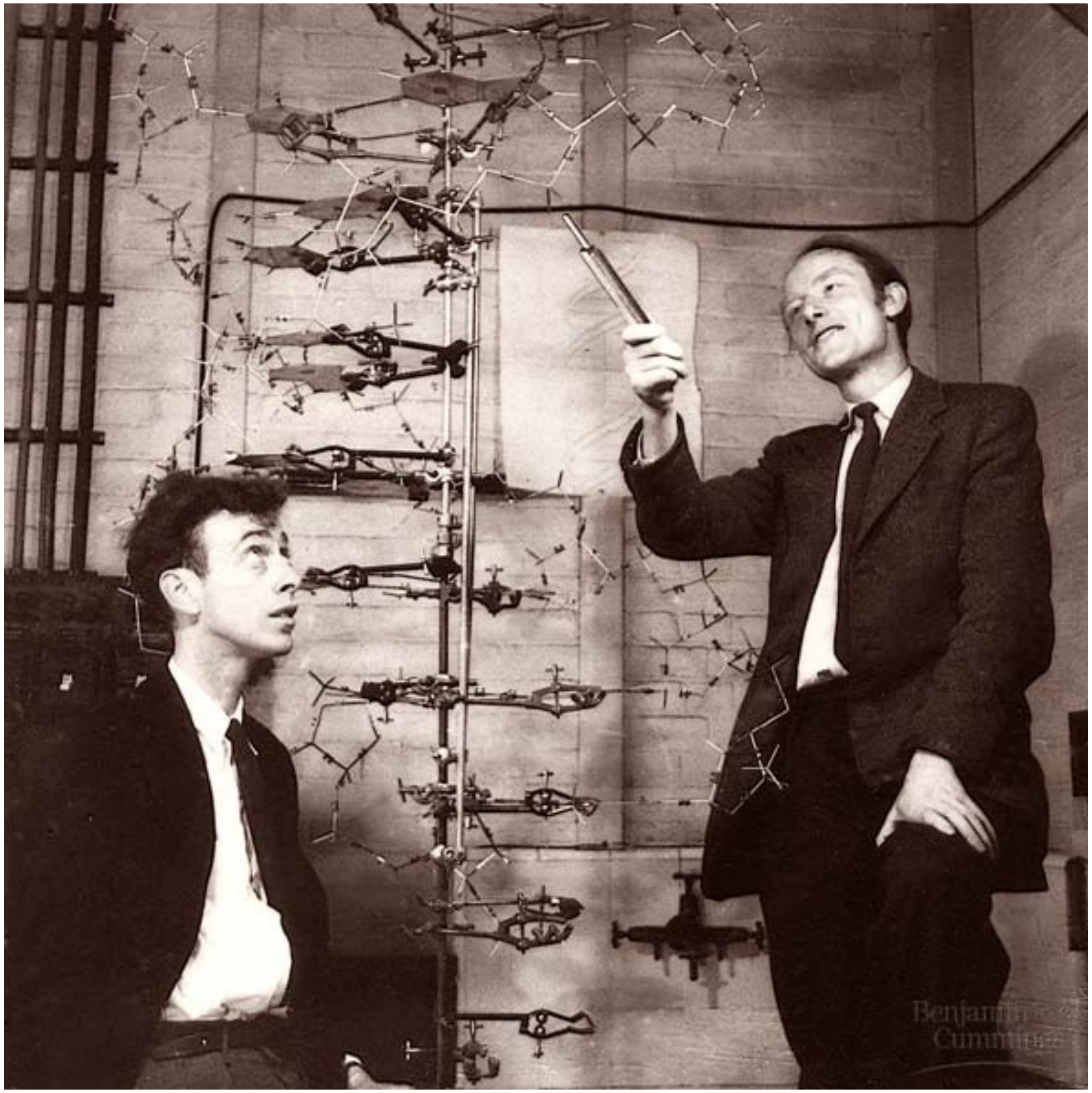
"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material."

Watson, J. D., & Crick, F. H. C.. *Nature* **171**, 737–738, 1953

Wilkins , M. H. F., Stokes, A. R. & Wilson, H. R. *Nature 171*, *738–740, 1953*

Franklin, R. & Gosling, R. G. *Nature* **171**, 740–741; 1953

Watson, Crick and Wilkins



Based on the rules of **Chargaff** and the information from the work of **Rosalind Franklin**, *James Watson* and *Francis Crick,* determined the structure of DNA by making models.

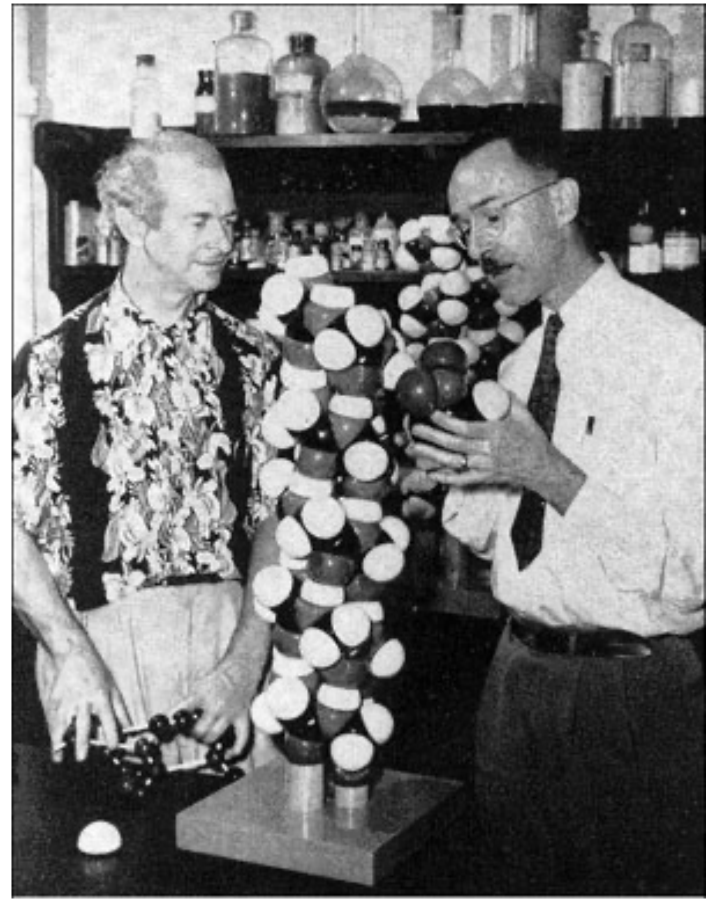
Watson and Crick

James Watson was an American, born in 1928, was only 24 when the discovery was made. He went to University of Chicago at the age of 15.

Francis Crick was born in 1916. He went to London University and trained as a physicist. After the war he changed the direction of his research to molecular biology.

