

Structure & History of DNA



Chelsea Malayny Chantel Rice Ben Ruckpaul James Specker Alexander Thibodeau

The History and Structure of DNA

- Background
- What went into the Discovery
- The Paper
- Implications

Background

- In 1953, James Watson and Francis Crick announced their discovery of double helix, twisted later structure of deoxyribonucleic acid (DNA)
- Milestone in molecular biology
- A large amount of groundwork led to this discovery

No. 4356 April 25, 1953

NATURE

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹Young, F. B., Gerrard, H., and Jevons, W., Phil. Mag., 40, 149 (1920).

² Longuet-Higgins, M. S., Mon. Not. Roy. Astro. Soc., Geophys. Supp., 5, 285 (1949).

 Von Arx, W. S., Woods Hole Papers in Phys. Ocear.og. Meteor., 11 (3) (1950).
 *Ekman, V. W., Arkiv. Mat. Astron. Fysik. (Stockholm), 2 (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

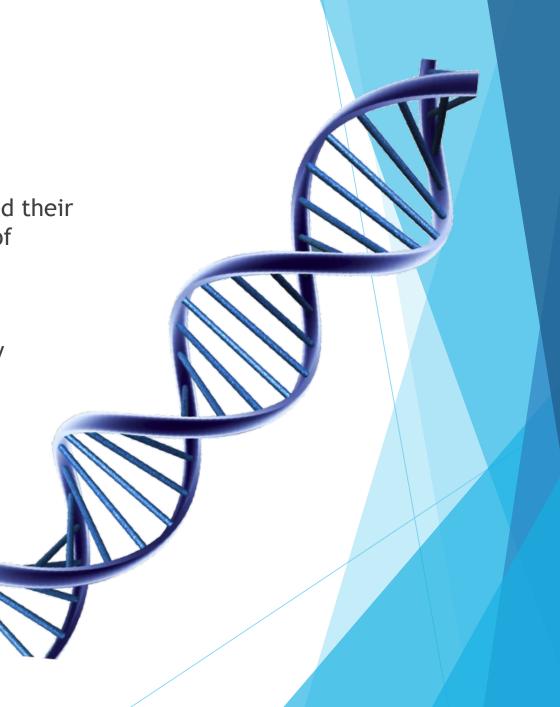
WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

is a residue on each chain every $3\cdot 4$ A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phospharus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

737

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to till so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows : purine position



Leading up to the Discovery....

- 1868: DNA "Saga" began when Swiss biochemist Miescher isolated Nuclein
- 1910: Levene Tetranucleotide Hypothesis
- 1928: Griffith Transforming Principle
- 1944: Avery, MacLeod & McCarty DNA is Transforming Principle
- 1950: Chargaff's Rules A=T, G=C
- 1952: Hershey & Chase Blender Experiment
- 1953: Watson & Crick A Structure for DNA

1944: Avery, MacLeod & McCarty Paper Published



STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

INDUCTION OF TRANSFORMATION BY A DESOXYRIBONUCLEIC ACID FRACTION ISOLATED FROM PNEUMOCOCCUS TYPE III

> By OSWALD T. AVERY, M.D., COLIN M. MACLEOD, M.D., AND MACLYN McCARTY,* M.D.

> (From the Hospital of The Rockefeller Institute for Medical Research)

PLATE 1

(Received for publication, November 1, 1943)

Biologists have long attempted by chemical means to induce in higher organisms predictable and specific changes which thereafter could be transmitted in series as hereditary characters. Among microörganisms the most striking example of inheritable and specific alterations in cell structure and function that can be experimentally induced and are reproducible under well

DNA is the transforming principle!!!!

The Race to Discover DNA's Structure



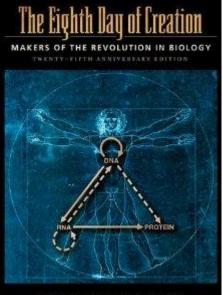
The 1950's saw 3 separate groups working intensively on the DNA structure:

- Maurice Wilkins and Rosalind Franklin at King's College in London
- Linus Pauling, an American Chemist at the California Institute of Technology
- James Watson and Francis Crick at Cambridge

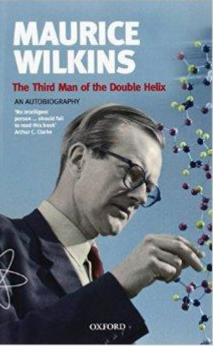


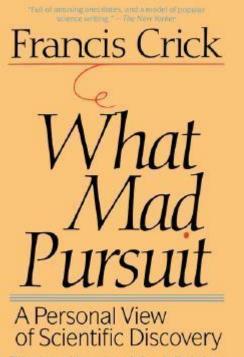
"The Secret of Life" (2003)

If you have a lot of time on your hands...



HORACE FREELAND JUDSON





Willeen by one of the grand memori science, hooking back on a antier that has been a smushing success." - George Johnson, Now York Tures Book Bouley

DOUBLE HELIX

JAMES D. WATSON



EDITED BY ALEXANDER GANN MID JAN WITKOWSKI

- Maurice Wilkins
 - Initially a nuclear physicist, became disillusioned with his subject when it was applied to the creation of the atomic bomb; then turned to biophysics and molecular biology
 - 1950: X-ray diffraction work on ram sperm and DNA from calf thymus obtained from Singer
 - With grad student Raymond Gosling produced x-ray photographs of DNA showing crystalline structure
 - These photographs, shown at a conference in Naples, sparked James Watson's interest in DNA



"We realized that if DNA was the gene material, then we had just shown that genes could crystalize..."

