A Brief History of DNA

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Introduction

On April 2, 1953 JD Watson and FHC Crick published their now famous paper on the structure of deoxyribonucleic acid (DNA). That publication in a sense marked the end of a story that began nearly a century earlier in a laboratory in Tübingen, Germany. It was in this laboratory, under the direction of the great German physiologist Felix Hoppe-Seyler, that an unknown 25-year old Swiss scientist named Friedrich Miescher discovered a cellular substance that was unlike anything that had previously been seen (Figure 1). The year was 1869.

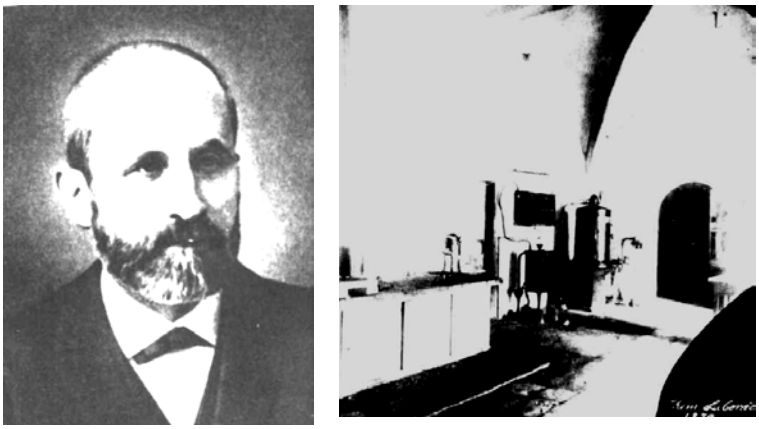

Figure 1. Photographs of Friedrich Miescher and of the laboratory in which he worked in Tübingen (Source: Portugal and Cohen, 1977).

Meischer had trained to follow his father, Johann, into medicine and to do research as both his father and his uncle, the famous Swiss embryologist, Wilhelm His, had done. Meischer was, however, quite hard of hearing and this eliminated many possible avenues for a medical career. As an alternative, he suggested to his father and uncle that he might pursue additional education in physiology. Having secured their assent, he arrived in Tübingen in 1868. There, he joined the laboratory of physiological chemistry that had, under Felix Hoppe-Seyler, gained a considerable reputation in the newly founded field of tissue chemistry, what, today, has become known as biochemistry.

As it was the chemistry of the cell that was of primary interest to him, Meischer initially chose to study lymph cells. He quickly found that lymph cells could only be obtained from lymph glands directly and were available in small quantities. On the other hand, in the days before the adoption of antiseptic techniques was widespread there was another cell type that was available in larger quantities and on a daily basis. One need only go to the local hospital and collect bandages from infections to have a usable supply of pus cells. After developing a method to isolate cells from bandages using a sodium sulfate solution, Meischer began an attempt to learn what materials formed tissues in pus cells. His goal was the same as nearly every physiological chemist of his day, to isolate and characterize proteins. Proteins had been discovered in the 1830s by Gerardus Johannes Mulder and were considered to be the most important of cellular materials. In fact, the name protein comes from the Greek word *proteios* which means "of the first importance" (Portugal and Cohen, 1977).

Meischer began his studies of pus cells by treating them with various combinations of salts. He observed that the cells would react very differently to different salts and that one class in particular gave a curious result,

> "In the experiment with weakly alkaline fluids, precipitates were obtained from the solutions by neutralization that were not soluble in water, acetic acid, in very dilute hydrochloric acid, or in sodium chloride and consequently cannot belong among any of the protein substances known hitherto."
> (F Meischer, from [1]).

Meischer was convinced that he had discovered a new type of cellular material and went on to determine where in the cell it came from. He noted that cell nuclei were particularly affected by the weak alkaline solutions and, "According to this fact, known to some degree by histologists, the substance could belong to the nuclei … The most rational approach was to prepare pure nuclei." (F Meischer, from Portugal and Cohen, 1977). Meischer subsequently found that this new substance was unique to the nuclei not only of the pus cells he started with but also the nuclei of yeast, liver, kidney, and nucleated blood cells. He called this new substance nuclein.