Watson and Crick's Method of Choice:
The Model Building Approach Pioneered by Linus Pauling

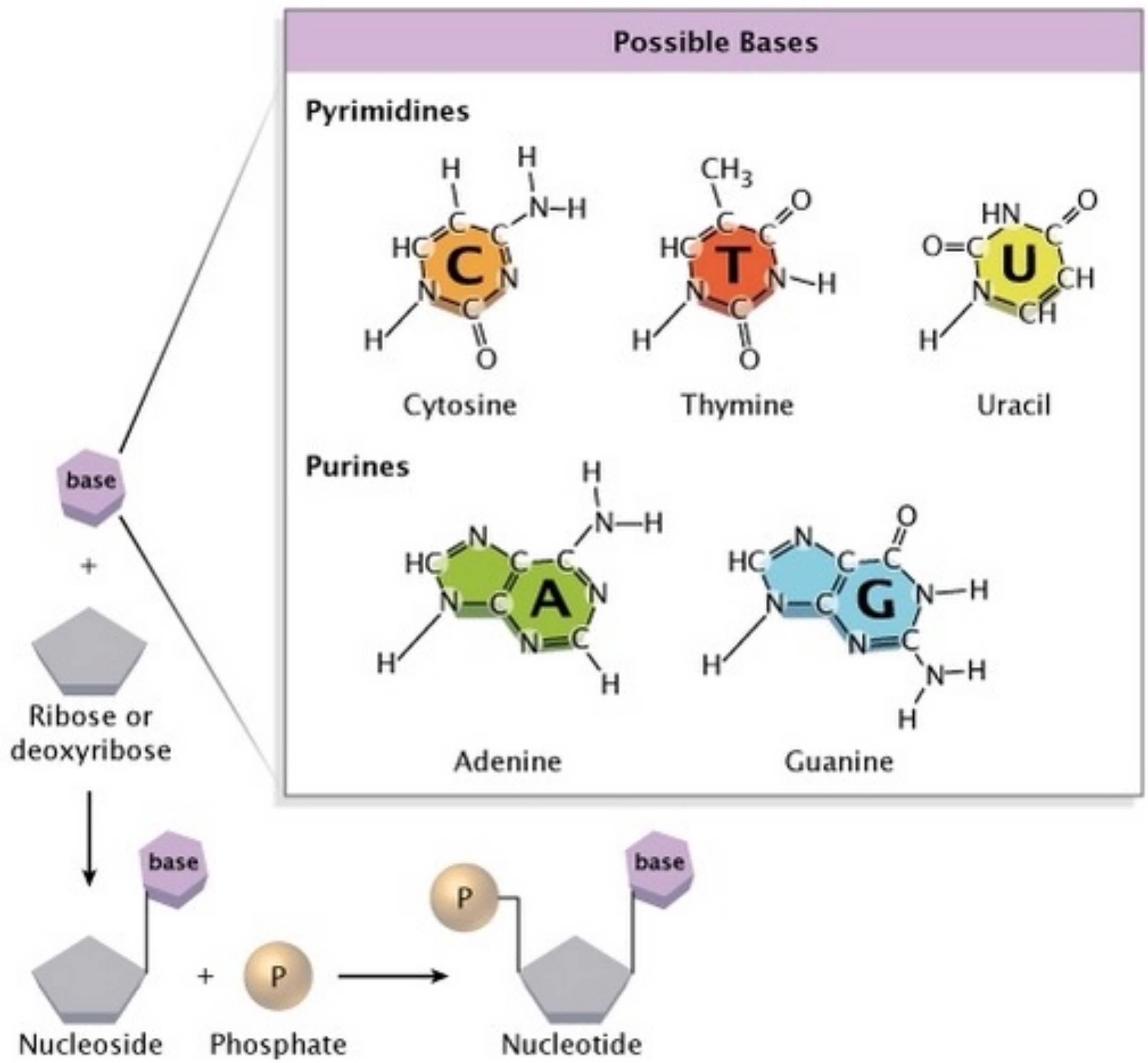
Crick and Watson wanted to work on DNA's structure, but they didn't have the high-quality DNA samples necessary for X-ray diffraction. They approached it building a physical model of how its atoms fit together. This is the approach pioneered by L. Pauling and R. M. Corey for their protein structure solution.



Building a model with space filling CPK model set is similar to building toys with LEGO blocks

Corey, Linus Pauling, and Walter Koltun

DNA is made up of three parts

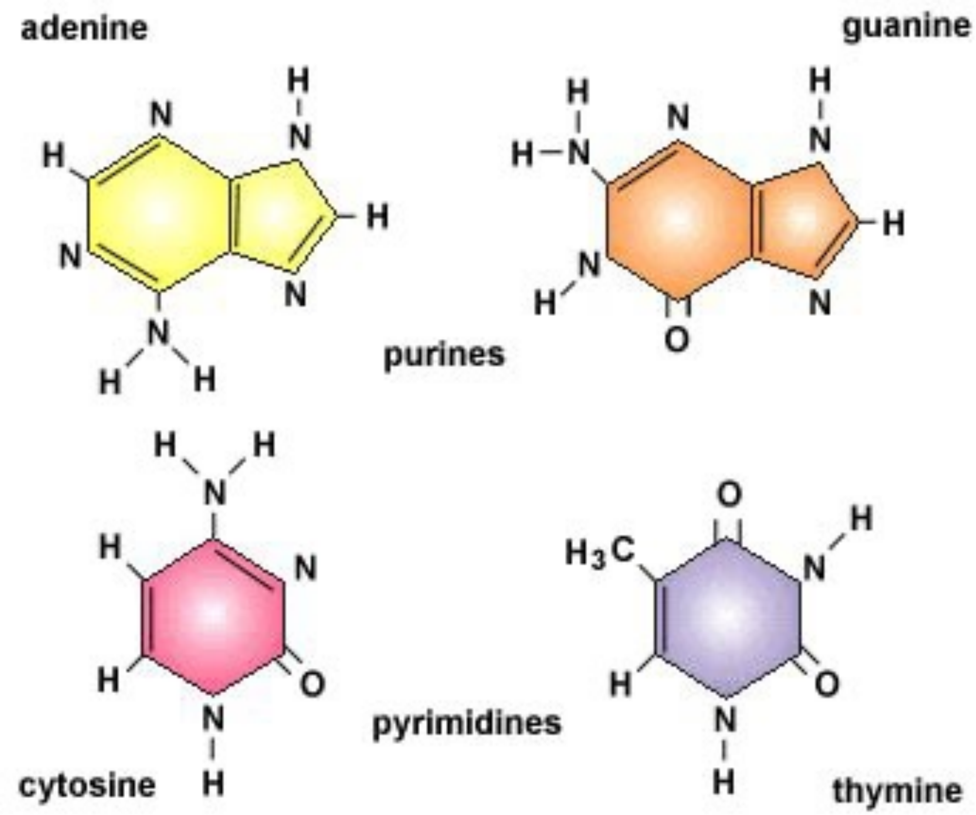


Four DNA bases

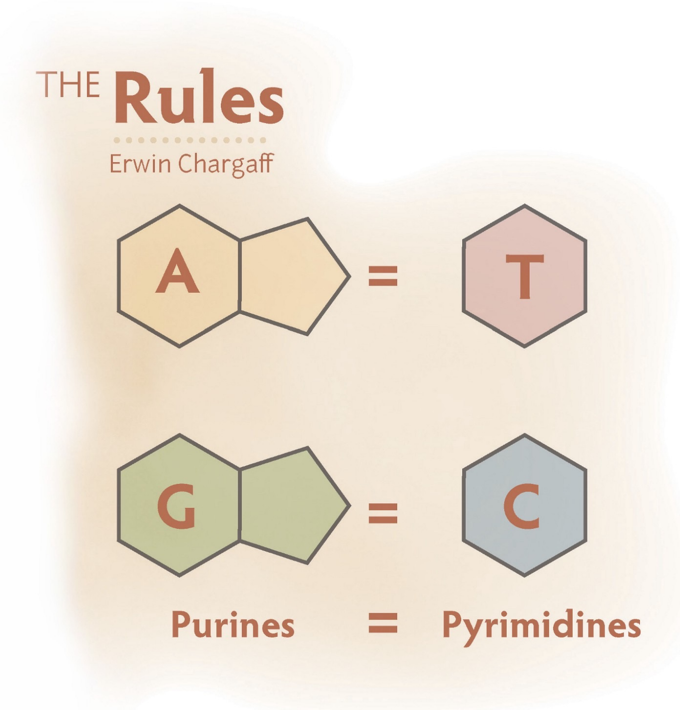
Four kinds of nitrogenous bases:

