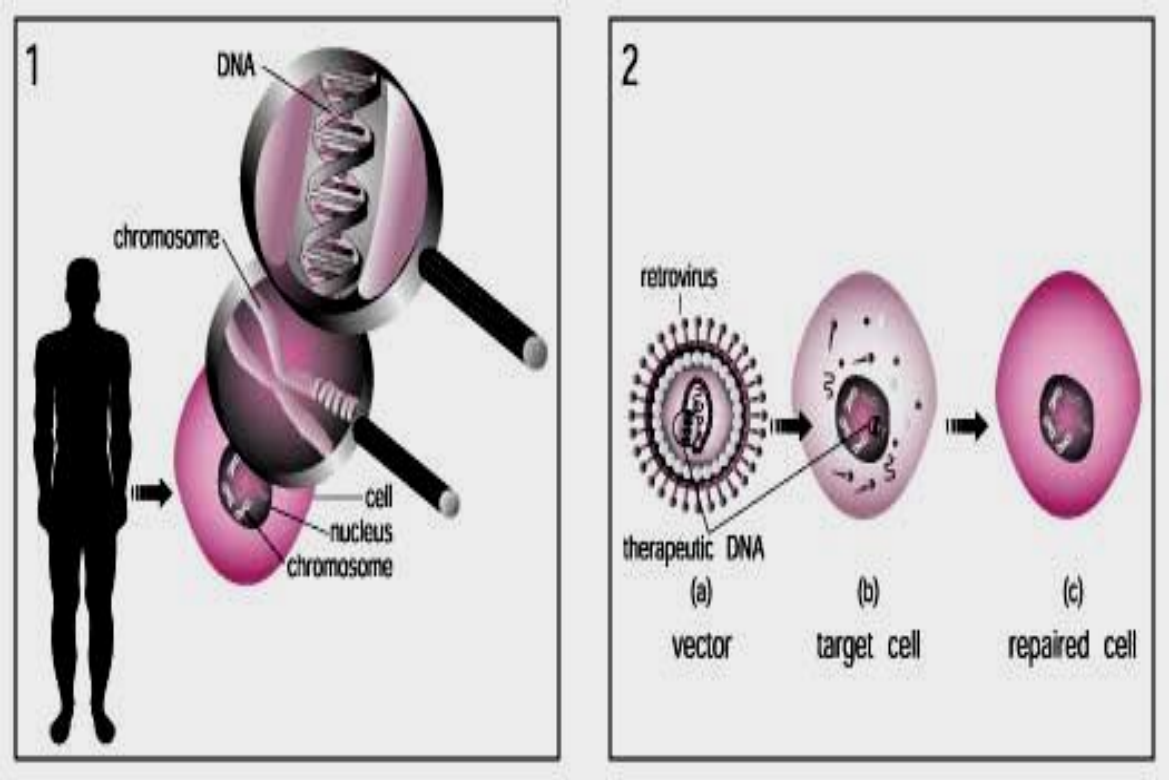
Genetic Engineering for Medicine and Food in History



Submitted by

Abdul Nasser Kaadan, MD, PhD[•]

Yasser AL-KHDR [••]

[*]Chairman, History of Medicine Department, *Institute for the History of Arabic Science*, Aleppo University, Aleppo-Syria
President of ISHIM (www.ishim.net)
P.O. Box: 7581 ,Aleppo ,Syria
e-mail: ankaadan@gmail.com
Phone 963 944 300030, Fax 963 21 2236526

[**]Bachelor of Pharmacy, Master stage student, Institute for the History of Arabic Science, Aleppo University

Contents:

Interduction about Components of DNA:.....……. **1**

The Scientists whom studied of DNA :…….. **6**

DNA Previous :……..……..……..**11**

Genetic Engineering and Medicine: …………...…. ……**16**

Gene Therapy History:…….....**19**

useing of recombinant DNA to produce human insulin:……..**23**

Genetically Modified Food:.....**25**

Abstract.....**35 -36**

Components of DNA:

DNA is a polymer. The monomer units of DNA are nucleotides, and the polymer is known as a "polynucleotide." Each nucleotide consists of a 5-carbon sugar (deoxyribose), a nitrogen containing base attached to the sugar, and a phosphate group. There are four different types of nucleotides found in DNA, differing only in the nitrogenous base. The four nucleotides are given one letter abbreviations as shorthand for the four bases.

