

# Molecular Biology Through Discovery

## DNA Structure

### Outline:

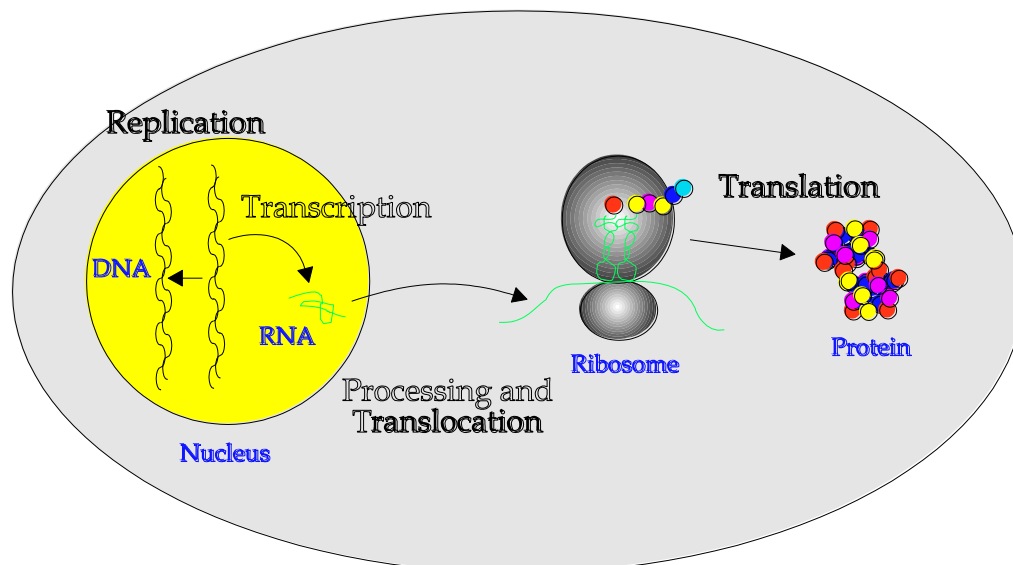
- A. Overview
- B. DNA world prior to the double helix
- C. The double helix
- D. Directionality and palindromic sequences

### A. Overview

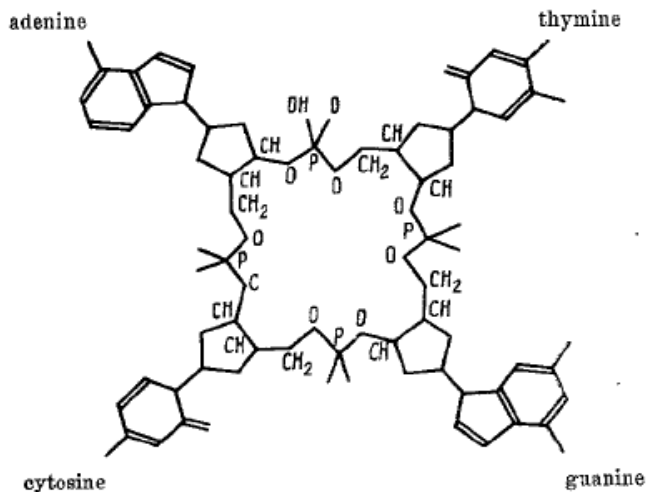
The information contained within DNA determines the potentialities of a cell. The information within protein present within a cell determines the actuality of a cell. Between the two are enough details to fill several thick textbooks (see **Fig. 1** for a crude view of the whole). We've already considered the end product of this flow of information – proteins – and how the information in the form of an amino acid sequence can determine their structures and properties. Now we turn our attention to the beginning, to DNA. What is its structure, and how does that structure determine its properties, particularly the property of self replication?

### B. DNA world prior to the double helix

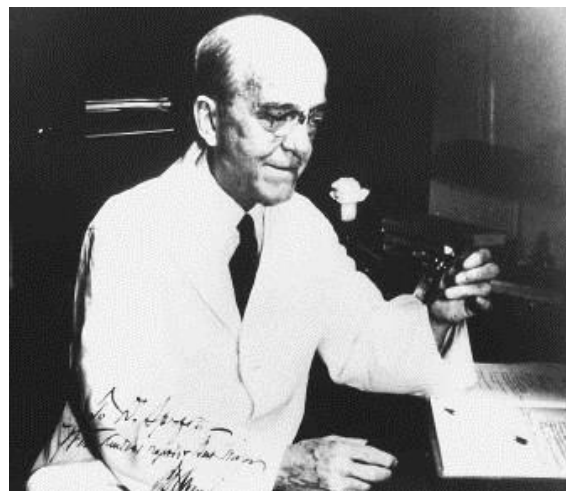
DNA, or at least a phosphorus-rich compound found in nuclei, has been known since the 19<sup>th</sup> century, but even as late as Dorothy Wrinch's hypothesis in 1936 concerning chromosome structure,<sup>1</sup> it was thought to play a minor, purely structural role. This is understandable, considering the view of DNA structure prevalent at that time (**Fig. 2**). DNA was thought to be uniform in its composition and structure. Even though it soon became apparent that DNA was much bigger than a tetranucleotide, the thought remained that the large molecule might be merely a polymerization of a tetranucleotide monomer.<sup>2</sup> DNA was clearly a poor candidate to carry genetic information. That role was given to protein, recognized to be highly variable in structure.