-Raymond Gosling



- Late 1950: Randall arranged for a three-year research fellowship that would fund Rosalind Franklin in his laboratory
 - Needed expertise in interpreting x-ray images
- Rosalind Franklin
 - English physical chemist and x-ray crystallographer expert
 - Previously worked on x-ray diffraction patterns in coal and carbon fiber technology in Paris

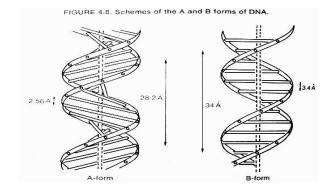


- **1951:** Franklin arrives
 - Miscommunication with regards to their roles in the DNA research lead to tension amongst Wilkins and Franklin
 - Many think this opened the door to Watson and Crick
 - Franklin was given Gosling as a grad student as well as Singers DNA
 - Wilkins was left with Chargaff's DNA sample which was of poorer quality



Rosalind Franklin

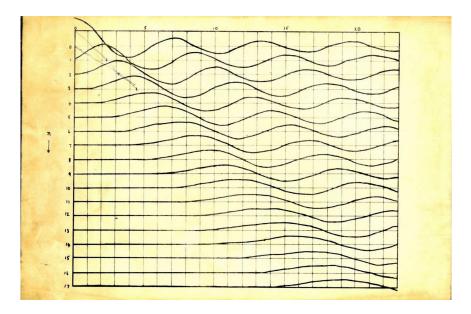
- In her first few months at King's began taking the most high quality photos of DNA ever documented
- Discovered 2 forms of DNA: A form (dehydrated) and B form (hydrated)
- Focused on the crystalline "A" form while Wilkins was interested in "B" form, as it was the biological form
- Opposed idea of model building





November 1951: Alec Stokes solved basic mathematics of helical diffraction theory and proposed Wilkin's x-ray diffraction data indicates a helical structure of DNA

- But was it two strands? Or 3?
- Stimulated Watson and Crick to build 1st DNA model



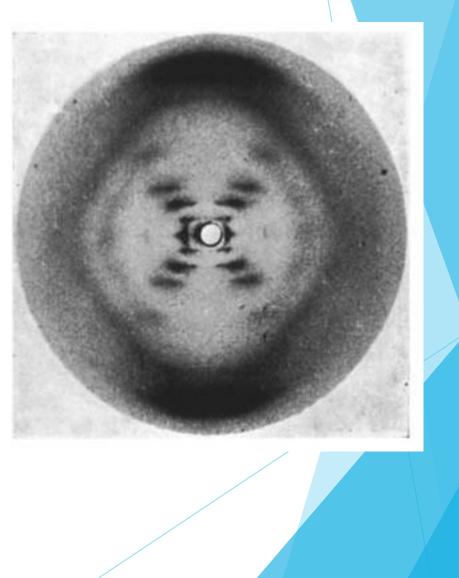


Photograph 51

- Taken by Raymond Gosling in March 1952 under Franklin's instruction
- Franklin instructed Gosling to give photo to Wilkins
- In 1953 James Watson visited King's College and was shown this image by Wilkins
- Image pointed to a helical structure of B-form of DNA

"The instant I saw the picture, my mouth fell open and my heart began to race"

- James Watson, A Double Helix



Controversies....

- If Gosling took the photo under Franklin's instruction (his superior), is it his property/discovery? Or hers?
- Was it wrong of Wilkins to show Watson?
- Also note timeline: Photo 51 taken more than <u>a year</u> prior to Watson seeing it



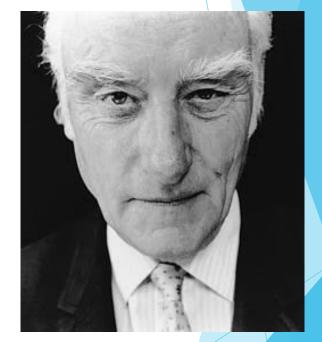
Meanwhile in Cambridge....

- Watson and Crick had the same dream, they wanted to find the structure of DNA too.
- <u>James Watson</u> was a Molecular biologist with expertise in phage genetics.
- Became fascinated with molecular structure of DNA after hearing Wilkins talk at a Naples conference about DNA and x-ray crystallography photographs of DNA



Francis Crick

- Physicist and mathematician
- Was initially working on a dissertation on the X-ray crystallography of hemoglobin 1949-1950 when Watson arrived in search of a colleague to work on finding the structure of DNA



Watson & Crick: A Different Approach

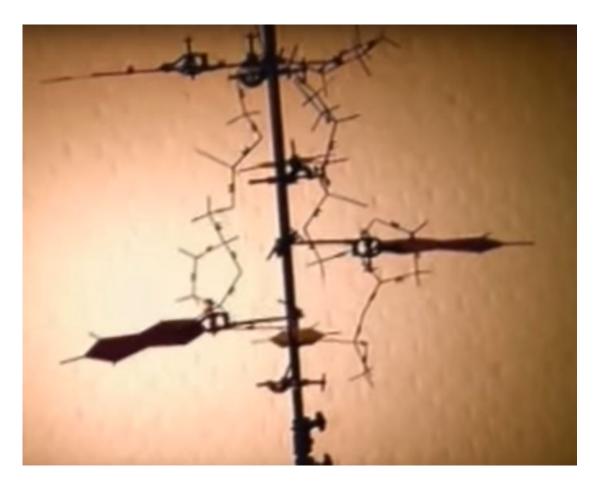
• Unlike Franklin and Wilkins who favored data collection, measureable results and interpretation, Watson and Crick utilized the model building approach.





They thought that by looking at DNA's four ingredients and how they were rearranged they could figure out what DNA's function was so they begun to model build.

When you fail once, try again...

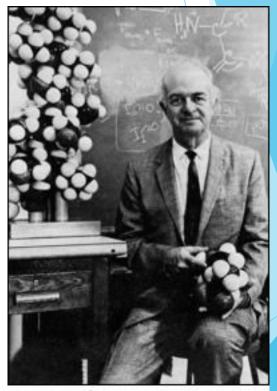


- Nov 1951 Rosalind revealed her latest x-ray data to the department, and one outsider (Watson)
- In 1951 long before Pauling released his paper proposing a structure for DNA, Watson and Crick built a model
- Model they had built was announced to King's College.
- It was a failure



Linus Pauling 3rd player in the RACE!

