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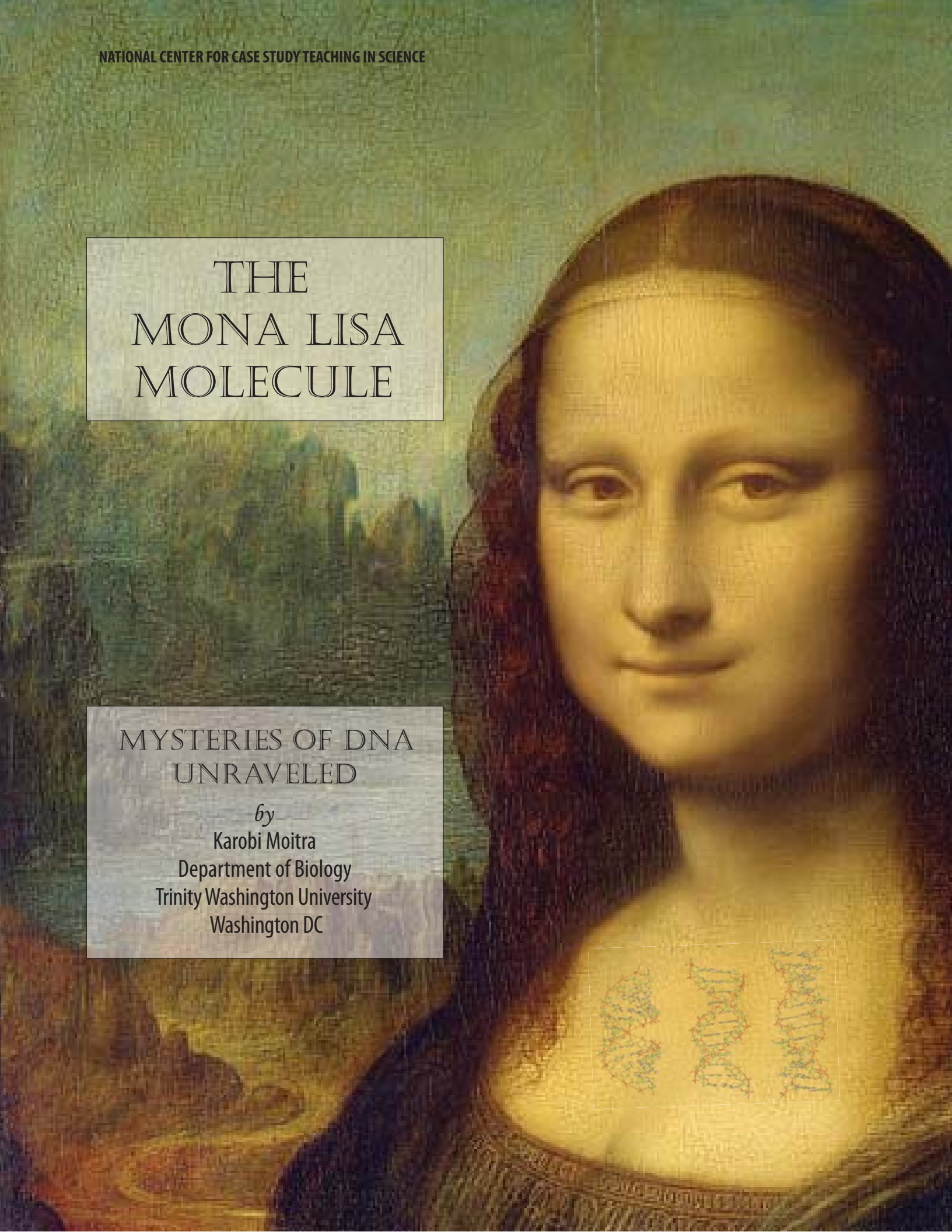

THE MONA LISA MOLECULE

MYSTERIES OF DNA UNRAVELED

by
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Feb. 28, 1953, Cambridge, England

Dear Diary:

Today I have been witness to a most singular event. The day for me started off fairly uneventfully at the Cavendish Laboratory where I work as a laboratory assistant. As I recall, there was quite a nip in the winter air and as I watched the hands of the clock move forward I realized that a pint and a spot of lunch might well be in order if I were to make it through the long winter day. I decided on the spot to take an early lunch break at the nearest pub, 'The Eagle' on Benet Street near the old church. I walked in well before noon and seated myself on one of the benches and ordered some fish and chips and some ale to go with it. As I sat ruminating, the pub began to fill up fairly quickly. I called over a few familiar faces from the Cavendish and we sat and ate together while complaining mostly about the weather, politics, jobs, the economy, etc. Just as I was biting into a particularly crispy piece of fish, there was a commotion up front. A couple of our lads from the Cavendish were kicking up quite a ruckus. I recognized Francis Crick immediately, tall, balding and always up for a debate, trust him to be right in the middle of this! He was with the American kid, long hair, lanky — Jim Watson. We made room at the bench for them. This should be interesting, I thought to myself, but nothing could have prepared me for what came next. Crick, the showman as usual, was working himself up for a big reveal; I could tell just by the look in his eye. "Gentlemen," he said with a flourish, "today we have discovered the secret of life itself!"

Questions

1. Taking the clues from the diary entry, speculate on what Francis Crick and James Watson had discovered.
2. Why do you think that he specifically mentioned that they had "discovered the secret of life itself"?

Fig. 1: Jim Watson (left) and Francis Crick (right). Detail of "Physics Research Students, Cavendish Laboratory," 1952, courtesy of Wellcome Library (http://wellcomelibrary.org/), reference ID: PP/CRI/A/1/2/1, CC BY-NC 4.0.

Feb. 28, 1953, Cambridge, England, diary entry continued. . . .

Yeah, right, big deal—seemed like old Francis had been hitting the bottle hard since the early hours. But then again he didn't really look inebriated, so what was going on? We were all used to Francis Cricks' "bragging" by now, but this was really pushing it. Even us lab boys knew that there had been gossip going around the labs that Crick and Watson had been trying to solve the structure of this new-fangled molecule called DNA—deoxyribonucleic acid—but discovering the secret of life itself? This was a new height, even for Francis.

I decided that I needed to take a trip down memory lane. I had been trying to educate myself ever since I had landed this job at the Cavendish to try and move up in the world. Francis had taken pity on me. He had made me privy to his work and acted as my unofficial mentor so that in time I too could also understand the amazing process of science. To be really honest, I think that Francis really needed someone with excellent listening skills to survive the mental onslaughts, i.e., his tendency to sometimes "brag" about how brilliant his theories were. But, in truth, I did appreciate his interest in me and in time I did learn a lot from him. To this day, I do not regret a single moment that I spent with him. I went back to my old diary that I had been keeping from 1951 of my experiences at the Cavendish to try and put together the pieces of the puzzle of how the structure of DNA had been solved.

Questions

3. Why was it important to solve the structure of DNA? (*Hint:* Type DNA into a search engine on the internet to try and figure out the answer to this question.)
4. How do you think that solving the structure of DNA could move the field of genetics forward? (*Hint:* This site http://www.dnai.org/d/index.html would be helpful in answering this question.)
5. With the aid of the information on the following websites, explain how the Hershey-Chase experiment conclusively proved that DNA and not protein was the genetic material.
   - DNA Interactive. *DNA Learning Center*. http://www.dnai.org
   - Double Helix: 50 Years of DNA. *Nature.* http://www.nature.com/nature/dna50/index.html

Older Diary Entries

Early October 1951, Cambridge, England.

Dear Diary:

Today a new member joined the group. There was quite a buzz throughout the Cavendish; rumor had it that the newcomer was an alien from a newly discovered planet! Well, almost. He was in actual fact an American by the name of James Watson.