- A is for adenine
- G is for guanine
- C is for cytosine
- T is for thymine

Purine Bases:

Adenine and guanine are purines. Purines are the larger of the two types of bases found in DNA. Structures are shown below:

Structure of A and G

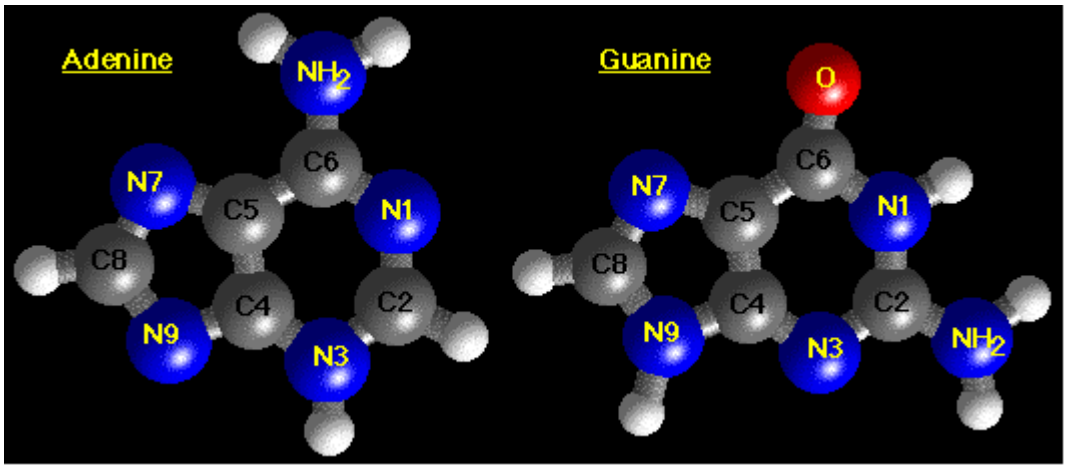


figure 1

The 9 atoms that make up the fused rings (5 carbon, 4 nitrogen) are numbered 1-9. All ring atoms lie in the same plane.

Pyrimidine Bases

Cytosine and thymine are pyrimidines. The 6 stoms (4 carbon, 2 nitrogen) are numbered 1-6. Like purines, all pyrimidine ring atoms lie in the same plane.

Structure of C and T

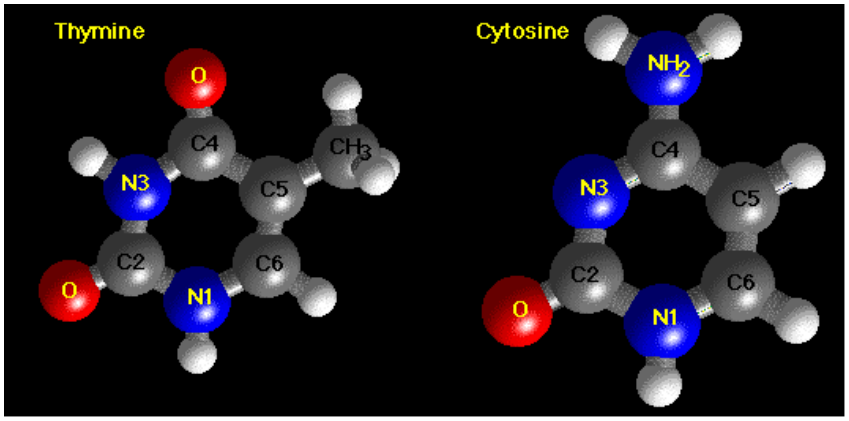


figure 2

Deoxyribose Sugar

The deoxyribose sugar of the DNA backbone has 5 carbons and 3 oxygens. The carbon atoms are numbered 1', 2', 3', 4', and 5' to distinguish from the numbering of the atoms of the purine and pyrmidine rings. The hydroxyl groups on the 5'- and 3'-carbons link to the phosphate groups to form the DNA backbone. Deoxyribose lacks an hydroxyl group at the 2'-position when compared to ribose, the sugar component of RNA.