Purine bases

Pyrimidine bases



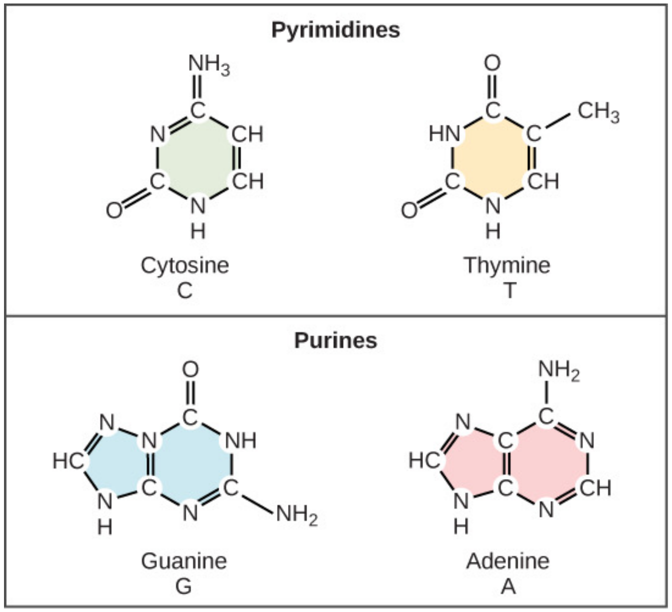
Chargaff's experiments and conclusions

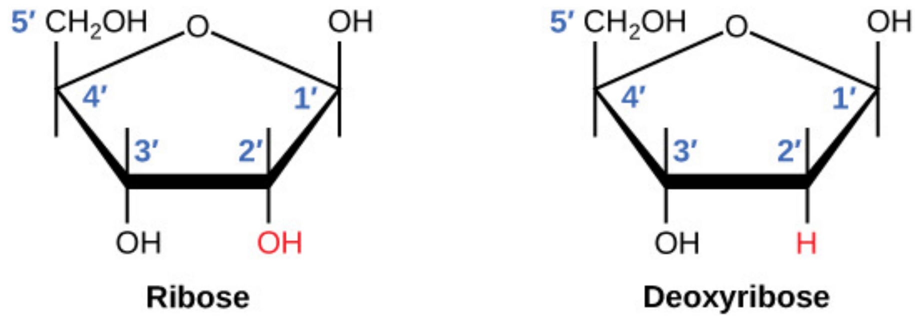


Chargaff's Rule -> A+G=C+T=50%				
Percentage of Various Nucleotides in Genome				
Organisms	A	T	G	C
Humans	30.9	29.4	19.9	19.5
Wheat	27.3	27.1	22.7	22.8
Sarcina lutea	13.4	12.4	37.1	37.1
T 7	26.3	26	23.8	23.9

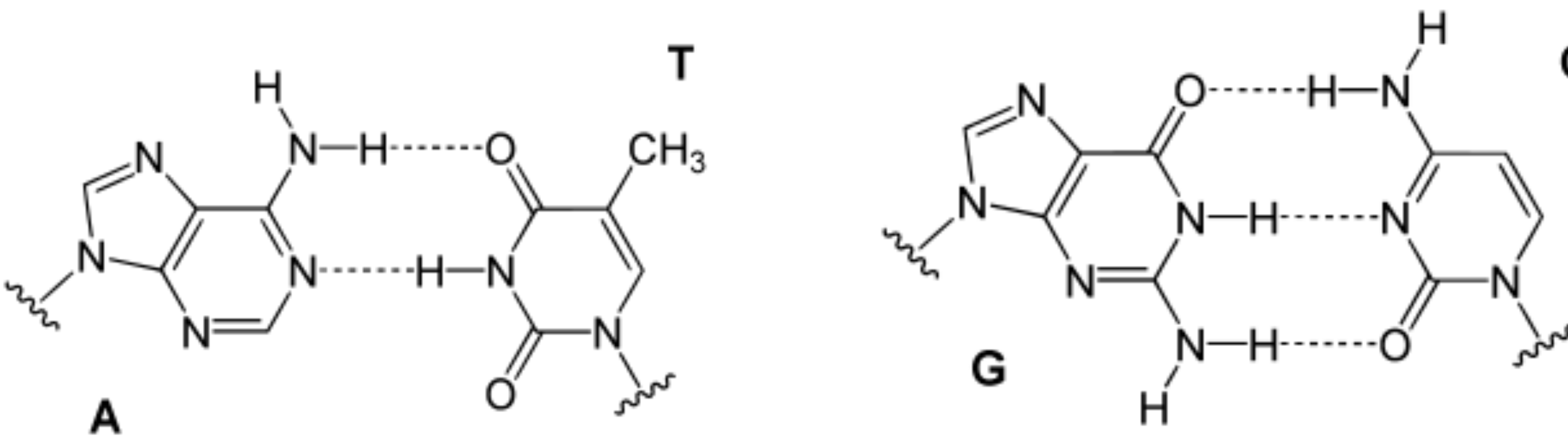
Based on the observations above, two rules can be deduced

1. A + G = C + T
2. The percentages of the nucleotide vary for different species





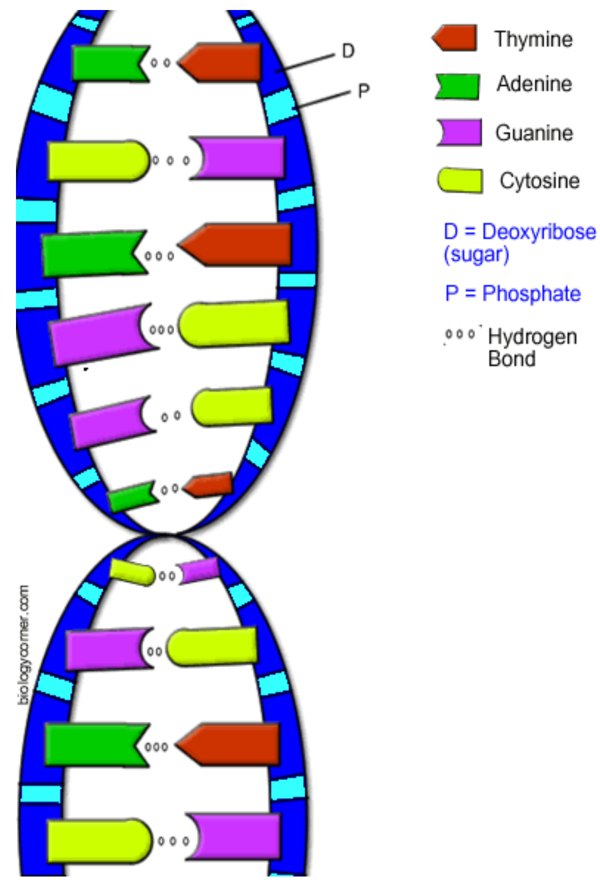
Base-pairing Paradigm



Chargaff's Base-Pair Rule

- Chargaff determined that in any sample of DNA:
  - The <u># of adenines (A) = the # of thymines (T)</u>
  - The <u># of cytosines (C) = the # of guanines (G)</u>

- Thus in DNA, the bases <u>A and T</u> pair together, and <u>C and G</u> pair together.