I really don't know why Americans can't get a decent haircut but, as Americans go, Jim seems to be a fairly decent sort of chap in spite of the long unkempt locks of hair. He drinks beer and likes his fish and chips with a decent dose of vinegar, which is always a good sign. I initially thought he was one of us lab boys, but rumor has it that the "kid" earned his PhD from Indiana University when he was just 21, so I guess appearances can be quite deceptive. The real gossip is that Jim Watson had a little conversation with Francis Crick, which I somehow managed to overhear—not too difficult a feat considering that Francis doesn't exactly have a soft voice. The crux of the matter seemed that both of them are interested in solving the structure of DNA. Jim initially wanted to focus on using X-ray crystallography to try and solve its structure, but Francis convinced him that model building was the way to go, based on Linus Pauling's work on deciphering protein structure. Francis convinced Jim that these structures were solved by common sense (and a basic knowledge of chemistry) and not by complex mathematical reasoning (Jim seems to have an inherent fear of mathematics – kind of odd really considering that most prodigies seem to excel at mathematics). Rumor has it that they are going to ask the crystallographer Maurice Wilkins from Kings College in London to come over for a cozy little tête-a-tête.

Questions

6. What is "model building"? How can this technique be used to solve the structure of biological molecules? (*Hint:* Discuss both computational model building and physical model building; this Wikipedia article is useful: http://en.wikipedia.org/wiki/Homology_modeling.)
7. Use the following websites to help you describe the "bare bones" basic principle behind X-ray diffraction.
   - Franklin's X-ray diffraction, explanation of X-ray pattern. *DNA Learning Center*. http://www.dnalc.org/view/15014-Franklin-s-X-ray-diffraction-explanation-of-X-ray-pattern-.html
   - X-ray Diffraction Techniques. Dissemination of IT for the Promotion of Materials Science (DoITPoMS), University of Cambridge. http://www.doitpoms.ac.uk/tlplib/xray-diffraction/printall.php
8. Explain very simply how the X-ray diffraction process aids in solving structures of biological molecules.
9. Compare and contrast the two techniques above (model building and X-ray crystallography) and discuss their usefulness in structure determination of biological molecules.

Before proceeding to the next section, read the paper cited below as a homework assignment and make extensive notes:

Watson, J.D., and Crick, F.H. 1953. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 171 (4356): 737–738.

Late October 1951, Cambridge, England

Dear Diary:

Looks like the boys managed to snare Maurice into coming up to the Cavendish with his pretty pictures of DNA. But scientifically speaking, not much was accomplished since all Maurice wanted to do was to complain about his devilish assistant "Rosy" (Rosalind Franklin). Apparently she had snagged all the "good DNA" and produced some pretty spectacular X-ray pictures of DNA, but Maurice hadn't seen the photographs yet. He told Jim that Rosy would be presenting her work at Kings in three weeks' time in mid-November and apparently invited Jim over. Boy, did Jim look scared! He started to pour over crystallography articles to prepare so that Rosalind would not speak over his head. Turns out he needn't have bothered; yes, she did have some very pretty pictures, but she spoke over his head anyway. To while away the time, he sat in the audience and daydreamed. Was Francis mad! Jim couldn't give Francis any correct details about the talk. Anyhow, they both decided it was high time to start building models of DNA.

To get down to the details: It had been previously discovered that DNA was made up of a sugar-phosphate backbone and that DNA also contained the nitrogenous bases adenine, thymine, guanine, and cytosine. Erwin Chargaff had shown that the percentage of adenine (A) was equivalent to the percentage of thymine (T) and also that the percentage of guanine (G) was equivalent to the percentage of cytosine (C) in DNA of most organisms (%A~%T, %G~%C). Armed with this information and a smattering of information from the X-ray diffraction data, Jim set about constructing a model of DNA.