Structure of deoxyribose

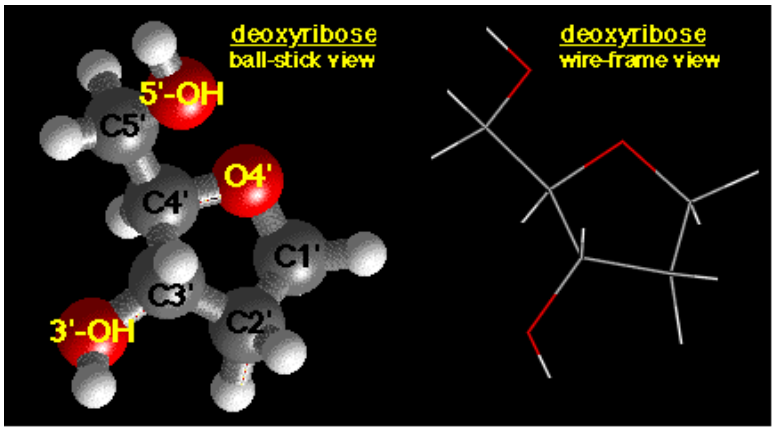


figure 3

Nucleosides

A nucleoside is one of the four DNA bases covalently attached to the C1' position of a sugar. The sugar in deoxynucleosides is 2'-deoxyribose. The sugar in ribonucleosides is ribose. Nucleosides differ from nucleotides in that they lack phosphate groups. The four different nucleosides of DNA are deoxyadenosine (dA), deoxyguanosine (dG), deoxycytosine (dC), and (deoxy)thymidine (dT, or T).

Structure of dA

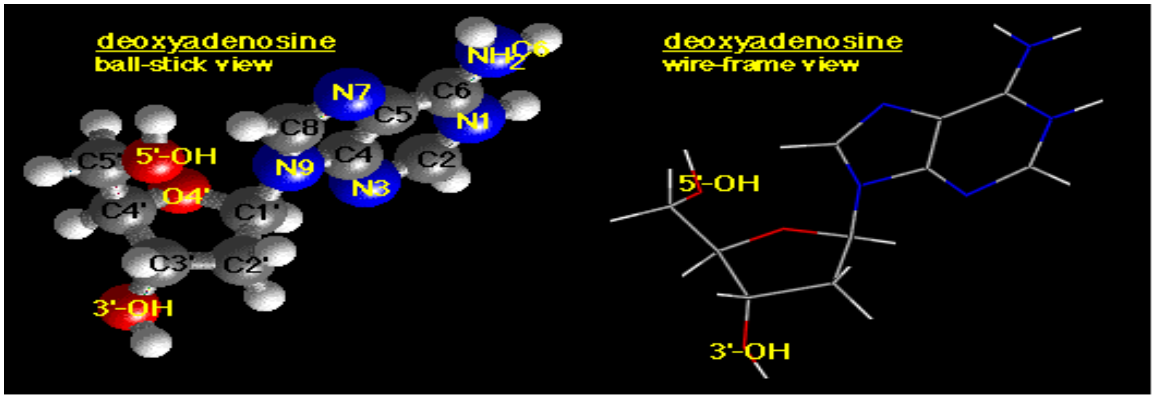


figure 4

In dA and dG, there is an "N-glycoside" bond between the sugar C1' and N9 of the purine.

Nucleotides

A nucleotide is a nucleoside with one or more phosphate groups covalently attached to the 3'- and/or 5'-hydroxyl group(s).