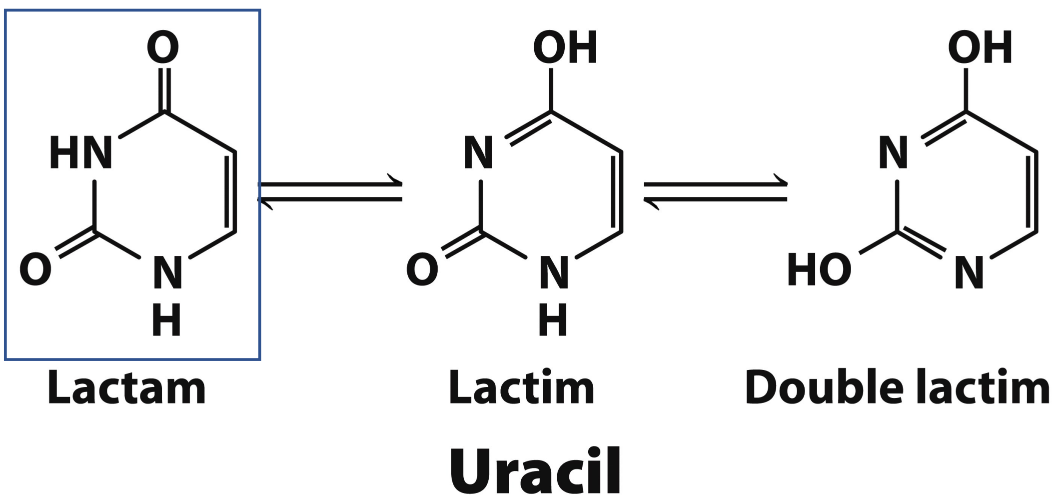
Chargaff's Contribution: Base pairing

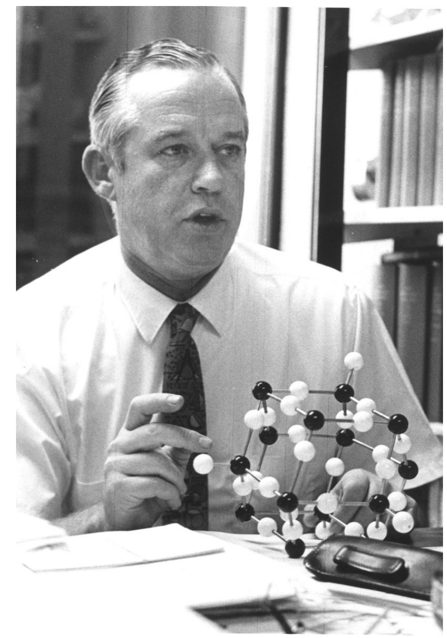
"I told them all I knew. If they had heard before about the pairing rules, they concealed it. But as they did not seem to know much about anything, I was not unduly surprised. I mentioned our early attempts to explain the <u>complementarity</u> relationships by the assumption that, in the nucleic acid chain, adenylic was always next to thymidylic acid and cytidylic next to guanylic acid...I believe that the double-stranded model of DNA came about as a consequence of our conversation."

Chargaff, 1978

"The base composition was an essential clue for finding the structure of DNA, there's no doubt about that. 'We could have come up with the answer, but no one would have believed it." *Watson*

The correct structure of bases revealed by Jerry Donohue, Pauling's student





Before he told them the correct structure, they were using the enol form copied from a book that was wrong.

Linus Pauling to Alexander Todd and The President of Guggenheim Foundation

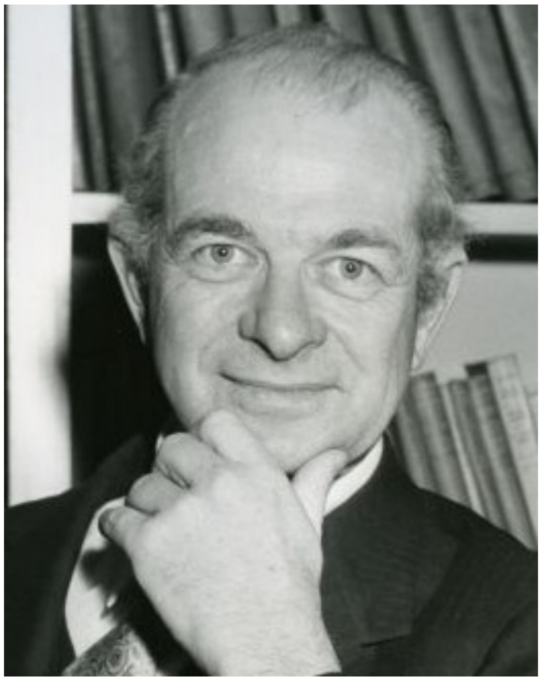
"We have, we believe, discovered the structure of the nucleic acids. I think that it will be about a month before we send off a manuscript describing the structure, but I have practically no doubt about the correctness of the structure that we have discovered ... The structure is really a beautiful one."

Dec 19, 1952

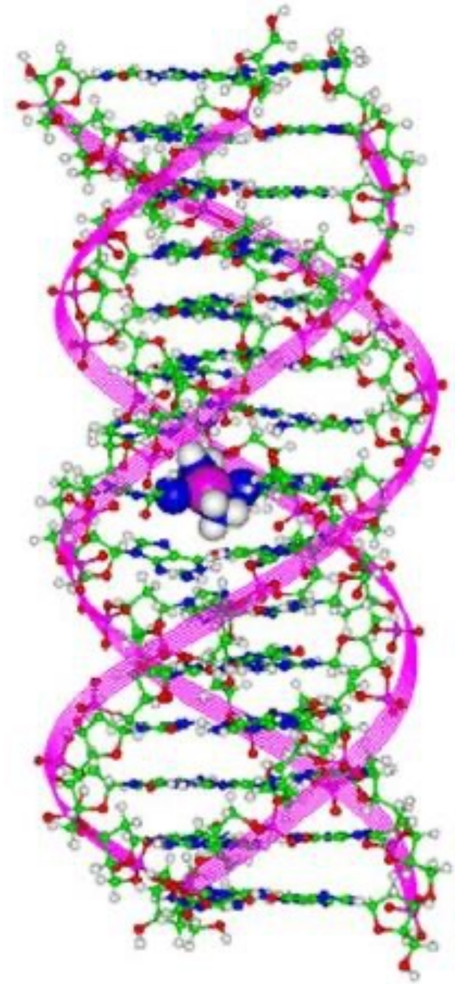
Briliant Blunders, M. Livio, Simon & Schuster, 2013

Pauling's triple helix for DNA

The Great Man's Blunder

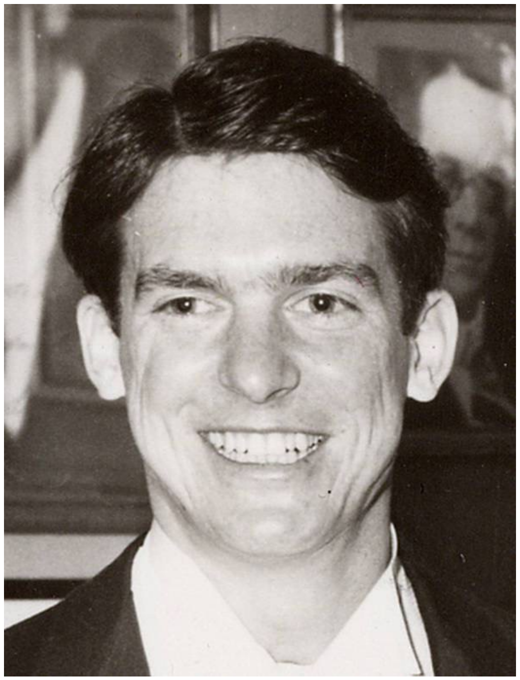


Linus Pauling



L. Pauling and R. M. Cory, "A proposed structure for the nucleic acids."
Proc. Natl. Acad. Sci. 39, 84-97, February **1953**.