- American chemist, biochemist, peace activist
- Contributions to science include discovery of alpha helix and beta sheet structure of proteins, quantum chemistry resonance work and the discovery of sickle cell anemia as a molecular disease
- "The Nature of the Chemical Bond"
- Considered to be one of the 20 greatest scientists of all time



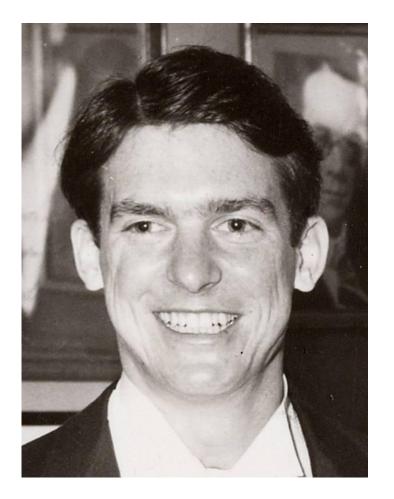
Linus Pauling

Speculation

- Politics had unpleasant consequences for him though, during April 1952 he was suppose to travel to London but was refused a passport.
- Speculation..
- Wasn't until the end of 1952 that Pauling took a serious stab at solving the structure of DNA using the model building approach



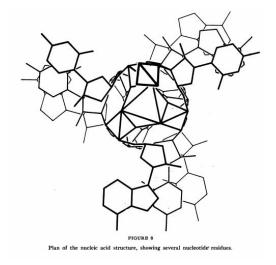
Peter Pauling



• Put the fear of god in Watson and Crick, when he told them his dad Linus Pauling was working on the DNA structure too.

Linus Pauling

- In early 1953, announced that he had discovered the structure of DNA
- Proposed a 3-chain helix with a sugar phosphate backbone core and nucleic acid bases facing outward



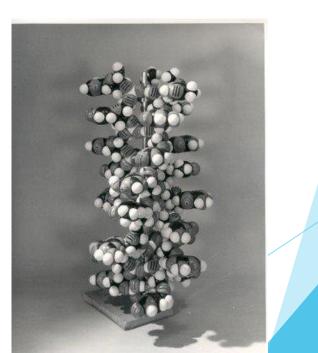
would be attached to one of the two harm organ nature, and presumably add the introduced in therefore the integration of the i



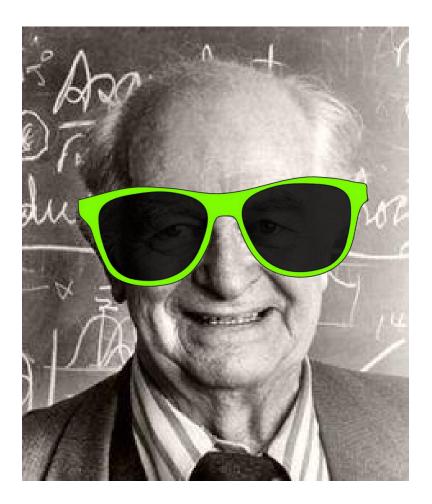
Perspective drawing of a portion of the nucleic acid structure, showing the phosphate etrahedra near the axis of the molecule, the *β*-n-hlodramose rings connecting the tetraoleria into chains, and the attached pointies and sprinnible rings (represented as partice ings in this drawing). The molecule is inverted with respect to the coordinates given table 1.

and a group in the layer above or below it. Accordingly we assume th hydrogen bonds are formed between the oxygen atoms of the phospha groups in the same basal plane, along outer edges of the octahedron foure 1.

The maximum distance between the oxygen atoms 3' and 5' of a rib furanose or deoxyribofuranose residue permitted by the accepted structur parameters (C-C = 1.54 Å, C-O = 2.43 Å, bond angles tetrahedral, wi the minimum distortion required by the five-membered ring, one atom



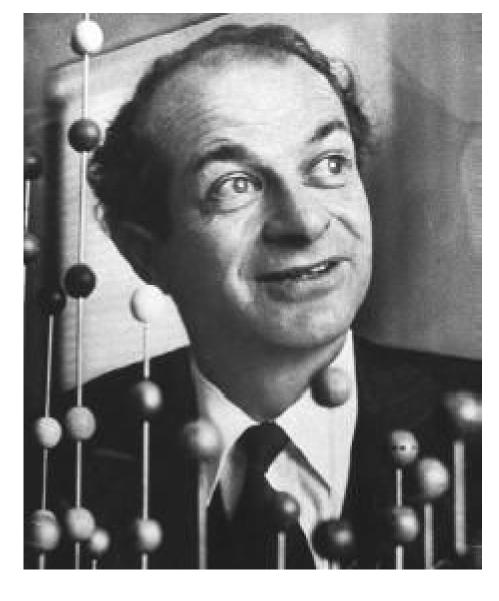
Linus Pauling





- Nobel Prize in Chemistry (1954)
- Nobel Peace Prize (1962)

SNAG



Linus Pauling = Based God

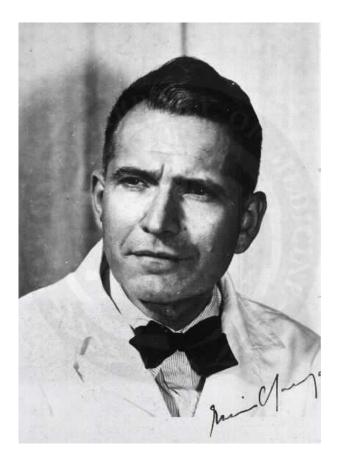
Right back to Work

- Watson and Crick were bubbling at the fact that they had another chance to find out the structure of DNA
- Photograph of the double helix was shown to Watson by Wilkins
- Spring 1953 Watson and Crick was given official orders to work structure of DNA again
- They needed more information, they needed to figure out how the four components of DNA went together.Erwin Chargaff was the key.