DNA Backbone

The DNA backbone is a polymer with an alternating sugar-phosphate sequence. The deoxyribose sugars are joined at both the 3'-hydroxyl and 5'-hydroxyl groups to phosphate groups in ester links, also known as "phosphodiester" bonds.

Features of the 5'-d(CGAAT) structure:

- Alternating backbone of deoxyribose and phosphodiester groups
- Chain has a direction (known as polarity), 5'- to 3'- from top to bottom
- Oxygens (red atoms) of phosphates are polar and negatively charged
- A, G, C, and T bases can extend away from chain, and stack atop each other
- Bases are hydrophobic

DNA Double Helix

DNA is a normally double stranded macromolecule. Two polynucleotide chains, held together by weak thermodynamic forces, form a DNA molecule.

Structure of DNA Double Helix

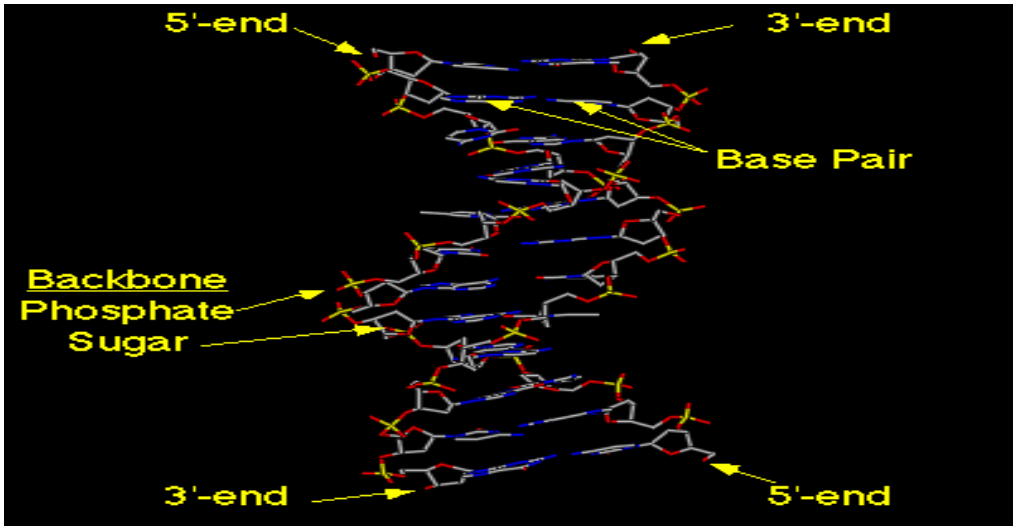


figure 5

Features of the DNA Double Helix

- Two DNA strands form a helical spiral, winding around a helix axis in a right-handed spiral
- The two polynucleotide chains run in opposite directions
- The sugar-phosphate backbones of the two DNA strands wind around the helix axis like the railing of a sprial staircase
- The bases of the individual nucleotides are on the inside of the helix, stacked on top of each other like the steps of a spiral staircase.

Base Pairs

Within the DNA double helix, A forms 2 hydrogen bonds with T on the opposite strand, and G forms 3 hyrdorgen bonds with C on the opposite strand.