The Structure of DNA

At about the same time as Miescher was writing about nuclein, major advances in histology were taking place. Among these was the development of a battery of stains that would selectively highlight sub-cellular structures. These selective stains led to the demonstration that the nucleus was a distinct structure and that much of the material contained in the nucleus was not protein but, rather, it was Miescher's nuclein. In the latter part of the 1870's landmark research established the role of chromosomes in cell division. It was the work of both Eduard Zacharias and Walther Flemming that showed it was, in fact, the chromosomes themselves that were composed of a mixture of protein

and nuclein (Portugal and Cohen, 1977). This launched the search for the role of the chromosomes and nuclein in heredity. By the end of the nineteenth century and mainly due to the work of Albrecht Karl Ludwig Martin Leonard Kossel, the basic chemical components of nuclein were known. These were the pentose sugar deoxyribose, phosphates, and the four bases Adenine, Cytosine, Guanine, and Thymine. It was also discovered that there was another component in the cell that was similar to nuclein except for the identity of the pentose sugar as ribose and the substitution of Uracil for Thymine. This discovery was responsible, in part, for the term nuclein being replaced with nucleic acid and the designation of the two nucleic acids as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (Figure 2).

In the early part of the twentieth century the stage was set for work to advance on understanding how the nucleic acids were put together and how they actually functioned. One of the first models of a DNA strand was proposed by Steudel in 1912. He suggested that the phosphate groups were linked together to form a polyphosphate backbone. In the same year Levene and Jacobs offered a model in which the sugars were joined via ether linkages (Portugal and Cohen, 1977). Neither these nor any other models were based upon a solid understanding of the structures of the components.