Chargaff

A=T G=C



- Erwin Chargaff was an Australian chemist
- Pioneered the paper chromatography of nucleic acids, using this to determine how much of each of the component nucleotides was contained in a DNA sample. He rapidly demolished Levene's tetranucleotide hypothesis to discover his rule on ratios

Watson and Crick Probe Chargaff for Information

- They saw Chargaff's rule to be the first clue in understanding how DNA came together
- Chargaff never meant to help Watson and Crick, despite his dislike for them, he still explained his rules to them
- Although Chargaff successfully discovered that the nucleotide bases were equimolar, he failed to realize the that this meant they were likely bonded



What went into the model

- Watson and Crick's scale model came off of the ideas:
 - The laws of chemistry should be obeyed
 - The polynucleotide must be coiled in a way so that it's atoms would not be placed too close together
 - Take into account the results of other investigations into the structure of DNA
 - Account for Chargaff's discoveries of equimolarity between the nucleotides; A=T & C=G
 - Respect the X-ray Diffraction Pattern provided
 - Photograph 51 provided from Franklin & Wilkins showed DNA as a helix
 - Calculations were done based on this picture to reveal the helix's two periodicities of 0.34 nm and 3.4 nm

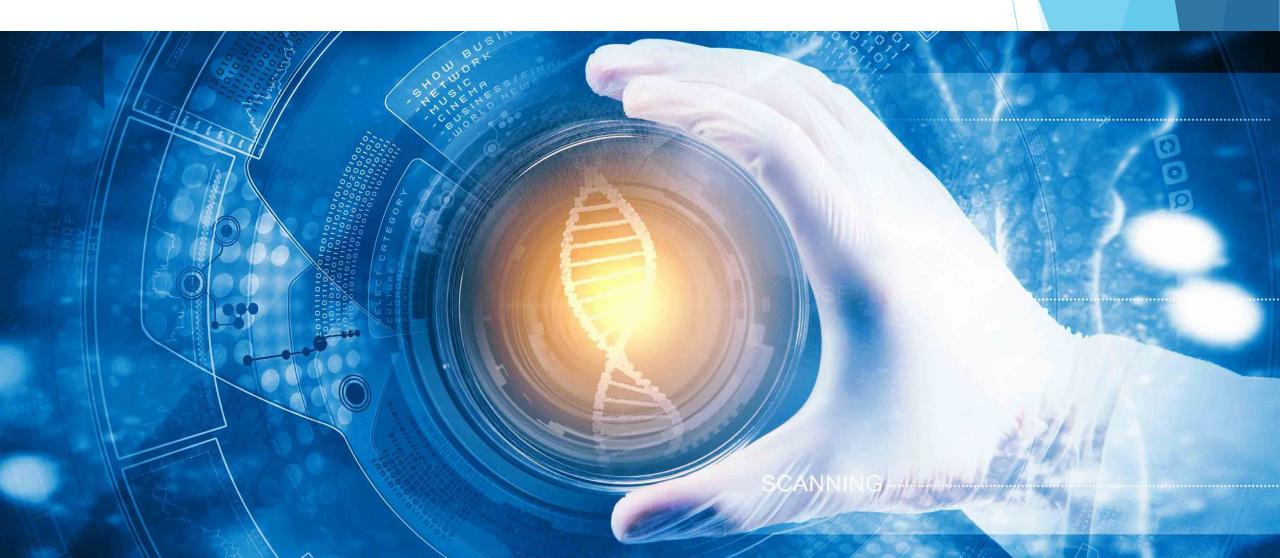


Model Building with Watson & Crick

- Watson realized while trying to figure out the DNA structure that:
 - The purine adenine, a fused double ring, could form two hydrogen bonds with the pyrimidine thymine, a single ring.
 - Guanine and Cytosine made Hydrogen bonds the same way
 - These pairings could not be switched
- Watson Noticed:
 - The hydrogen bonds were the correct length and were straight lines
 - N H - O or N - H N
- Crick pointed out the way the bases in these pairs would attach to their sugars meant that the two backbones ran in opposite directions

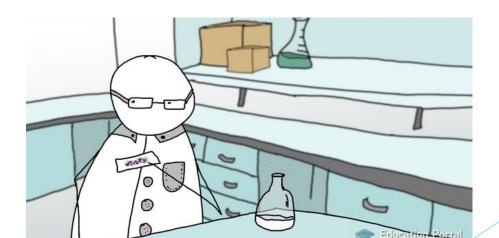


The DNA model was within reach!



Main hurdle to overcome!

- The main difficulty turned out to be the determination of the amount of polynucleotides present in an individual model
- This could be estimated from the density of DNA in one fiber
- EXCEPT, earlier reports did not agree...
- Some had suggested 3 polynucleotides, and others 2.
- Basing their decision on the previous 3 stranded helix suggested by Pauling that had failed.
- Watson and Crick decided to based their model off of 2 polynucleotides instead



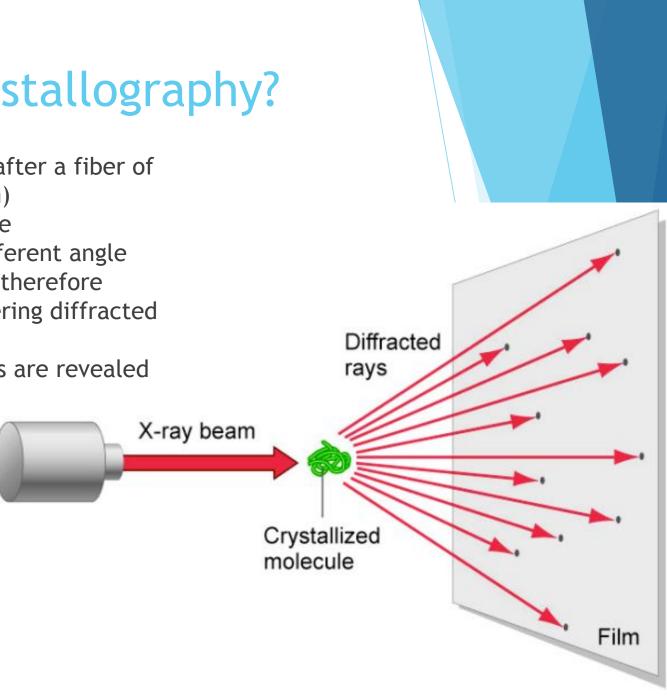
Decision of a Lifetime

- By deciding on 2 polynucleotides instead of 3 they were able to determine the following:
 - The sugar-phosphate backbone would need to be located on the outside of the molecule
 - Accounting for the spacing within their model
 - That the helix must contain 2 strands that were:
 - Antiparallel
 - Right-handed helixr

be careful. one bad decision can have a lifetime of consequences.