Linus Pauling's Role in DNA double helix

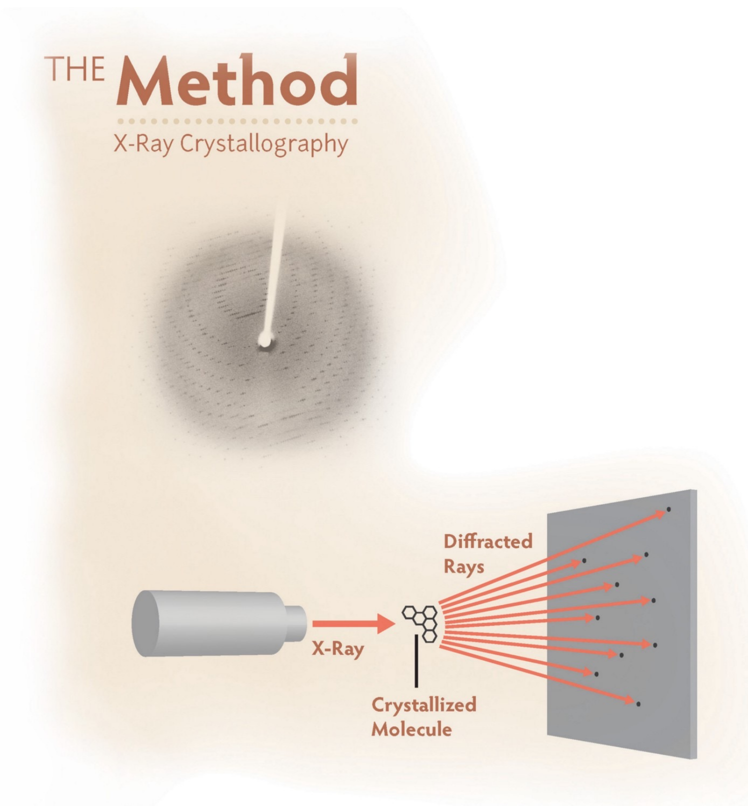


Peter Pauling

- Peter Pauling, before publication, revealed to Watson and Crick that the Pauling-Corey model was a triple helix. This moment was a major turning point for Watson and Crick, who only then realized that they still had a chance to discover the structure before Linus Pauling.

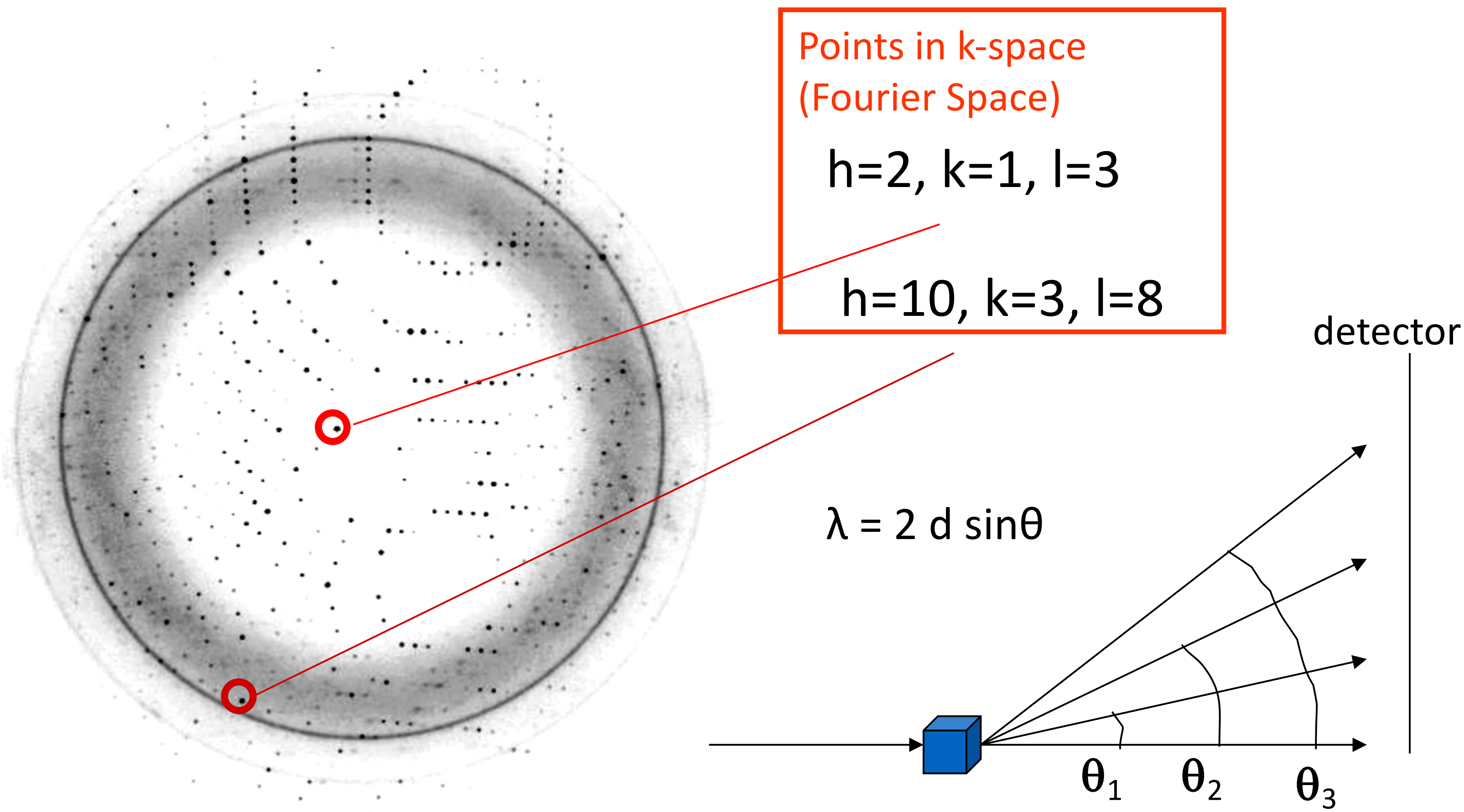
- They did not reveal to Linus Pauling that the structure is wrong based on X-ray diffraction pattern of Rosalind Franklin. They were delighted to find a major flaw in his concept, but, instead of warning him, they basked in his humiliation when the mistake was publicly discovered.

X-ray Diffraction Experiments Played a Crucial Role



Sir Lawrence Bragg, NL 1915
at the age of 25

X-ray differaction: developed by Bragg (father and son)
Each Spot Represents a Unique Set of Bragg Planes



Rosalind Franklin

Trained as a chemist, Franklin created an X-ray photograph that provided evidence of the double-helix structure of DNA molecules. In 1953, Watson, who had been investigating the structure of DNA as well, was shown the image and immediately knew its significance.

Rosalind Franklin

- Born in London, England July 25,1920
- Graduated from Newnham College 1941
- Earned a doctorate in physical chemistry from Cambridge University 1945 (coal chemistry)
- From 1947-1950 Franklin learned the technique of X-ray diffraction in Paris.
- Franklin decided to move back to London in 1951 to work in a laboratory at King's College.
- However, she had a very difficult time when she was there as women didn't have the same rights as men, such as not being allowed in certain parts of the university including faculty lunchroom.

Life in London

During 1951-1953 Rosalind's worked primarily on the DNA project. Took the famous photograph entitled photo 51

Her research partner, Maurice Wilkins, treated her like an assistant, rather than being head of her own project.

Rosalind Franklin used x-ray crystallography to determine that DNA was double stranded, a helix, phosphates were on the outside and three distances, 2.0 nm, 0.34 nm, and 3.4 nm showed up in a pattern over and over again in the diffraction pattern.

She presented her work to colleagues at King's College. James Watson attended the lecture, took notes and informed Francis Crick.

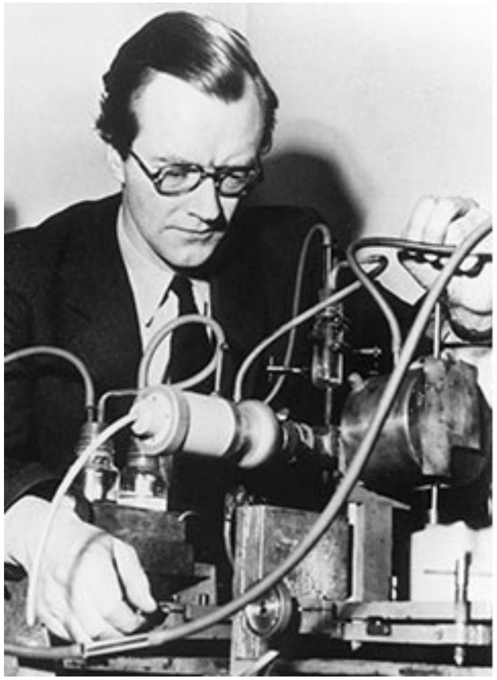
Stop it

Maurice Wilkins wrote to Crick on December 11, 1951
(*Letter discovered in 2010)*

I am afraid the average vote of opinion here [at King's College], most reluctantly and with many regrets, is against your proposal to continue to work on nucleic acids in Cambridge. An argument here is put forward to show that your ideas are derived directly from statements made in a colloquium and this seems to me as convincing as your own argument that your approach is quite out of the blue.