Example of dA-dT base pair as found within DNA double helix

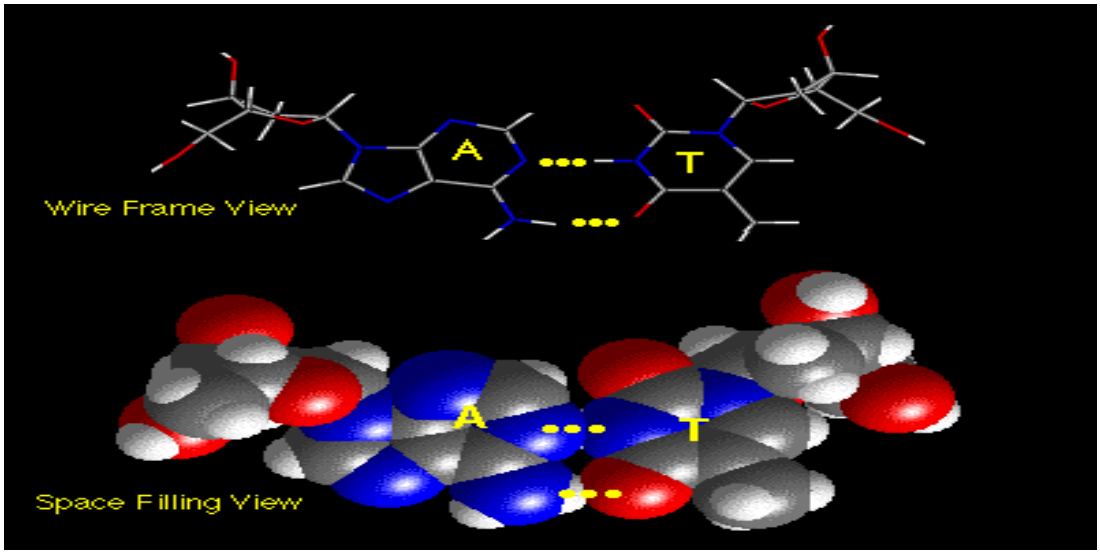


figure 6

- dA-dT and dG-dC base pairs are the same length, and occupy the same space within a DNA double helix. Therefore the DNA molecule has a uniform diameter.
- dA-dT and dG-dC base pairs can occur in any order within DNA molecules

DNA Helix Axis

The helix axis is most apparent from a view directly down the axis. The sugar-phosphate backbone is on the outside of the helix where the polar phosphate groups (red and yellow atoms) can interact with the polar environment. The nitrogen (blue atoms) containing bases are inside, stacking perpendicular to the helix axis.

The Scientists whom studied of DNA :

- Gregor Mendel
- Frederick Griffith
- Oswald Avery
- Erwin Chargaff
- Rosalind Franklin & Maurice Wilkins
- James Watson & Francis Crick

Gregor Mendel

Gregor Mendel the "Father of Genetics" performed an experiement in 1857 that led to increased interest in the study of genetics. Mendel who became a monk of the Roman Catholic church in 1843, studied at the University of Vienna where he mastered mathematics, and then later performed many scientific experiments. The greatest experiment that Mendel performed involved growing thousands of pea plants for 8 years. He was forced to give up his experiment when he became abbot of the monastery because of the political problems of the time. He died in 1884, but has been remembered for the great contribution to science that he made.

Frederick Griffith

In 1928 a scientist named Frederick Griffith was working on a project that enabled others to point out that DNA was the molecule of inheritance. Griffith's experiment involved mice and two types of pneumonia, a virulent and a non-virulent kind. He injected the virulent pneumonia into a mouse and the mouse died. Next he injected the non-virulent pneumonia into a mouse and the mouse continued to live. After this, he heated up the virulent disease to kill it and then injected it into a mouse. The mouse lived on. Last he injected non-virulent pneumonia and virulent pneumonia, that had been heated and killed, into a mouse. This mouse died.

Why? Griffith thought that the killed virulent bacteria had passed on a characteristic to the non-virulent one to make it virulent. He thought that this characteristic was in the inheritance molecule. This passing on of the inheritance molecule was what he called transformation.

	**Died**	Mouse with virulent pneumonia	Mouse with heated virulent pneumonia and non-virulent pneumonia mixed together
	**Lived**	Mouse with non-virulent pneumonia	Mouse with heated, killed virulent pneumonia

Oswald Avery

Fourteen years later a scientist named Oswald Avery continued with Griffith's experiment to see what the inheritance molecule was. In this experiment he destroyed the lipids, ribonucleic acids, carbohydrates, and proteins of the virulent pneumonia. Transformation still occurred after this. Next he destroyed the deoxyribonucleic acid. Transformation did not occur. Avery had found the inheritance molecule, DNA!