**Figure 1: Flow of information from DNA to protein.**



**Figure 2. Proposed structures of DNA based on equal composition of nucleotides.** From Reference 1.



**Figure 3. Oswald Avery.** <http://www.chemistryexplained.com/Ar-Bo/Avery-Oswald.html>

**SQ1. Why is it difficult to imagine that a regular polymer consisting of repeated 4-nucleotide units might be the genetic material?**

The tetranucleotide hypothesis, championed by Phoebus Levene, achieved the status of dogma,<sup>3</sup> even though the idea of equal molar ratios was based on data of limited quantitative reproducibility.<sup>4</sup> In 1938, William Astbury reported the first X-ray crystallographic photographs of DNA and concluded that the order of nucleotides must be irregular.<sup>4</sup> However, the quality of the photographs was not very good, and the argument for irregularity was indirect.

For many, work published by Oswald Avery (**Fig. 3**), Colin MacLeod, and MacLynn McCarty in 1944<sup>5</sup> turned the genetic world in its head. They found that a cell-free component from a pathogenic bacterium, *Pneumococcus* (now called *Streptococcus pneumoniae*), was able to transform a nonpathogenic strain to pathogenicity. The transforming component appeared to be DNA, with no discernible contamination by protein, lipid, or polysaccharide. How could a repetitive molecule, as DNA was envisioned to be, contain sufficient information to specify the production of something as complex as the pathogenic envelope capsule of the bacterium? The article was highly influential, even though its conclusions were not widely accepted. Many worried that Avery et al's transforming principle contained contaminating protein – thought far more likely to be the true genetic material.<sup>6</sup> The controversy brought to mind a famous clash a decade earlier in which catalysis was claimed for preparations that were substantially protein-free, preparations that later turned out to have traces of protein, the true agent of catalysis.<sup>7</sup> It is also reminiscent of a more recent controversy in which many insisted that preparations of prions must be contaminated with nucleic acid in order to explain their transmissibility.<sup>8</sup>

**SQ2. What experiments can you imagine that might resolve each of the three controversies just described?**

Erwin Chargaff (**Fig. 4**) was one of the few who accepted the conclusions of Avery, MacLeod, and McCarty, and he changed the course of research in his lab to test the validity of the tetranucleotide hypothesis, by analyzing the composition of DNA from many organisms.<sup>9</sup> To do



**Figure 4: Erwin Chargaff.** National Library of Medicine.

**TABLE 1**  
*Composition of desoxyribonucleic acid of ox (in moles of nitrogenous constituent per mole of P)*

CONSTITUENT	THYMUS			SPLEEN		LIVER
	Prep. 1	Prep. 2	Prep. 3	Prep. 1	Prep. 2	
Adenine	0.26	0.28	0.30	0.25	0.26	0.26
Guanine	0.21	0.24	0.22	0.20	0.21	0.20
Cytosine	0.16	0.18	0.17	0.15	0.17	0.16
Thymine	0.25	0.24	0.25	0.24	0.24	0.25
Recovery	0.88	0.94	0.94	0.84	0.88	0.87

**Figure 5: Nucleotide composition from DNA of ox.** This is one of many organisms studied by Chargaff's group. Numbers represent the total nucleotide identified in the preparation as a fraction of the whole. Note that the sum of the four fractions does not add up to 1.0. Each preparation represents the result from a separate experiment. Taken from Chargaff (1951), reference 10.

this, Chargaff had to devise new analytical tools that were suitable for the analysis of small amounts of DNA, but once this was accomplished, experimental results came quickly. By 1951, results such as those shown in **Fig. 5** provided convincing evidence that the tetranucleotide hypothesis was not applicable to natural DNA.<sup>10</sup>