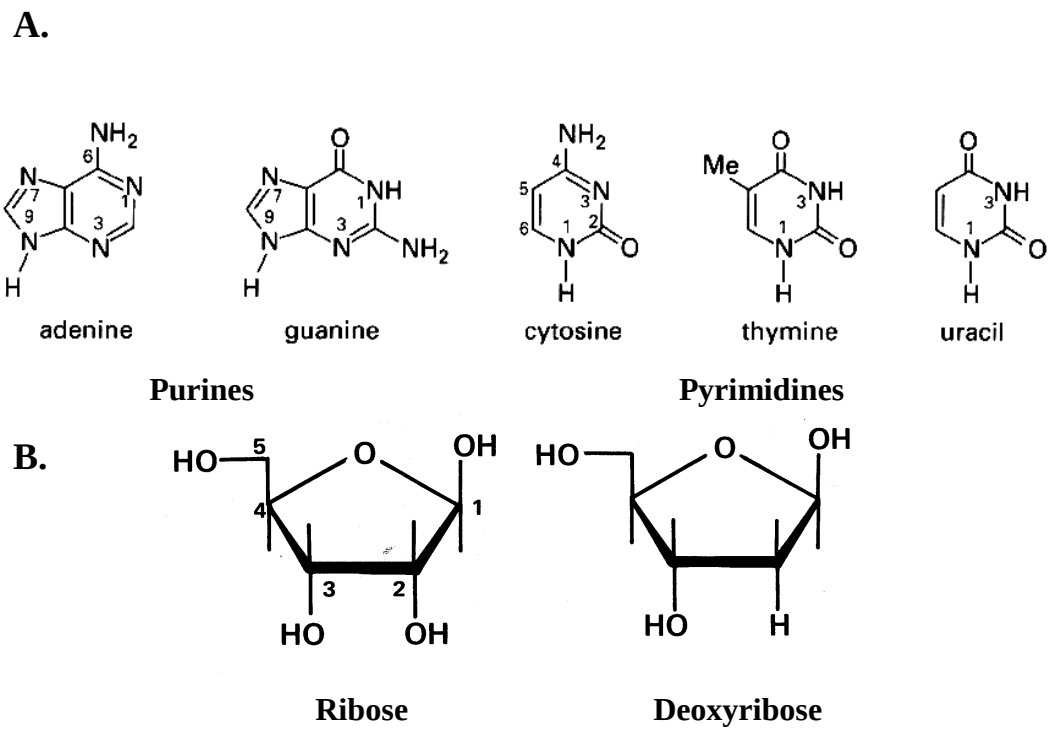

Figure 2. A. The five purine and pyrimidine bases of DNA and RNA. B. The pentose sugars of DNA and RNA.

In the 1920's the Russian-born chemist named Phoebus Aaron Theodore Levene began to form an idea about the structure of a DNA strands based upon his structural studies of hydrolysis products. His first model, proposed in 1921, was based upon his elucidation of the form of the sugars. This model correctly assumed that the linkages would involve the phosphates connecting the sugars but, unfortunately, the sugar structures were not right. He continued his work until, in 1935, he came up with the correct structure of the sugars and the linkages (Figure 3). The connections between the DNA bases on one strand were
through the deoxyribose sugars. The unit of a DNA molecule is the deoxyribose sugar, with a phosphate group, linked to one of the four bases. The bases are two pyrimidines; thymine (T) and cytosine (C) and two purines; adenine (A) and Guanine (G). This unit is called a nucleotide. Minus the phosphate it is called a nucleoside. Levene's model showed that the links between nucleotides were phosphodiesters from the 5' carbon of one nucleotide to the 3' carbon of the next nucleotide and that the bases were bound to the sugar through the 1' carbon.

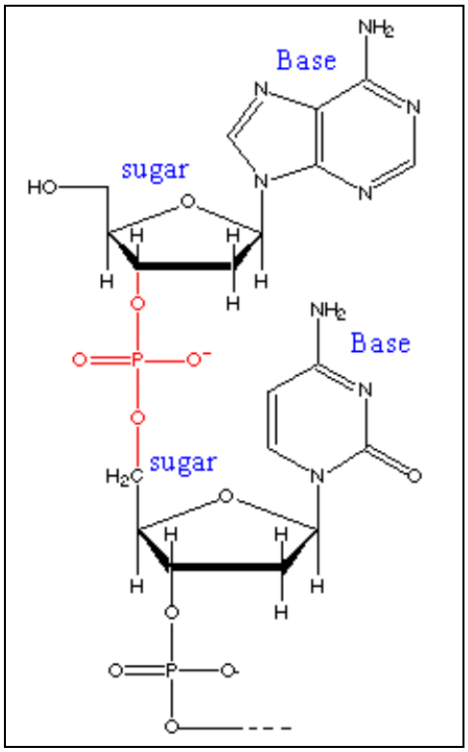

Figure 3. DNA strand model proposed by Levene in 1935 indicating the linkage of the base and sugar units (nucleosides) through an intervening phosphate group. Together, the sugar-base-phosphate unit is called a nucleotide. Direction in a DNA or RNA molecule is determined by the system established for numbering the carbon atoms in the sugar. The 1' to 4' carbons lie in the ring and the 5' carbon lies above it. Links between nucleotides are always through the 3' and 5' carbons.