Erwin Chargaff

To understand the DNA molecule better scientists were trying to make a model to understand how it works and what it does. In the 1940's another scientist named Erwin Chargaff noticed a pattern in the amounts of the four bases: adenine, guanine, cytosine, and thymine. He took samples of DNA of different cells and found that the amount of adenine was almost equal to the amount of thymine, and that the amount of guanine was almost equal to the amount of cytosine. Thus you could say: A=T, and G=C. This discovery later became Chargaff's Rule.

Rosalind Franklin and Maurice Wilkins

Two scientists named, Rosalind Franklin and Maurice Wilkins, decided to try to make a crystal of the DNA molecule. If they could get DNA to crystallize, then they could make an x-ray pattern, thus resulting in understanding how DNA works. These two scientists were successful and obtained an x-ray pattern. The pattern appeared to contain rungs, like those on a ladder between to strands that are side by side. It also showed by an "X" shape that DNA had a helix shape.

James Watson and Francis Crick

In 1953 two scientists, James Watson and Francis Crick, were trying to put together a model of DNA. When they saw Franklin and Wilkin's picture of the X-ray they had

enough information to make an accurate model. They created a model that has not been changed much since then. Their model showed a double helix with little rungs connecting the two strands. These rungs were the bases of a nucleotide. At first Watson and Crick were set back with a problem, how to bond the bases together, and how to solve the problem of the sizes of the bases. Adenine and Guanine were purines having two carbon-nitrogen rings in their structures. Thymine and Cytosine were pyrimidines having one carbon-nitrogen ring in its structure. If DNA were to have its bases pair up so that the purines and the pyrimidines were together, then it would look wobly and crooked. Watson and Crick then found that if they paired Thymine with Adenine and Guanine with Cytosine DNA would look uniform. This pairing was also in accordance with Cargaff's rule. They also found that a hydrogen bond could be formed between the two pairs of bases. In all DNA strands if one side has a Thymine base then the other has the opposite: Adenine and so on with Guanine and Cytosine. Each side is a complete compliment of the other.

By using the picture of the crystallized DNA, Watson and Crick were able to put together the model of DNA. Some have speculated that they did not give Rosalind Franklin enough credit for her work; she had certainly made history. Watson and Crick did use the new information very quickly as it is shown by the fact that their paper showing the model of DNA was published in the same issue of *Nature* as Franklin's picture. Watson and Crick, did, though, use this new information and information from Avery, Chargaff, Griffith, and others. They simply pieced together the puzzle. The Nobel Prize was awarded a few years after the presentation of the model to Watson, Crick, and Maurice Wilkins. Rosalind Franklin did not receive the prize because she had died of cancer by this time. Maurice Wilkins was able to share the prize with Watson and Crick, though, because of his work with Franklin. Her accomplishment should never be forgotten.

DNA History

The Race to Solve the Mystery: The Structure of DNA



James Watson



Francis Crick

Working together at the University of Cambridge in England, James Watson, an American scientist, and Francis Crick, a British researcher, made a major scientific breakthrough when they discovered the famous "double helix" -- the structure of DNA, the molecule of life.

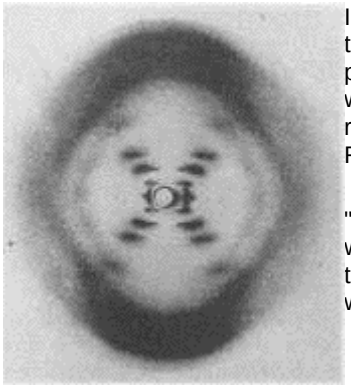
In the April 25, 1953, issue of the science journal *Nature,* Watson and Crick wrote: ""We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest."

Those modest words were an understatement. Nine years later, in 1962, they received the Nobel Prize for answering one of science's long-pondered mysteries, advancing the emerging field of molecular biology in the process.

Watson and Crick's quest helps illustrate how collaboration, creativity, hard work, and serendipity often conspire on the path to scientific achievement.