**SQ3. What in Fig. 5 might persuade you that the tetranucleotide hypothesis was not tenable, at least in ox DNA?**

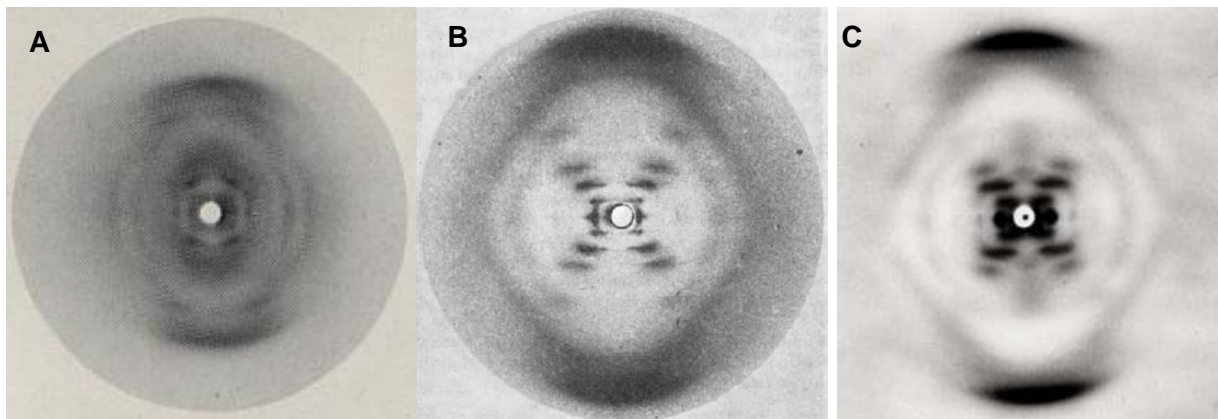
That was the first order of business. With the tetranucleotide hypothesis out of the way, there was no clear reason why DNA could not carry genetic information, as indicated by Avery, MacLeod, and McCarty's experiment. But there was more. If DNA were indeed the genetic material, you would expect that its composition would vary from one organism to the next, and this is what Chargaff's group found. Furthermore, you would expect that the composition would *not* vary from tissue to tissue within the same organism, since all tissue derives in the end from the same fertilized egg.

**SQ4. Does Fig. 5 support the idea that the composition of DNA is constant within a single organism?**

**SQ5. What if Chargaff found that the composition of DNA varied from one tissue to the next. Would that kill the idea of DNA as the genetic material? Why (not)?**

Finally, Chargaff's results indicated certain statistical relationships that bear in an important way on the model of DNA structure that would soon appear. Since Chargaff's work and its influence has been a matter of some controversy, it may be best to let him speak with his own words. After having dispensed with the equal molarities demanded by the tetranucleotide hypothesis, he continues:

*There appear, however, to exist several peculiar regularities. I think, we should formulate them not without trepidation, since we ought to avoid falling into a streamlined version of the old trap which in the past tripped so many excellent workers in the field of nucleic acid chemistry. It is quite possible that future work will show these generalizations to be unjustified. But as matters stand, it seems that in most specimens*



**Figure 6. X-ray photographs of DNA.** (A) From Astbury (1947), reference 13, (B) DNA form B, from Franklin & Gosling (1953), reference 14, (C) From Elwyn Beighton and William Astbury, unpublished (1951; [http://www.leeds.ac.uk/heritage/Astbury/Beighton\\_photo/index.html](http://www.leeds.ac.uk/heritage/Astbury/Beighton_photo/index.html)).

*examined until now- the ratios of adenine to thymine, of guanine to cytosine, and of total purines to total pyrimidines were not far from one.*<sup>10</sup>

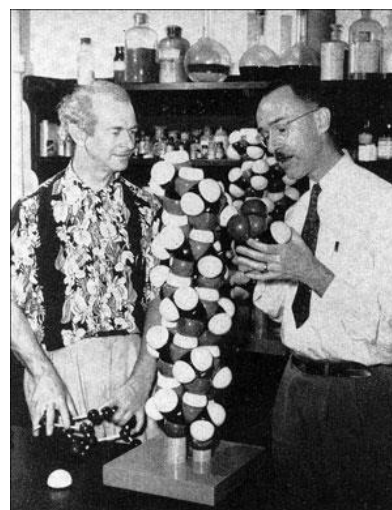
**SQ6. Does Fig. 5 support the idea that the A:T and G:C ratios are close to one? If it isn't close enough for your tastes, what could be the reason for the discrepancy?**

Chargaff's experiments led to many more interesting regularities in nucleotide composition besides the most famous ones sometimes called the Chargaff Rules, including some that whose basis is not understood even today.<sup>11</sup> But that's for another time.