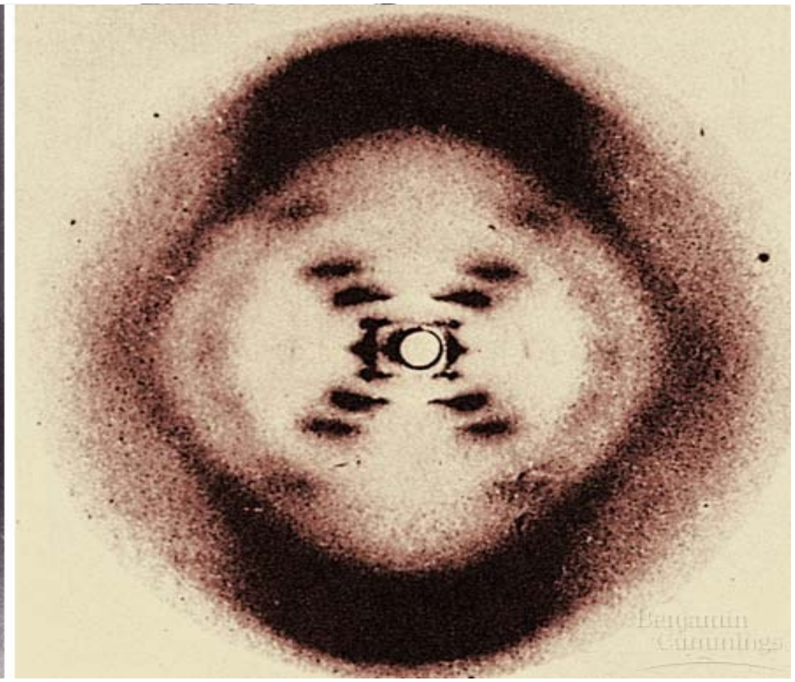
Briliant Blunders, M. Livio, Simon & Schuster, 2013

Work of Rosalind Franklin



Maurice Wilkins

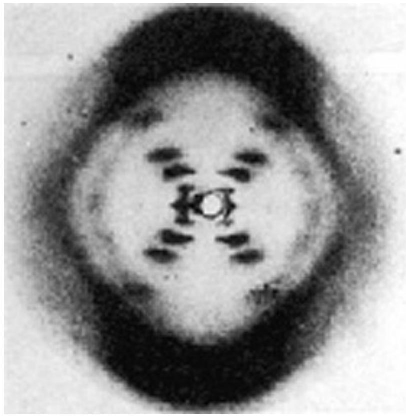
Rosalind Franklin



The famous photo 51

Rosalind Franklin used x-ray crystallography to determine that DNA was double stranded, a helix, phosphates were on the outside and three distances, 2.0 nm, 0.34 nm, and 3.4 nm showed up in a pattern over and over again in the diffraction pattern.

What did Franklin discover and what happened to it?



Wilkins (her research partner) showed Franklin's picture of DNA (which is known as Photo 51) to their colleagues Watson and Crick, in secret, without Franklin knowing!

After a few years of tough fights with Wilkins she was transferred to Birbeck's College with the condition she should not work on DNA. She worked on the structure of viruses. Her colleague Aaron Klug continued her work that led to Nobel Prize.

Died in London, England April 16, 1958, of ovarian cancer (38 yrs).

Wilkins had a tough time dealing with Rosalind Franklin, celebrated her departure

"I think you will be interested to know that our dark lady leaves us next week…I am now reasonably clear of other commitments and have started up a general offensive on Nature's secret strongholds…At least the decks are clear, and we can put all hands to the pumps!"

It won't be long now.
Regards to all
Yours ever
M

Watson-Crick Model for the Structure of Double-helical DNA

A model for the structure of DNA was proposed by Watson and Crick in 1953. Their model was based on a number of pieces of information that were available at the time about the composition of DNA and the x-ray diffraction properties of DNA fibers. Most importantly, x-ray diffraction studies of DNA fibers performed by Rosalind Franklin and Maurice Wilkins showed that DNA molecules are helical and exhibit two periodicities repeating along the length of the fiber--a primary repeat of 3.4 Å and a secondary repeat of 34 Å.

Erwin Chargaff and colleagues had shown through DNA compositional analysis that the number of T residues always equals the number of A residues (A = T), and the number of G residues always equals the number of C residues (G = C).

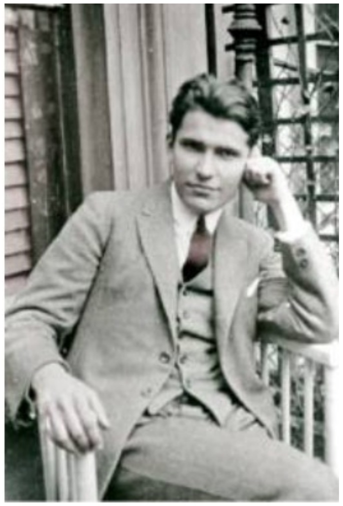
Linus Pauling paid the price

Pauling on Bragg, Kendrew, and Perutz protein structure (*Protein Science*, *2*, 1060-1063, **1993**, reminescence).
(Bragg, L., Kendrew, J. C., and Perutz, M. F., Proc. Roy. Soc., A203, 321 (1950).

Then a paper was published by Bragg, Kendrew, and Perutz, in Cambridge, describing a number of helical structures of polypeptide chains obtained in their search for an alpha-keratin structure. From my point of view, all of these structures were wrong, because they did not involve planarity around the nitrogen atom. I thought that it was likely, however, that in the course of time they would learn enough chemistry to see what peptide group had a planar structure, and would discover the alpha helix, so Professor Corey and I decided to publish a short description of the alpha helix and the gamma helix.

Watson and Crick on Pauling's DNA structure (*Nature* **171**, 737, 1953)
(Pauling, J,., and Corey, R. B. Proc. U.S. Nat. Acad. Sci., 39, 84 (1953).

A structure for nucleic acid has already been proposed by Pauling and Corey. Their model consists of three intertwined chains, with the phosphates near the fiber axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons --.