What is X-ray Crystallography?

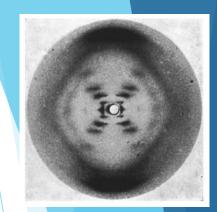
- An X-ray diffraction pattern is obtained after a fiber of DNA is bombarded with X-rays (0.1-10nm)
- Some rays pass through the DNA molecule
- Some are diffracted and emerge at a different angle
- A fiber consists of many DNA molecules, therefore resulting in overlapping circles of interfering diffracted waves
- Using photographic film spots and smears are revealed giving a X-ray diffraction pattern
- They had a hunch :)



Collaboration of Picture 51

- X-ray Diffraction data enabled the devious duo to understand the dimensions of the helix:
 - The periodicity of 0.34 nm indicated the spacing between individual base pairs within the helix
 - The periodicity of 3.4 nm indicated the distance needed to complete a turn of the helix
 - Indicating the number of turns in a helix to be:

• Watson also noted that if this was true then the rotation from one nucleotide to the next must be 36°.

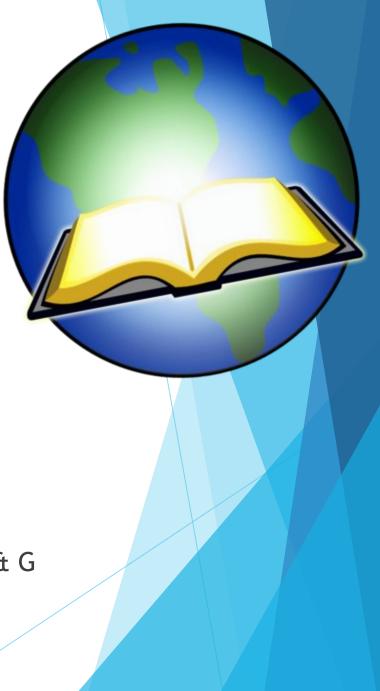


Shoutout to Franklin & Wilkins

From The winners, Watson & Crick

Chargaff's Enlightening Visit

- After Chargaff visited the two in the summer of 1952
- Watson and Crick were enlightened by Chargaff's discoveries
- Determined to incorporate it into their model they had realized:
 - The pairing A = T & C = G were almost identical in shape (3 Rings)
 - Each pairing fit neatly into the double helix giving a regular spiral with no bulges
 - And if only these pairs were allowed then:
 - The amount of A = The amount of T, and held true for C & G as well



What were the observations?

Thymine

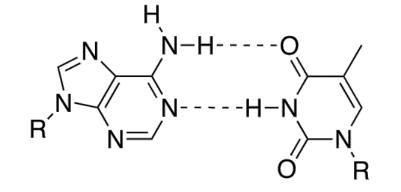
A = T

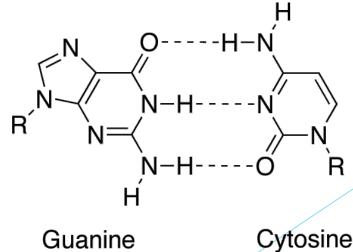
- [Purine = Pyrimidine]
- Combined had 3 rings
- Connected by H-bonds

Adenine



- [Purine = Pyrimidine]
- Combined had 3 rings
- Connected by H-bonds

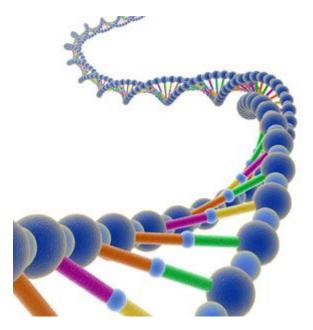




Cytosine

DNA 101 - What the model shows

- Each chain includes both purines and pyrimidines with pairs flipped over.
 - Dyadic symmetry & Chargaff's rules are met
- Bases could appear in any order on one chain
- Once the order was fixed though, the base pairing then determined the complementary order on the opposite chain



Sizing up DNA

- 20 angstrom units in diameter
 - 79 billionths of an inch
- Two chains twining:
 - Coaxially
 - Clockwise
 - One up & one down
- A complete rotation was 34 angstroms
- 10 turns made one DNA molecule
- 36° was the rotation angle
- Keto configuration is the most plausible tautomeric form (enol configuration suggests weaker bonds than keto)



"We have found the secret to life."



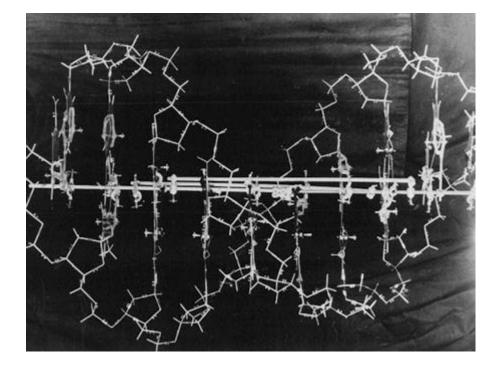
• The Eagle, Cambridge



https://www.youtube.com/watch?v=u-D9uHmx8xo

April 25, 1953

"We wish to suggest a structure for the salt of Deoxyribose Nucleic Acid (DNA)"



No. 4356 April 25, 1953 NATURE

captain and officers of R.R.S. Discovery II for their part in making the observations. ¹ Young, F. B., Gerrard, H., and Jevons, W., Phil. Mag., 40, 149 (1920).