### C. The double helix

Any physical model of the genetic information must explain two remarkable features: (1) Genetic information is replicated from parent to progeny, and (2) Genetic information somehow determines the structure and function of the whole organism. In 1935 Wrinch<sup>1</sup> proposed a plausible model to explain these features, based on her understanding of protein structure, as she, like most everyone else, believed that proteins lay at the heart of genetic information. But by 1951, this model was as dead as its central premise. Any model now must be based on the structure of DNA.

Linus Pauling and Robert Corey (**Fig. 7**) offered the first complete model of DNA structure based on X-ray crystallographic evidence,<sup>12</sup> fresh on the heels of monumental work determining the secondary structure in various proteins, work that garnered Pauling the Nobel Prize in chemistry in 1954. Pauling and Corey used X-ray photographs published by William Astbury's group in 1947<sup>13</sup> and earlier (**Fig. 6A**), along with their deep understanding of molecular structure and a penchant for model building.



**Figure 7. Linus Pauling and Robert Corey.** Copyright California Institute of Technology

Before going any further, it is necessary to gain some understanding on what X-ray crystallography is about, since that plus model building is at the core of both Pauling and

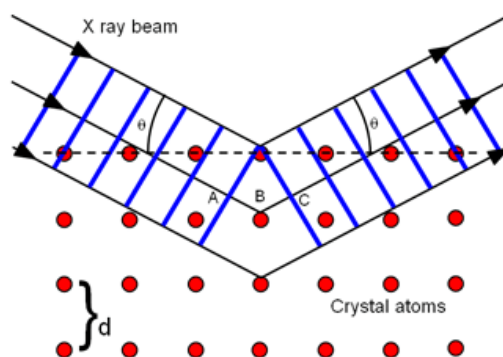
Corey's work and the work by Watson and Crick that led to the accepted model of DNA. X-ray photographs come from the diffraction of x-rays through a regular crystal, leading to interference of the waves captured on the photographic plate. The principle is similar to interference of light in the famous double slit experiment. If this experiment is not famous to you, I suggest going to the following:

- Double slit experiment

(<https://www.youtube.com/watch?v=DfPeprQ7oGc>)

Waves passing through two slits create patterns of destructive and constructive interference

The lessons learned from the double-slit experiment can be applied to x-ray crystallography. Playing the role of slits are regularly spaced atoms that diffract the incoming x-rays (**Fig. 8**). There's a major difference, however. Slits produce lines of interference maxima, while dots (atoms) produce spots. If X-rays bouncing off two different atoms reach a point on the photographic plate in the same phase, then constructive interference will produce a spot. As with the double-slit experiment, the spacing between the spots increases as the spacing between the atoms decreases, so by measuring the spacing of the spots, it's possible to deduce the spacing between atoms.



**Figure 8. X-rays diffracting off of regularly spaced atoms.** The spacing,  $d$ , between equivalent atoms of the repeating unit determine the spacing of the interference maxima.

[http://tap.iop.org/atoms/xray/530/page\\_47297.html](http://tap.iop.org/atoms/xray/530/page_47297.html)

Now you may be ready to apply the principles of x-ray crystallography to DNA. Here's a good place to start:

- X-ray diffraction of DNA

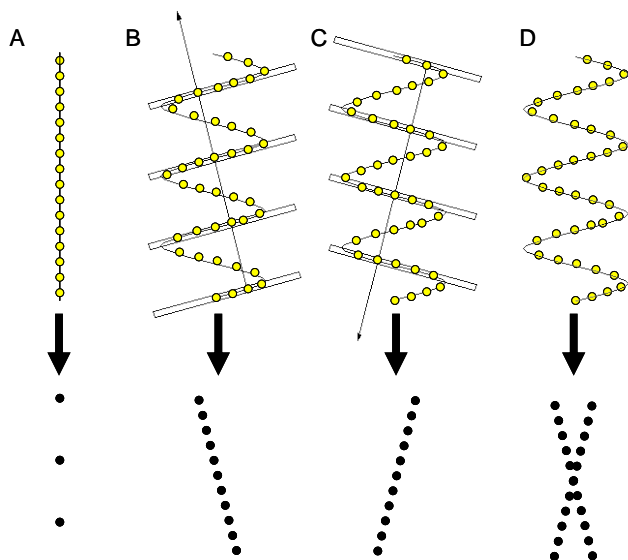
(<http://www.youtube.com/watch?v=u7RrXAJuNRk>)

Warning! The DNA is misrepresented as swimming in a test tube. Randomly oriented DNA would not give spots. Rosalind Franklin use stretched, uniformly oriented DNA.