The model building itself proved to be difficult at first; I could hear Jim cursing from down the hall, but apparently as it progressed it became much easier. The pieces of the model were actually metal templates of the components of a polypeptide chain that Jim had modified with copper wire to make the molecules that he needed for constructing a model of DNA. Because these were rough templates, they needed to be put together with the aid of claw-like metal clips called pincers. Unfortunately, the atoms kept falling out of the pincers that held them, but it seemed that finally a shape was emerging from the unruly pile of metal and wires. Was this the elusive structure of DNA? Jim constructed the model with three chains twisted about each other to give rise to a crystallographic repeat every 28Å along the helical axis to keep it in tune with the x-ray diffraction data.

The next day, Jim corrected several atomic contacts and the three-chain model was complete with the sugar-phosphate backbone in the middle. The Kings College group was asked to come over and inspect the model. Long story cut short, Rosy hated the model; she pointed out some very major flaws and that proverbially was that. Jim and Francis were forbidden to work on DNA by our laboratory director, Sir Lawrence Bragg. The duo seemed to be really dejected, if you ask me, but they still followed the current literature on DNA on the sly.

December 1952, Cambridge, England.

Dear Diary:

Francis and Jim recently got hold of a manuscript written by Linus Pauling describing a triple helical structure for DNA through Linus's son, Peter Pauling, who also worked at the Cavendish. Francis and Jim knew that they had to start model building in earnest because if the triple helical structure was published and found to be at fault, Linus Pauling would start working in earnest to redeem himself and probably come up with the correct structure on his second try. It was a race against time, but they still needed more information if they were to build the model. I was wondering how they would come up with the X-ray crystallographic data that they needed.

Questions

10. Describe the building blocks of DNA in detail. (*Hint:* This webpage on DNA structure will help you: http://www.chemguide.co.uk/organicprops/aminoacids/dna1.html.)
11. Define Chargaff's Laws.
12. Why were Chargaff's Laws important in regards to solving the structure of DNA?

Late December 1952, Cambridge, England

Dear Diary:

Jim decided to go and pay Rosy a visit when he stopped by Kings College. I heard through the grapevine that Rosalind gave him a regular dressing down. She thinks that the sugar-phosphate backbone is on the outside (she used a complicated technique called Patterson superposition method to show this). Jim didn't believe her at the time and honestly thought she was a bit off her rocker. A few days later Jim and Francis had a grand stroke of luck: Maurice (Wilkins) showed them an X-ray crystallographic image of DNA* that apparently Rosalind had taken which had been published as a technical report. Jim's mouth fell open. He apparently acted like he was off his rocker when he saw the X-ray picture of B-DNA with clear cross-like reflections, indicative of a helical structure. Watson talked to Crick about the 3.4 Å meridional reflection (a diffraction pattern produced along the axis of the meridional plane) ** indicative of the pyrimidine and purine bases being stacked on top of each other separated by a distance of 3.4Å and also discussed electron microscopic and X—ray images which indicated that the diameter of the helix is 20Å. I suspect that they saw a picture emerging from the data at this very point: 3.4 Å separated the bases stacked on top of each other in a helical structure of 20 Å diameter. Based on this new data, and on the (non) scientific principle that the "best things in nature come in pairs" Watson decided on the spot to build two-strand models of DNA. In the meantime, we hear that Rosalind's pictures are getting "prettier and prettier." Now here's where everything gets a little hazy: Some say that Jim and Francis had been shown Rosalind's "photo 51" (an X-ray crystallographic image of B DNA) by Wilkins, which to me doesn't seem at all fair to Rosy, but you really can't believe everything you hear.

* For the X-ray diffraction pictures described, visit this website: http://askabiologist.asu.edu/Rosalind_Franklin-DNA & http://en.wikipedia.org/wiki/Photo_51.

** Take a look at this website for an explanation: fttp://fbio.uh.cu/sites/genmol/adic/na_arch.htm.

Questions

13. What critical pieces of information did Watson and Crick gather from the new X-ray crystallographic picture of B-DNA?
14. Why was the picture called photo 51? Who took this picture? Use the diary and the following website to help you: "The Anatomy of Photo 51" at http://www.pbs.org/wgbh/nova/body/DNA-photograph.html
15. Do you think that Photo 51/Rosalind's X-ray diffraction data was crucial to solving the structure of DNA? Why/why not?