A Eureka Moment

Deoxyribonucleic acid (DNA) was first isolated in 1869 by the Swiss scientist Friedrich Miescher. He called the white, slightly acidic chemical that he found in cells "nuclein." By the late 1940s, scientists knew what DNA contained -- phosphate, sugar, and four nitrogen-containing chemical "bases": adenine (A), thymine (T), guanine (G), and cytosine (C). But no one had figured out what the DNA molecule looked like.



In 1953, Linus Pauling, the great American chemist, claimed to have discovered the structure of the DNA molecule, but when Watson saw Pauling's research paper (which had not yet been published) on January 28, 1953, he knew it was wrong. A few days later at King's College in London, Watson was shown an X-ray diffraction photograph ***(see left)*** of the DNA crystal taken by scientist Rosalind Franklin.

"The instant I saw the picture, my mouth fell open and my pulse began to race," wrote Watson in his book *The Double Helix* (1968). The photo convinced him that the DNA molecule must consist of two chains arranged in a paired helix, which resembles a spiral staircase or ladder.

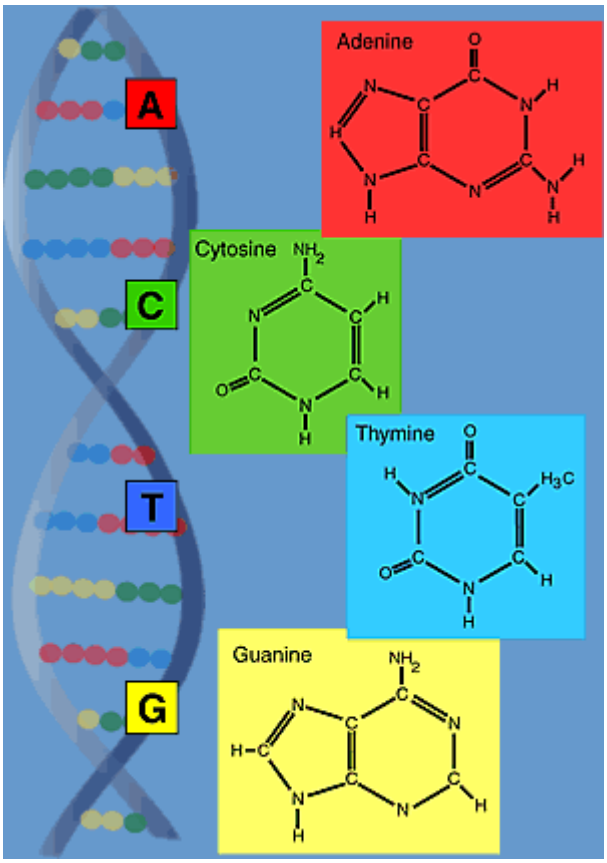


figure 7

The DNA molecule resembles a spiral staircase or ladder. The sides of the ladder are made up of alternating molecules of phosphate and the sugar deoxyribose, while each rung is composed of a pair of nitrogen-containing chemical bases connected in the middle. DNA has four bases - Adenine, Thymine, Cytosine, and Guanine. These bases always join up with the same partners - A with T, and C with G. Graphic courtesy of **www.GenomeNewsNetwork.org**/J. Craig Venter Institute.

Watson and Crick set about developing a stick-and-ball model of DNA's possible structure. The sides of the ladder were made up of alternating molecules of phosphate and the sugar deoxyribose, while each rung on the ladder was composed of a pair of nitrogen-containing bases connected in the middle. At first, the scientists were uncertain how DNA's four bases -- A, T, C, and G -- link up with each other. Then thanks to a suggestion from a colleague, they realized that the bases always join up with the same partners - A with T, and C with G.

On March 7, 1953, Watson and Crick finished their model, which reached 6 feet tall. "A Structure for Deoxyribose Nucleic Acid" was published in *Nature* on April 25, 1953. By the late 1950s, their work had been widely accepted by the scientific community.