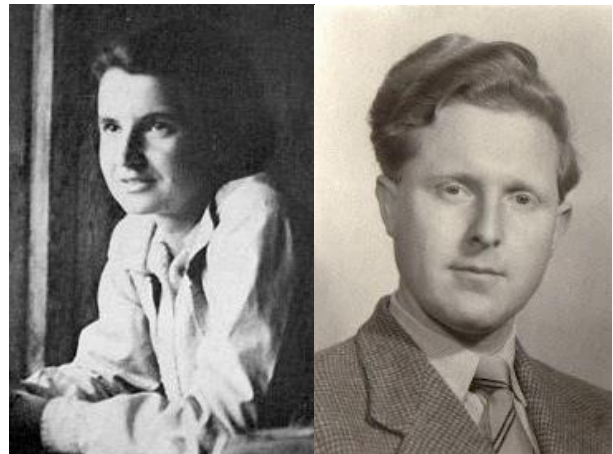
Now consider the diffraction pattern DNA would produce if it were a one-dimensional molecule (**Fig. 9A**). The equally spaced vertically arranged atoms should produce equally spaced vertically arranged spots on the x-ray photograph. However, if DNA were a helix (**Figs. 9B-D**), then the equally spaced atoms would be situated in two different parallel planes. Therefore, the resulting spots should be arranged in the same fashion, resulting in two lines of diffraction spots. The angle of the cross is the same as angle of the helix.

Anyone schooled in x-ray crystallography would see immediately from the cross in the picture of Rosalind Franklin and Raymond Gosling (**Fig. 6B, Fig. 10**)<sup>14</sup> that the compound that produced the image must be related to a helix. From a measurement of the distance between the spots in the cross, one could calculate from simple trigonometry that one turn of the helix was 3.4 nm.





**Figure 9. Relationship between DNA structure and interference maxima.** Hypothetical DNA structure is on top and resulting diffraction pattern below. Yellow dots represent phosphorus atoms. (A) One-dimensional DNA. (B) Single helix DNA, considering reflections from upward parallel regions. (C) Same DNA, considering reflections from downward parallel regions. (D) Same DNA, considering both sets of reflections, producing crossed diffraction pattern characteristic of helices..



**Figure 10. Rosalind Franklin and Raymond Gosling.**

**SQ7. What would you expect to happen to the diffraction pattern if the helix shown in Fig. 8B-D were squashed, i.e. the helix were more tightly wound, more like a solenoid?**

There was another immediately obvious feature from that photograph. The diffuse dark spots at the top and the bottom of the photographs (Fig. 6). These more distant reflections indicated more closely spaced repetitive elements – the spacing between consecutive units (the nucleotides). Distance to these reflections permitted a calculation of the nucleotide spacing – 0.34 nm. It followed from this and the previous measurement that there are 10 nucleotides per large repeating unit, that is per turn of the helix.

**SQ8. Where does this value "10 nucleotides per turn of the helix" come from?**

What could not be readily seen from the photographs was how many helices there were and how they were disposed to one another. Any number of helices, if evenly spaced, would give the same cross pattern on the x-ray photographs. Pauling and Corey postulated that there were three helices,<sup>12</sup> because of an erroneously high estimate of the density of DNA.<sup>15</sup> Jim Watson and Francis Crick (Fig. 11) also packed three helices into their first unpublished model of DNA structure.<sup>16</sup> How were these helices held together? Pauling and Corey put unionized phosphates of DNA on the inside, held together by hydrogen bonds. Watson and Crick did the same, except calling on magnesium to bind to ionized phosphate. In retrospect, neither model made chemical sense.



**Figure 11. Francis Crick and Jim Watson.**  
(Photo credit: The Warden Collection, NY)

**SQ9. Looking ahead to the structure of DNA shown in Fig. 12, what about the erroneous model of Pauling and Corey made no chemical sense? Why?**