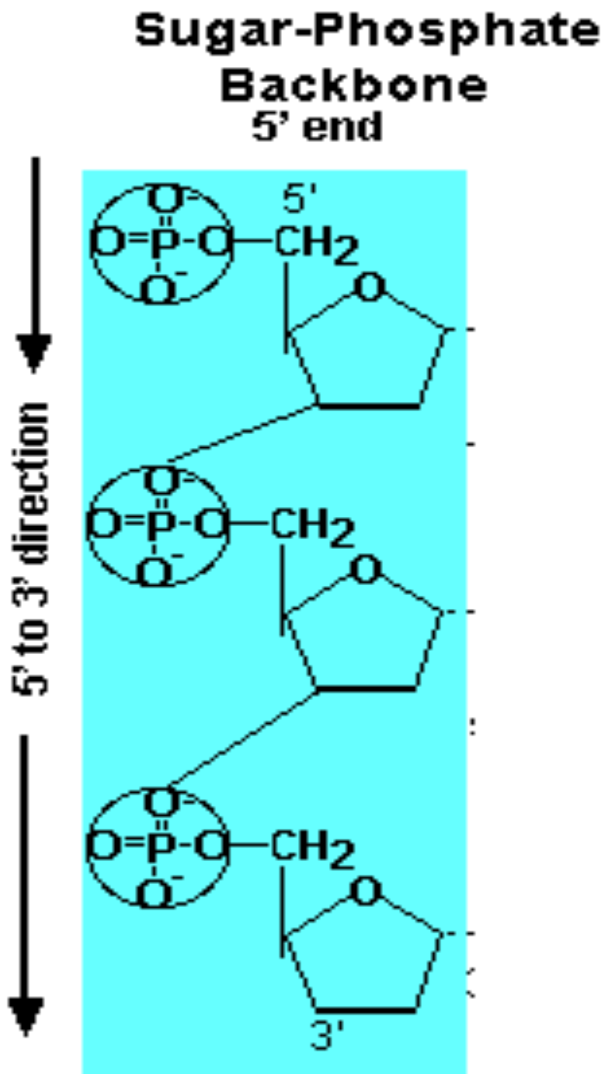
Chargaff Snubbed, Franklin ignored

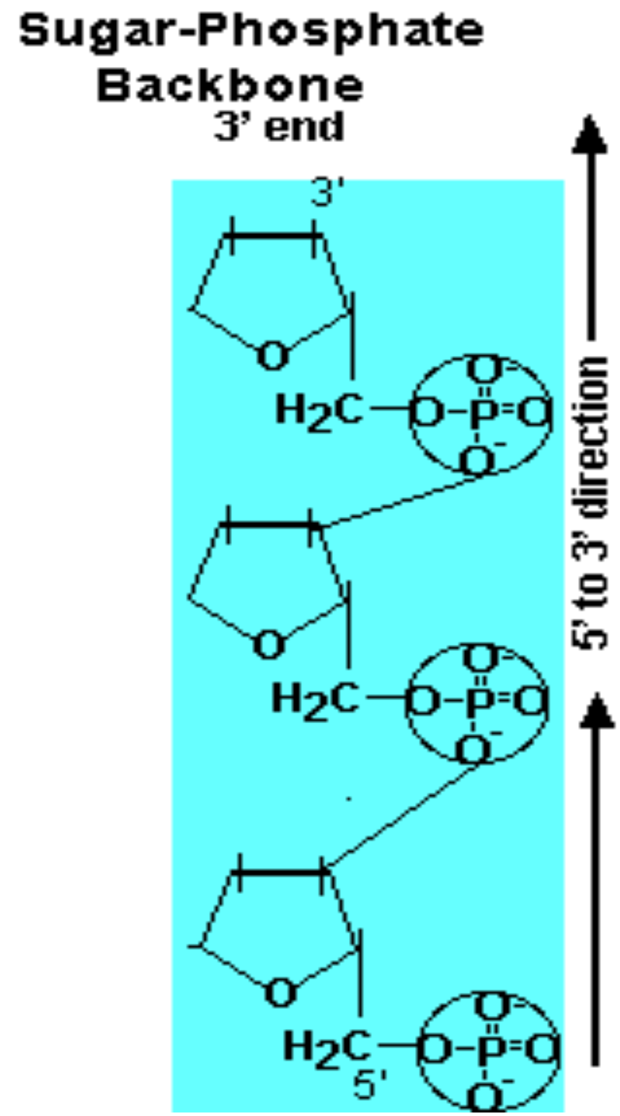
"The base composition was an essential clue for finding the structure of DNA, there's no doubt about that," Dr. Watson said in an interview. "We could have come up with the answer, but no one would have believed it."

Chargaff is quoted as saying, “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..”

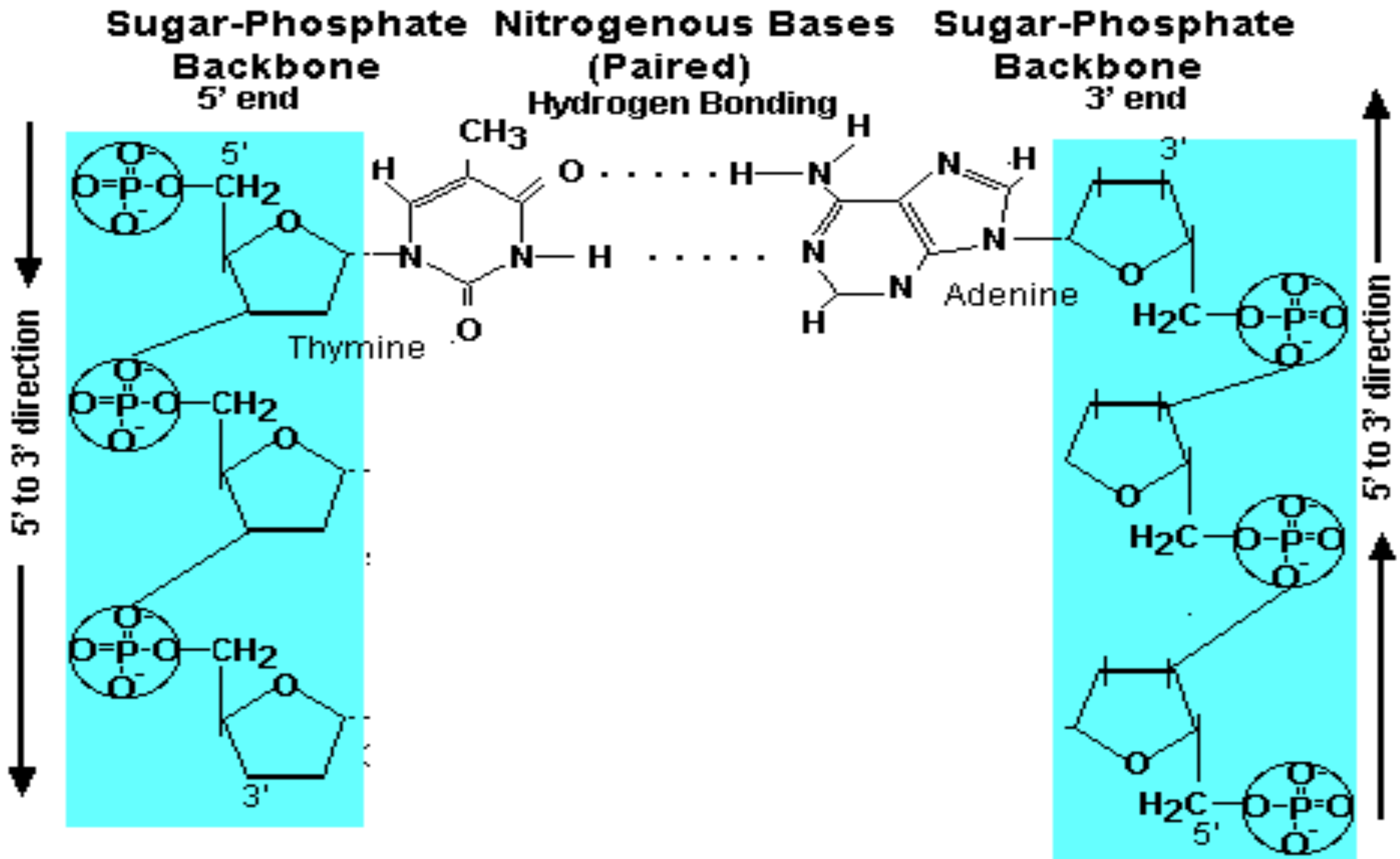
- Chargaff felt there had been an injustice done when he did not receive the Nobel Prize in 1962 along with Watson, Crick and Wilkins.
- Wilkins’ contribution to the structure of DNA was to show James Watson the work of Rosalind Franklin without her permission.
- Franklin did not share the Nobel Prize as she passed away from ovarian cancer in 1958 and posthumous nominations are forbidden.