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The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows : purine position

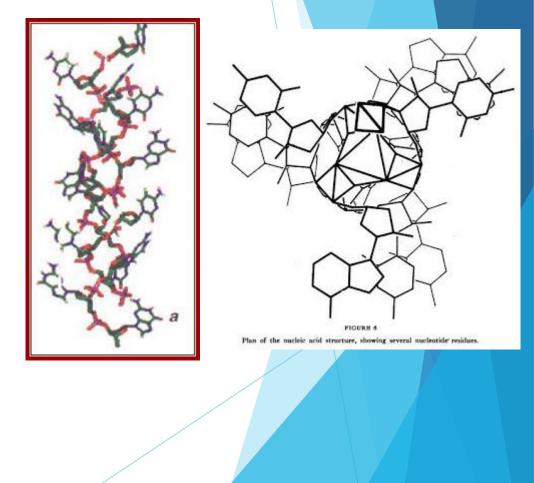
Watson and Crick looked at previous structures proposed by Pauling and Corey

Consisted of...

- Three intertwined chains
- Phosphate near fibre axis
- Bases on the outside

2 reasons it was unsatisfactory:

- 1) The material which gives the x ray diagrams is the salt not the free acid
- 2) Some of the Van der Waals distances appear to be too small



Watson and Crick looked at previous structure proposed by Fraser

Consisted of:

- Another three chain
- Phosphates on the outside
- Bases on the inside

Reason it was unsatisfactory:

1) It is ill defined and therefore could not be used

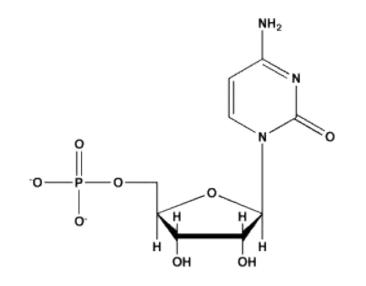
Watson and Crick's Structure

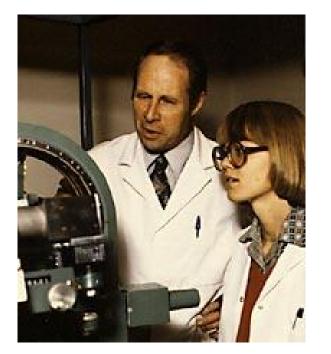
- 2 helical chains each coiled around the same axis
- Both chains are right handed
- The two chains are related by dyad perpendicular to fibre axis
- Each chain consists of phosphate diester groups
 - Joining β-d-deoxyribofuranose residues with 3-5 linkages
- Residues on each chain every 3.4 A
- 36° between each adjacent residues in the same chain
- Structure repeats itself after 10 residues
- Open structure with high water content
 - Bases tilt at low water content would compact it



Watson and Crick structure loosely resembles Furburg Model #1

Bases were on the inside Phosphates were on the outside Sugar perpendicular to attached base





Watson and Crick Novel Feature

The two chains are held together by Purine and Pyrimidine Bases

Planes of the bases is perpendicular to the fibre axis Single base from one hydrogen bonded to the other One must be purine and the other pyrimidine

11 2) 3)

paired between a pyrimidine and a purine.

Watson and Crick's X-ray data for DNA exhibited that the double helix was uniform in diameter. The following scheme illustrates

different pairing scenarios and why bases ultimately need to be

Pairing between two purines would result in a LARGER double helix width than was found in Watson and Crick's data.

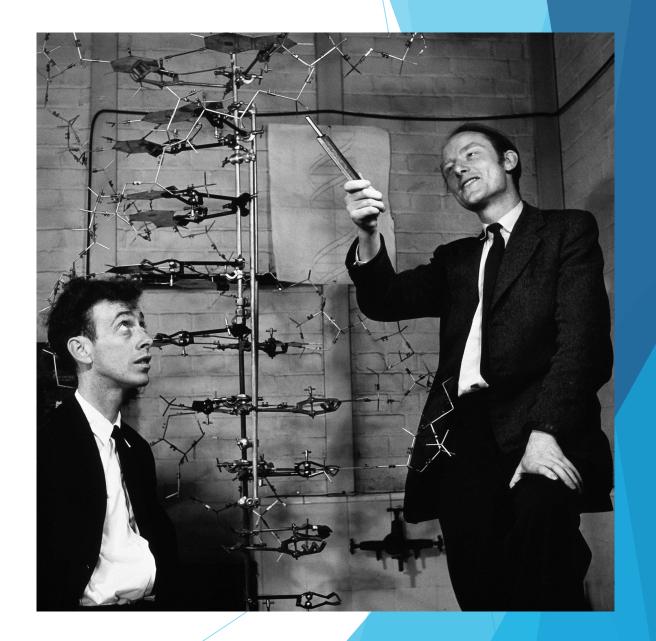
Pairing between two pyrimidines would result in a SMALLER double helix width.

Pairing between a pyrimidine and a purine MATCHES the width Watson and Crick had in their data.

Why deoxyribose?

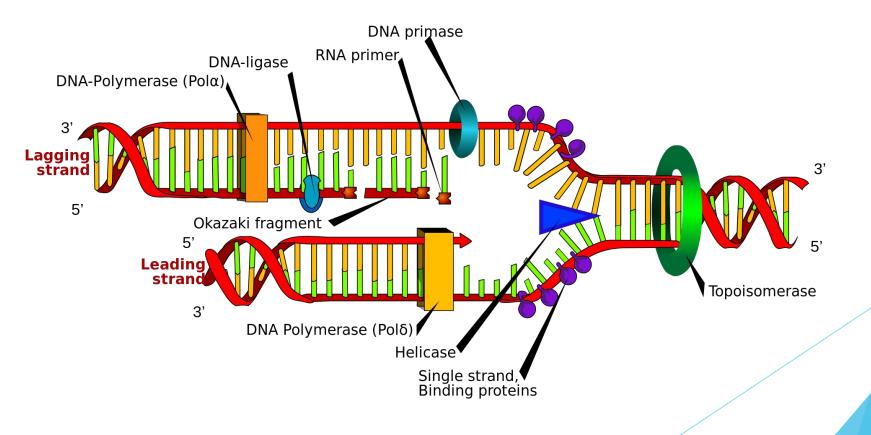
Watson and Crick discovered that the sugars must be Deoxyribose.