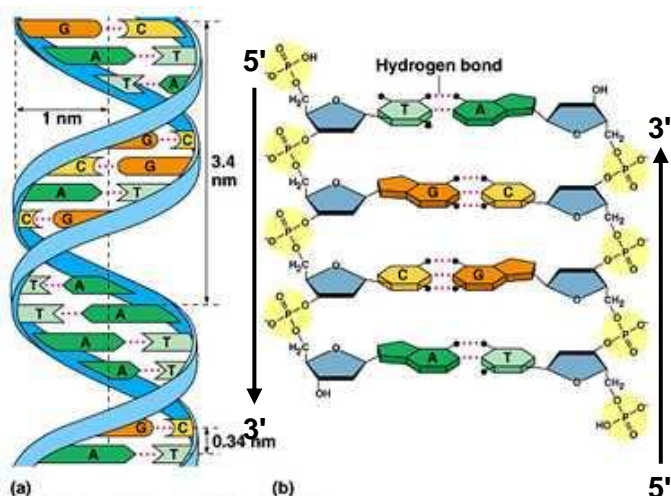
The DNA model published by Watson and Crick in 1953,<sup>17</sup> informed by the splendid photograph by Franklin and Gosling,<sup>14</sup> made two critical contributions. First, Crick recognized from the space group of DNA\* taken from Rosalind Franklin's work that the structure of DNA must have dyad symmetry, that is it should be the same if rotated 180°. This was possible only if the two helices were antiparallel to each other (**Fig. 12b**). We'll discuss soon the implications of this.

The second major contribution was the idea that the helices could be held together by hydrogen bonds between complementary nucleotides (**Fig. 12a**). Surprisingly, although Chargaff had made his work known to Watson and Crick, they and others on the scene asserted that the Chargaff rules played no major role in the formulation of the model, though the ability of the model to account for the equivalence between A:T and G:C was immediately gratifying.<sup>19</sup> The base pairing of complementary nucleotides is probably the main reason why their model achieved rapid acceptance. For the first time, a model had been put forward that could suggest a mechanism by which the genetic material could be replicated – the molecule already contained within it two copies of the same information. It was much less clear how DNA could specify the structure and function of a cell, but the model made clear that the answer lay in the order of nucleotides. There was nothing left that varied.

**SQ10. If one strand of DNA had the sequence 5'-GGACT-3', what would be the sequence of the second strand? Draw the double helix.**

**SQ11. How is it that Watson and Crick's model accounts for the replication of the genetic material?**

**SQ12. Could you have come up with the model yourself? No need to wonder... give it a try using *Build Your Own DNA*, available on the course web site!**



**Figure 12. Watson and Crick model of DNA.** (a) Base pairing and dimensions of double helix. (b) Antiparallel strands. (Figure slightly modified from one copyrighted by Pearson Education, Inc. publishing as Benjamin Cummings)

\* In crystallography, space group refers to the shape and symmetry of the crystal.

There was one more high quality x-ray photograph of DNA besides Franklin & Gosling's. In 1951, two years before Franklin obtained the photograph that set Watson's heart racing, a graduate student Elwyn Beighton, offered his mentor William Astbury the photograph shown in **Fig. 6C**. You'll note that both photographs share the same essential features, yet the earlier photograph was never published. Why didn't Astbury recognize it's value? It wasn't from lack of expertise. Astbury had been studying protein structure through x-ray analysis for decades, having learned the trade from William Bragg himself.<sup>†</sup> Nor could you explain the loss from lack of interest. His personal letters show his great excitement at learning of the work of Avery, MacLeod, and McCarty. Indeed, Astbury wrote to Avery and later to Chargaff asking for material with which he could begin his analysis of DNA structure. DNA sent by Chargaff was most likely that used by Beighton to make his photograph. So far from being a dilettante or disinterested, Astbury was ready and eager to face in DNA the same complications with which he was so familiar from his studies of protein, variability that he knew was necessary for a molecule that could describe life's rich diversity. No doubt he, of all people, recognized Beighton's photograph for what it was, a testament to a helix, but whereas Watson and Crick envisioned the variation of nucleotides within that structure, Astbury, was disappointed by its sameness – just a boring, uniform helix – an indication that perhaps the champions of the tetranucleotide hypothesis were right after all.<sup>4</sup>

**SQ13. What do you think disposed Watson and Crick, but not Astbury, to see the potential in DNA?**

#### **D. Directionality and palindromic sequences**

The fact that DNA has directionality – 5'-to-3', top to bottom in one strand and 5'-to-3', bottom to top in the other – lays on us the responsibility that we consider this when we talk about a DNA sequence. The sequence 5'-ATG-3' is an entirely different beast from 3'-ATG-5'. To keep our sanity, those who deal with sequences have stipulated that sequences will always be considered as 5'-to-3' unless explicitly specified 3'-to-5'. So if you are given a sequence ATG, you may be sure that it what is meant is the 5'-ATG-3' version or perhaps:

5'-ATG-3'  
3'-TAC-5'

The antiparallel nature of DNA has profound implications for the replication of DNA, a subject for later consideration.