February 28, 1953, Cambridge, England

Dear Diary:

Today Jim and Francis solved the mystery of life itself. Using Rosy's data (possibly unknown to her!), they refined the backbone of DNA on their model to the precise measurements suggested by her work. However, Jim got stuck on how to arrange the bases centrally on the model, although evidence has come to light that the bases were possibly linked by hydrogen bonds. Jim then started to draw the structure of the bases on paper and suddenly realized that adenine could possibly form hydrogen bonds to another adenine if the other adenine was at a 180 degree rotation (upside down) in relation to the other. Jim got excited and immediately wrote a letter to Max Delbruck (a former colleague of his and a renowned bacteriophage geneticist/biophysicist) in which he mentioned that he might have solved the riddle of DNA structure. The next morning his idea (of adenine pairing with adenine or like-with-like pairing) was torn to shreds by Jerry Donohue, an American crystallographer (working at the Cavendish), who very patiently pointed out that Watson had been using the wrong tautomeric forms of the bases (tautomers are structural isomers that have the same molecular formula but different structural formulas) - instead of using the keto conformation; Watson had been using the enol conformation, which tore his theory to shreds. Jerry had a strong intuition that the keto form was correct. The "like with like" would also have no explanation for Chargaff's findings. Two more days were required for the shop to make the proper metal templates of the bases, but Jim couldn't wait – he decided to make the bases himself from stiff cardboard. He cleared away the paper from his desk and proceeded to play around with the arrangement of the bases. As he was shifting them around, he realized that the A-T pair held together with hydrogen bonds was the same shape and distance as the G-C pair held together with hydrogen bonds.* He then showed Jerry the structure and this time around Jerry had no objections. Chargaff's rules were being obeyed and the whole structure fit together perfectly with the bases in the center being held together with hydrogen bonds and the sugar-phosphate backbone on the outside. Francis came in and played around with the arrangement and spotted that the two glycosidic bonds (nitrogen-carbon linkage between the nitrogen of purine /pyrimidine bases and a carbon of the sugar group) joining the base and the sugar were related by a symmetrical axis perpendicular to the helical axis, so that both pairs could be flipped-flopped over but still have their glycosidic bonds facing the same direction – suggesting that the helix was antiparallel.

* Visit this website to get a general idea of the concept: http://www.atdbio.com/content/5/Nucleic-acid-structure

April 1953, Cambridge, England

> Dear Diary:
>
> Jim and Francis called the Kings College group over to inspect the final model. Everyone including Rosy was very happy with the model and they decided to publish three back-to-back papers in the journal Nature appearing on April 25, 1953. The second-from-last paragraph of Jim and Francis' paper states: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a copying mechanism for the genetic material." This in my humble opinion possibly represents one of the greatest understatements in molecular biology.

Questions

16. Answer the following basic questions regarding the structure of DNA:
    a. Name the type of bond that holds the two strands of DNA together.
    b. Compare the components of a nucleotide versus that of a nucleoside.
    c. What is meant by "antiparallel helix" as it pertains to DNA?
    d. Where is a glycosidic bond located in DNA?
    e. Which component of DNA imparts a negative charge to the molecule?
    f. Write down the complementary strand of this DNA sequence:
    5′ a t t t a g g g g c g a 3′
17. Use internet resources/articles/your textbook to determine how the structure from the 1953 paper has been corrected in recent times. (Hint: you may use this resource to help you: http://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397)
18. Create a time-line of key events leading up to solving the correct structure of DNA starting from the discovery of DNA as the genetic material (you may use the following website http://unlockinglifescode.org/timeline?tid=4 to help you as well as the resource website in question16).
19. Explain this statement in detail and its underlying implications: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a copying mechanism for the genetic material."