Ribose sugars could not build the proper form because the extra Oxygen caused too close of Van der Waals forces in the model



The major importance of Watson and Crick's proposed structure

It immediately suggests method for copying mechanism for genetic material



Watson and Crick's Conclusion:

X rays done of DNA so far are insufficient to describe their structure proposed

Therefore...

Their structure must be regarded as unproved until it has been checked against more exact experimental results

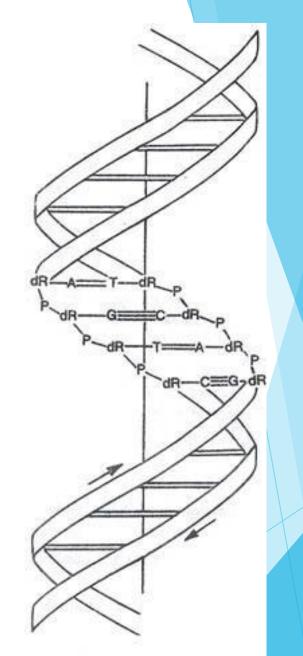


Fig. 38.4. Watson and Crick's double helical DNA molecule.

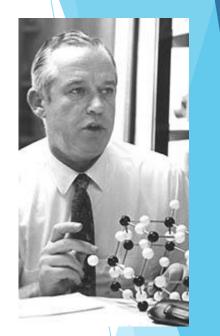
Watson and Crick's Acknowledgments

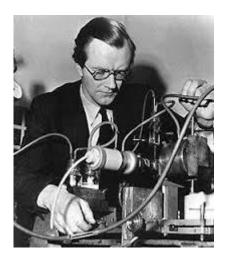
Within their paper, Watson and Crick stated that they were indebted to certain individuals for assisting in their research:

Dr. Jerry Donohue for his advice and criticism on the model

- Specifically with respects to interatomic distances

Wilkins and Franklin for their published works







What happened next?

1962: Nobel Prize

- In 1962, Crick, Watson and Wilkins were awarded the Nobel Prize in Physiology or Medicine for their work in the discovery of the structure of DNA
- The Nobel Foundation forbids any award to be given to more than 3 people, which led to certain controversial omissions such as Rosalind Franklin



Rosalind Franklin's Death

- 5 years after Watson and Crick published their paper, in 1958, Rosalind Franklin died of cancer aged 37
- There is speculation as to what caused her cancer, with some attributing her death to extended exposure to X-ray radiation
- As she died in 1958, she was unable to share the Nobel Prize with Crick, Watson and Wilkins, as the Nobel Foundation does not give posthumous honours
- Her colleague Aaron Klug won the Nobel Prize in 1982 for continuing her research on the molecular structure of viruses and crystallographic electron microscopy; a prize she would most likely have shared.



Watson and Crick - Where are they now?

CRICK

- Introduced the "central dogma" of information flow between macromolecules (1958)
- Held a research position at the Salk Institute until his death in 2004

WATSON

- Served as director of Cold Spring Harbour Laboratory from 1968 till 2007
- Was head of the Human Genome Project from 1990 till 1992

What if Watson and Crick did not make the Discovery?

- It would've taken much longer to determine the structure of DNA
- According to Crick, if the 1953 paper wasn't published, the discovery of the DNA structure would have been delayed for another decade

Implications of Watson and Crick discovery

- Revolutionised the field of biology into a global industry
- Enabled scientists to access genetic information about life that had not been available previously
- In the 1970's, scientists began developing mechanisms to swap portions of DNA between species
- Through knowing the DNA structure we have made advances such as:
 - GMOs
 - Cloning
 - Genome

Genetically Modified Organisms

- In 1972, Paul Berg, a biochemist at Stanford University, created the first recombinant DNA molecule by combining DNA strands from a monkey virus and a lambda virus.
- Rudolf Jaenisch, a Professor of Biology at MIT, created the world's first transgenic mouse, by introducing foreign DNA into the mouse embryo in 1973
- The Flavr Savr tomato, introduced in 1994, was the world's first genetically altered food (the first GM crop was an antibiotic resistant tobacco plant).

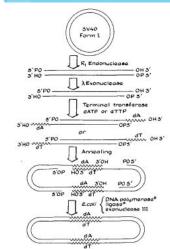
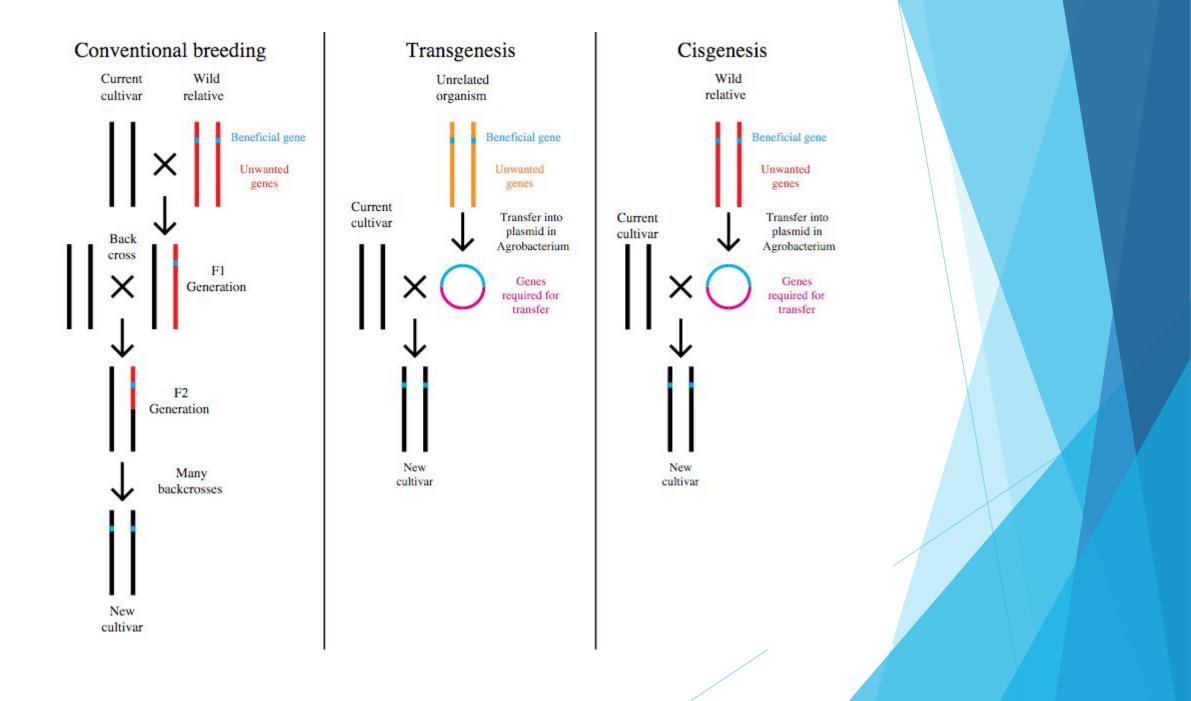