**SQ14. One strand of DNA has the sequence GGACT. What is the sequence of the opposite strand?**

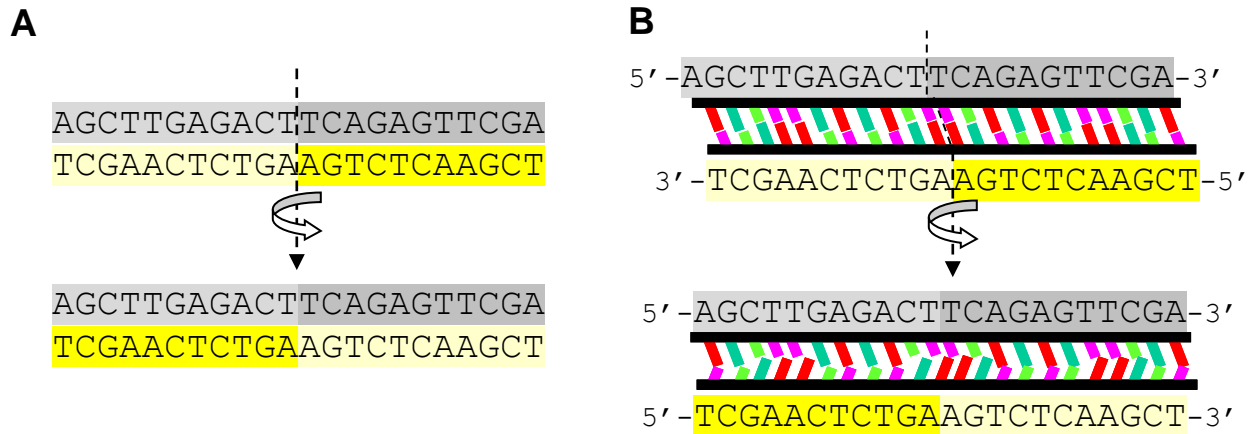
**SQ15. Which of the following represent two DNA sequences that will pair with each other?**

- a. 5'-GGAGTT-3' and 5'-CCTCAA-3'
- b. 5'-GGAGTT-3' and 3'-CCTCAA-5'
- c. 5'-GGAGTT-3' and 5'-AACTCC-3'
- d. 5'-GGATCC-3' and 5'-GGATCC-3'

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<sup>†</sup> You'll recall Bragg from the notes on Perutz et al (1965) as the head of Cavendish and co-inventor of x-ray crystallographic analysis.





**Figure 13: Directionality of DNA.** Two views of a DNA sequence that appears to be palindromic (reads the same forwards and backwards). (A) False picture of reality, implying that the bottom strand can be rotated 180° and still base pair with the top strand. (B) More realistic view, illustrating that rotating the bottom strand 180° prevents the nucleotides from aligning well enough to base pair. The bottom structure thus cannot occur.

Nucleic acid sequences that can basepair with themselves are called “palindromes” and play an important role in DNA and RNA function. Palindromes are sequences that read the same forwards as backwards. You may be familiar with palindromes from those in English, such as "Madam, I'm Adam", but don't be fooled: biological palindromes have an important difference. The sequence "AGTTGA" would be a palindrome in English but it is not a DNA palindrome, because DNA is always read 5' to 3'. Reading it backwards is not done by reading the same sequence 3' to 5' but rather by reading the *opposite*, antiparallel strand 5' to 3'.

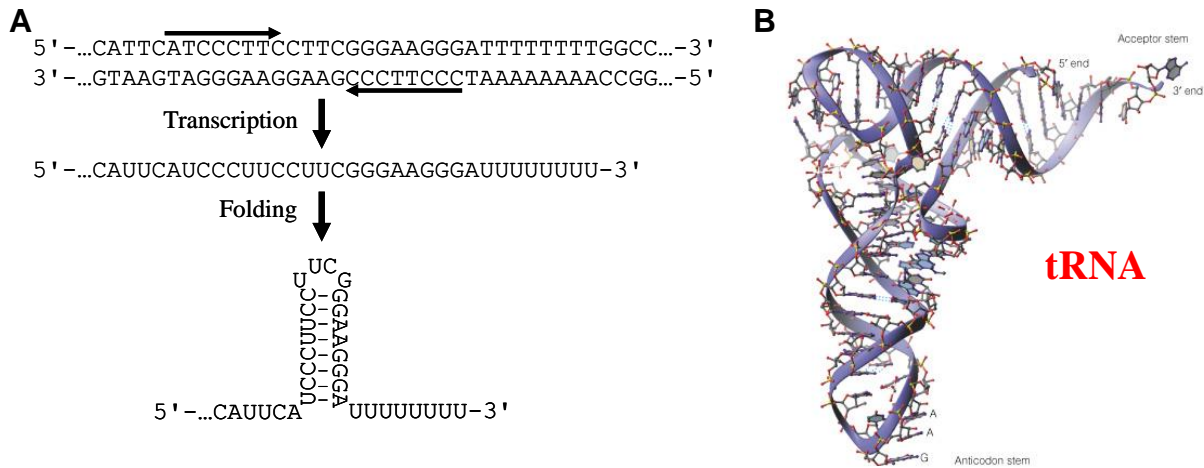
Consider the sequence shown in **Fig. 13A** (top strand), AGCTTGAGCTTCGAGTTCGA. It appears to read the same forwards and backwards, as does its opposite strand, TCGAACTCGAAGCTCAAGCT. Furthermore, flipping either sequence around 180° would seem to change nothing. This semblance of reality is far from the truth, as shown in **Fig. 13B**. Flipping the bottom sequence destroys the possibility of base-pairing, because a 5'-to-3' sequence cannot bind with in parallel to another 5'-to-3' sequence. 3'–TCGAA...AAGCT–5' is not the same as 5'–TCGAA...AAGCT–3'!