Last Diary Entry

Dec. 10, 1962, Stockholm, Sweden

Dear Diary:

Today Watson, Crick and Wilkins accepted the Nobel Prize in Physiology and Medicine. They did not acknowledge Rosalind Franklin in their acceptance speech. I thought it really bad form on their part, very remiss of them, it was the least that they could have done to just mention her name, but who am I to judge? All I know is that the poor girl passed away from cancer in 1958 at the young age of 39, not knowing the impact that her spectacular work would have in the years to come. What is apparent though is that the structure of DNA probably could not have been solved without Rosalind's superb images and that the Watson-Crick "model" is based on the X-ray structure and probably not the other way around.

Questions

20. What were Rosalind Franklin's contributions to discovering the structure of DNA?
21. Do you think that the structure of DNA could have been solved without Rosalind's X-ray diffraction data?

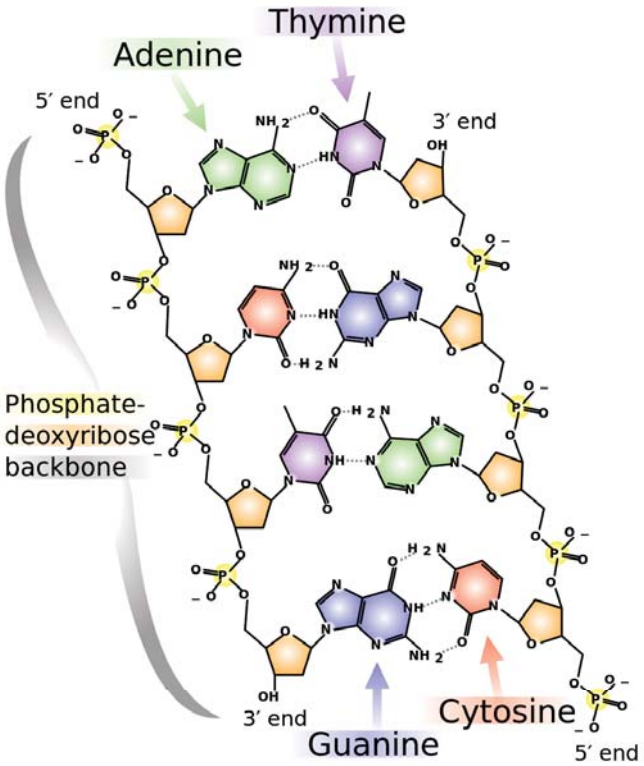

Fig. 2: DNA Chemical Structure. Image by Madeleine Price Ball, http://commons.wikimedia.org/wiki/File:DNA_chemical_structure.svg, PD.

Recommended Websites

All links last accessed at time of publication.

General

http://www.nature.com/nature/dna50/index.html
http://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/
http://video.vcu.edu/vod/sosq/sosq_149_1.mp4

DNA and the Cavendish Laboratory

http://www-outreach.phy.cam.ac.uk/resources/dna/fullstory.pdf

Readers guide to the Double Helix by James Watson

http://www.brown.edu/Courses/BI0020_Miller/dh/guide.html

Rosalind Franklin

http://profiles.nlm.nih.gov/ps/retrieve/Narrative/KR/p-nid/183
http://www.pbs.org/wgbh/nova/photo51/
http://www.biomath.nyu.edu/index/course/hw_articles/nature4.pdf

Francis Crick's Papers

http://archives.wellcomelibrary.org/DServe/dserve.exe?dsqIni=Dserve.ini&dsqApp=Archive&dsqDb=Catalog&dsqCmd=Show.tcl&dsqSearch=%28RefNo==%27PPCRI%27%29

Watson and Crick's DNA Structure Paper

http://www.exploratorium.edu/origins/coldspring/ideas/printit.html

Watson Constructing Base-Pair Models

http://www.hhmi.org/biointeractive/watson-constructing-base-pair-models

Useful textbook:

Klug ,W.S., Cummings, M.R., Spencer, C.A., and Palladino, M.A. 2011. *Concepts of Genetics*, 10th Edition. Benjamin Cummings Publications.

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