With the publication and subsequent validation of Levene's model for a single strand of DNA, the most pressing questions were how many strands are there in a DNA molecule and how do they go together? Again, many false starts and incorrect models were proposed including one by Linus Pauling which was helical (twisted about a central axis) but contained three strands. Another model proposed having the strands on the inside of the structure with the individual purine and pyrimidine bases sticking out. None of the DNA structures proposed before 1953 were fully, or in many cases even partly, consistent with experimental observation. In 1953 James Watson and Francis Crick hit

upon the correct three-dimensional molecular structure of DNA. They did so through building models based upon detailed chemical and physical observations. Among these observations was the work of Irwin Chargaff and colleagues at Columbia University around 1950. Until Chargaff it was generally believed that the four DNA bases were present in all DNA in equal amounts. Chargaff demonstrated that, while the amount of deoxyadenosine (dA) roughly equaled the amount of deoxythymidine (dT) and the amount of deoxycytosine (dC) roughly equaled the amount of deoxyguanosine (dG), the ratios of dA/dT to dC/dG differed from DNA source to DNA source. These rough equivalences were subsequently validated in the form of complementary base pairing in the Watson-Crick DNA structure. The question of how many strands and how they went together was answered by the X-ray crystallographic work of Rosalind Franklin at Kings College in London. Her x-ray studies showed that DNA was indeed helical and that two strands with the bases facing inward fit the observed data. Her other, less heralded contribution was the recognition that the two strands ran in opposite directions. Watson and Crick were able to put all of this disparate evidence together in the form of a molecular model for DNA in which the core was composed of A:T and C:G pairs with two backbone sugar-phosphate strands running antiparallel (Figure 4). This entire

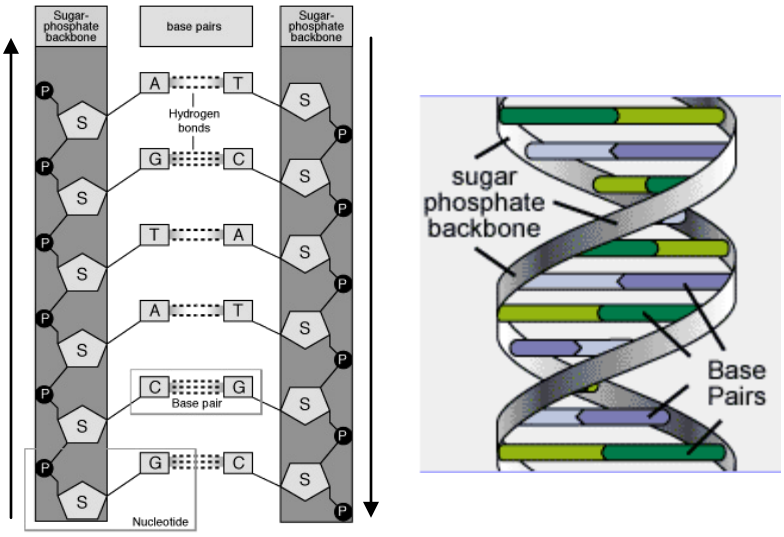

Figure 4. A representation of the relationship between base pairing and strand direction in a DNA molecule. Also shown is an idealized helix completing one turn.

structure was then wound around a central axis in which the molecule made one complete turn every ten bases. They announced their model in the April 25, 1953 issue of Nature (http://www.nature.com/genomics/human/watson-crick/watson_crick.pdf). In the final paragraph of that paper they remark "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material" (Watson and Crick, 1953a). In a subsequent paper in the same year they elaborated upon the replication mechanism in which each strand serves as a complementary template for copying and in which each daughter molecule is composed

of a new strand and the template strand (Watson and Crick, 1953b). Their work, along with that of Rosalind Franklin and Maurice Wilkins at King's College in London, was recognized in the awarding of the 1962 Nobel Prize in Medicine to Watson, Crick, and Wilkins. Roslaind Franklin, whose X-ray crystallographic studies were so instrumental to the final answer, left King's College for Birkbeck College in 1953. She became ill in 1957 and died of cancer in 1958 at age 37 years. The rules of the Nobel Committee prohibit posthumous awards of Prizes.

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Videos

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PBS: Cracking the Code of Life. NOVA (VHS and DVD)

Race for the Double Helix BBC 1994 (Jeff Goldblum plays Watson) (VHS)

DNA: The Amazing Double Helix 1999 (VHS)