**SQ16. With that definition, why is AGTTGA not a DNA palindrome?**

**SQ17. Make up a 6-nucleotide DNA sequence that *is* a palindrome.**

Such sequences may seem to you like artificial curiosities, but in fact palindromes are important determinants of RNA structure and are also frequent targets of DNA- and RNA-binding proteins, including proteins that regulate transcription. These sequences are therefore of great importance in the bioinformatic analysis of DNA.

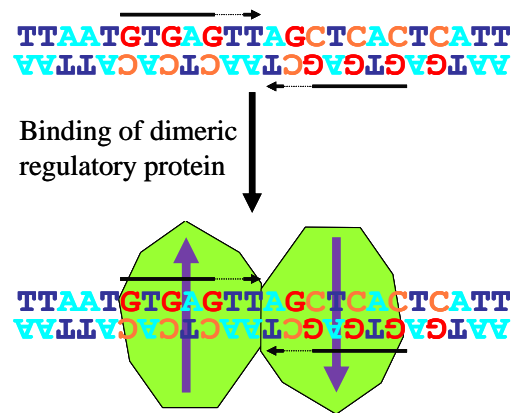
For example, **Fig. 14A** shows a DNA sequence that contains a gapped palindrome. The transcription of this sequence to single-stranded RNA allows the palindrome to fold up into a hairpin structure that is recognized as the termination of transcription. **Fig. 14B** shows the well-known structure of tRNA, which arises because of many self-annealing sequences, which can be thought of as gapped palindromes.



**Figure 14. Palindromic RNA sequences.** (A) Transcription of a DNA sequence containing a gapped palindrome produces an RNA that can fold to produce a common structure recognized as the termination of transcription. (B) RNA with many regions where self-base-pairing is possible, leading to the mature structure of a tRNA (copyright Benjamin/Cummings, an imprint of Addison Wesley Longman Inc).

Palindromic sequences in DNA hardly ever unpair from their complementary strands and form hairpins. However it is very common for palindromic DNA sequences to function as protein binding sites, as illustrated in **Fig. 15**. Regulatory DNA-binding proteins are often dimeric (two-subunit), with each of the two subunits binding to an arm of a palindromic sequence.

There is a sound evolutionary reason why this is the case. Regulatory proteins must bind to specific sequences in order to regulate specifically one gene and not another. It takes time – lots of time – for a protein to evolve to bind to a specific DNA sequence, and it ought to take more time the longer the sequence is to which the protein must bind. That means that it would take less time for a protein to evolve that binds to a 7-nucleotide sequence than a 14-nucleotide sequence. But if the 14-nucleotide sequence is a palindrome, then a 7-nucleotide-specific protein is all you need to bind to the full 14 nucleotides. It's true, evolving a 14-nucleotide palindrome takes more time than a 7-nucleotide sequence, but less than you might think, because there are genomic processes that cause gapped palindromes to arise much more frequently than expected by chance.



**Figure 15. Binding of dimeric protein to palindromic DNA.** Arrows show a region that is palindromic (dotted lines indicate a gap in the palindrome). The green blobs represent a subunit of a two-subunit regulatory protein, each subunit binding to one arm of the palindrome. The arrows indicate the opposite orientations of the subunits.

**SQ18. What is the relationship between a palindromic sequence and a potential hairpin structure?**

**SQ19. Using arrows, identify palindromic sequences in the tRNA shown in Fig. 14B.**

**SQ20. Speculate on how a dimeric structure might be necessary for the functioning of a DNA-binding protein.**

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