Fig. 1. General protocol for producing covalently closed V40 dimer circles from SV40(1) DNA. • The four decxynucleoside triphosphates and DPN are also resent for the DNA polymerase and ligase reactions, respecvalv.



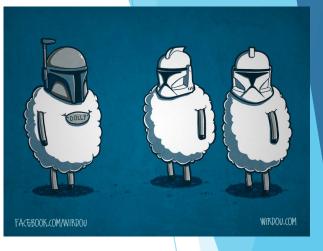




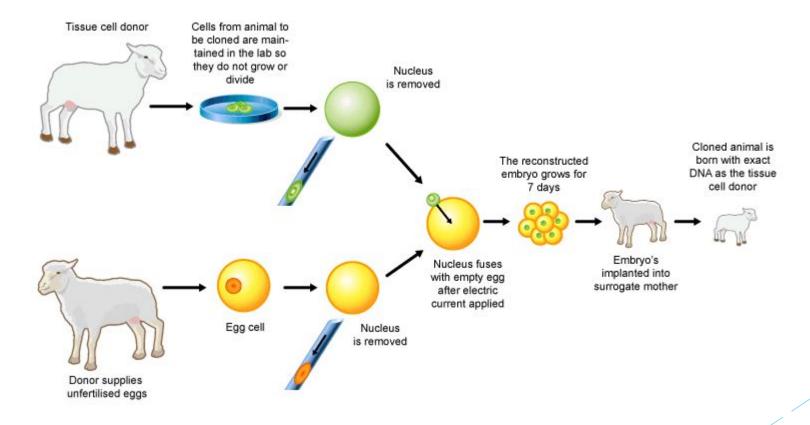
Cloning

- 1996: The first cloned mammal (a sheep) is created from differentiated cells at the Roslin Institute in Edinburgh, UK.
- Ian Wilmut and his team transferred the nucleus of a donor cell into a blank egg cell and inserted the cell into the mother
- The cloned sheep, named Dolly, lived for 6 years, about half of the average lifespan of a Finnish Dorset sheep
- This experiment sparked enormous controversy, and the debate about cloning and genetic engineering rages on to this day



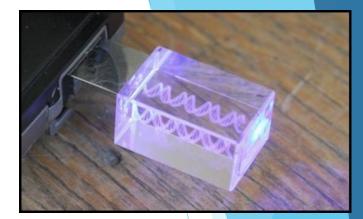


Cloning method



DNA as a storage unit

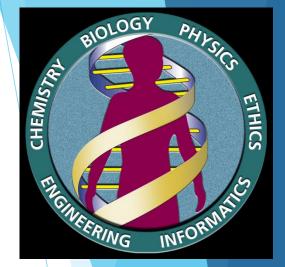
- Function of DNA: carrier of genetic instructions for the development and life of an organism
 - Biological USB drive
- The use of DNA for storing information was posited in the 1990's, but came to fruition after the millennium
- In 2010, Ewan Birney encoded Shakespeare's sonnets, Martin Luther King's "I have a dream" speech, and Watson and Crick's 1953 paper into a DNA sequence
 - The sequence was decrypted with zero margin of error





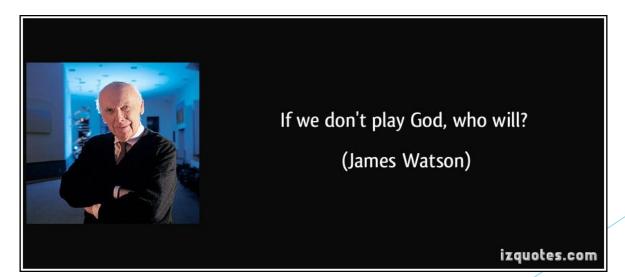
Genomes

- Thanks to the discovery of the structure of DNA, entire genomes of species are able to be sequenced
- The first free living organism to have a completely sequenced genome was the bacterium *Haemophilus influenzae* in 1995
- The human genome was completely sequenced in 2003, within the limits of our technology
 - This was handled by the Human Genome Project



Ethics

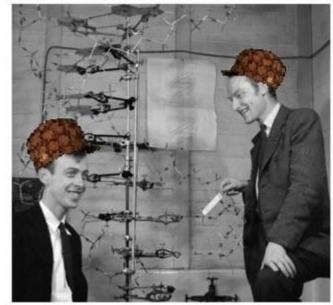
- Discovery of DNA structure led to the revolution of the field of biology
- With this revolution, controversy and fierce debate over the ethics of genetic experimentation has arisen
- The scientists who helped create the atom bomb have also given us the keys to understand life as we know it



Something else to ponder...

- Is it fair to say that Watson and Crick "stole ideas" as they are so often accused of doing???
- If they the results are published (ie Chargaff), then what's wrong with using them?
- Is there anything wrong with making scientific discoveries this way?

USE DATA FROM OTHER LABS



TAKE ALL THE CREDIT

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