Sides of the Ladder

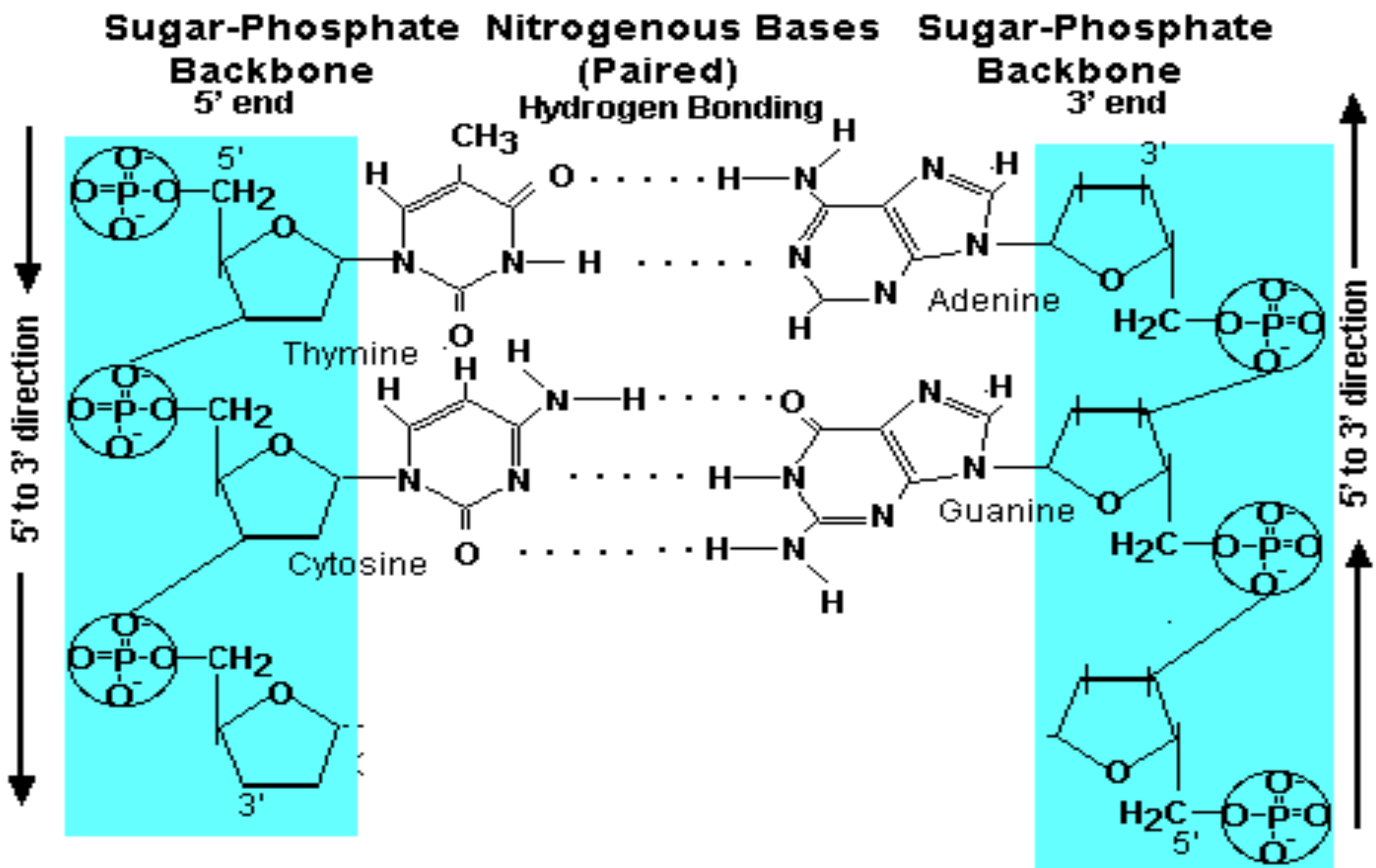




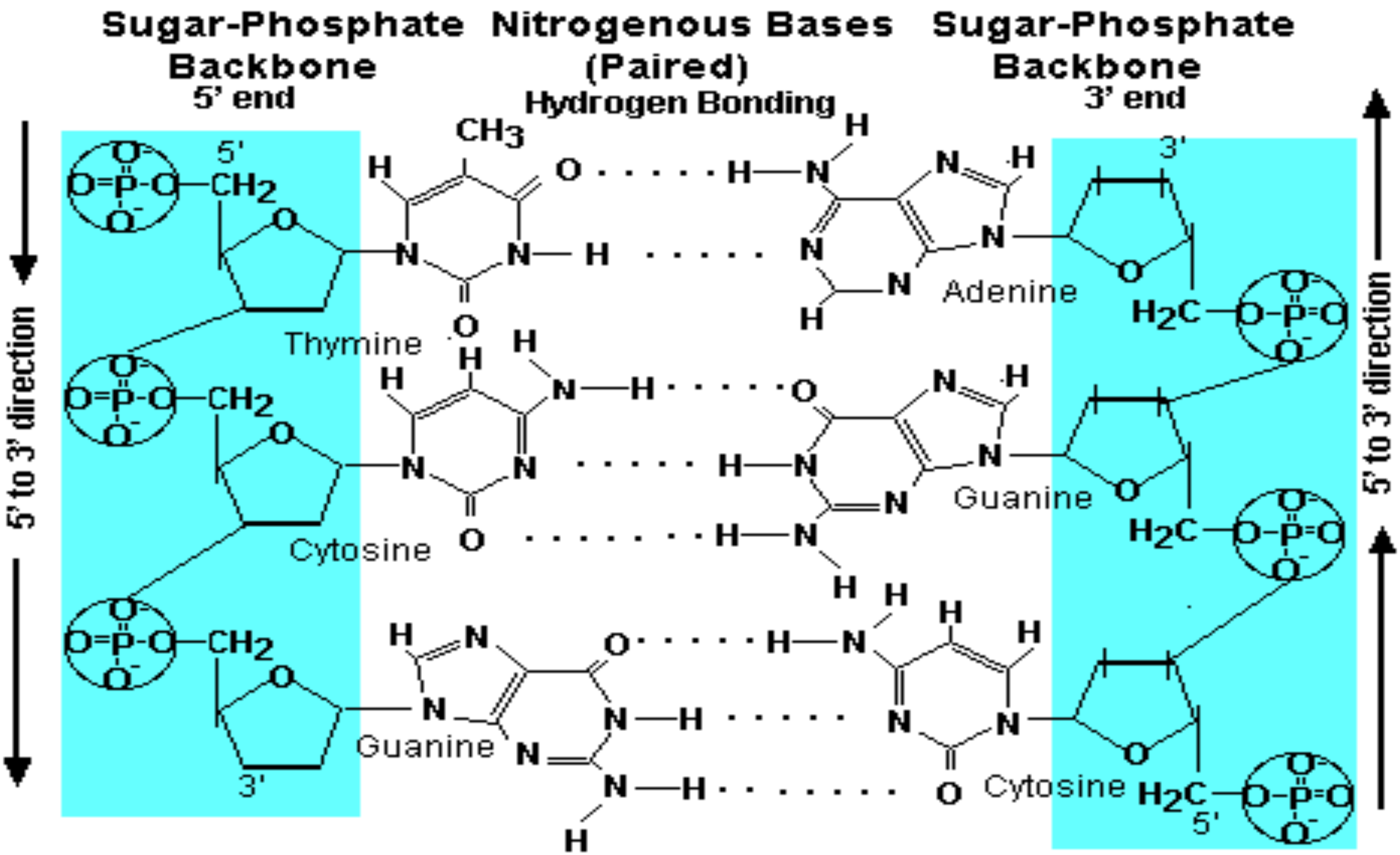
Hydrogen Bonding and Nitrogenous Bases



Hydrogen Bonding and Nitrogenous Bases



Hydrogen Bonding and Nitrogenous Bases



Many people were involved, very few got the credit