In 1962, Watson and Crick received the Nobel Prize for Physiology or Medicine with Maurice Wilkins. He had published important crystallography work relating to DNA at the same time as Watson and Crick. Rosalind Franklin, whose photograph provided "a Eureka moment" for Watson, died in 1958 of cancer. Scientists wonder if she would have been honored with the award as well, had she lived.

The Double Helix Game
Click Here
Nobelprize.org

DNA Previous

Although the scientific community has been aware of DNA for more than 150 years, it is only in the last 60 years that DNA was identified as playing a key role in our genetic information. It wasn't until the mid 1980's that the power of DNA analysis for identification purposes was revealed.

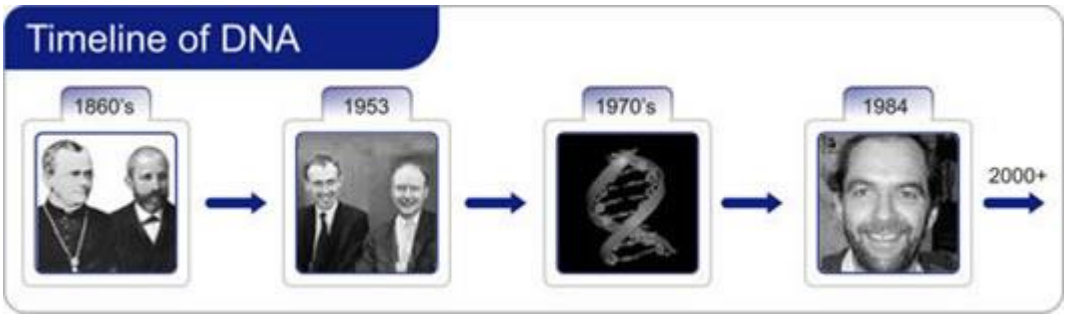


figure 8

1860's

In the late 1850's an Augustinian monk named Gregor Mendel performed a set of experiments that pointed to the existence of biological elements called genes. In 1865 he presented findings to the Natural History Society of Brunn, calling them the "Experiments in Plant Hybridization." Unfortunately his work was not appreciated in his own lifetime, however the principles and analytical procedures Medel developed are the basis of what today is the science of Genetics and Inheritance.

Although Mendel was responsible for the foundation of Genetics as a science, the biological elements responsible for the transfer of information from one generation to the other, was discovered by a Swiss biochemist Friedrich Miescher in 1869. Miescher was instrumental in disproving the current theory that all cells were made up of only proteins. While experimenting on pus cells he noted the presence of something that "cannot belong among any of the protein substances known hitherto." In fact he was able to show that it was not protein at all, being unaffected by the protein-digesting enzyme pepsin.

He also showed that the new substance was derived from the nucleus of the cell alone and consequently named it 'nuclein'. Miescher was soon able to show that nuclein could be obtained from many other cells and was unusual in containing phosphorus in addition to the usual ingredients of organic molecules - carbon, oxygen, nitrogen, and hydrogen.

In 1889 Richard Altmann renamed 'nuclein' to 'Nucleic Acid' and a few years later in 1893 Albrecht Kossel had succeeded in recognising four nucleic acid bases (nucleotides) Adenine, Thymine, Cytosine and Guanine.

1953

The structure of DNA had been a subject of great debate since 1944 when Avery et al. showed that DNA was responsible for the transference of information form one generation to the next. Many studies had been conducted and much was known about the composition of DNA, however its structure still eluded the scientific community. Then in 1953, James Watson (an American phage geneticist) and Francis Crick (An English physicist) ushered in a new age of biology when they published their paper in the journal Nature suggesting a structure for DNA. That structure — a double helix that can "unzip" to make copies of itself, not only confirmed that it was DNA responsible for genetic inheritance but also proposed a mechanism of action.

1970's

The advances of technology and methodology of DNA analysis in 1970's have made development of tools used for modern DNA testing possible.

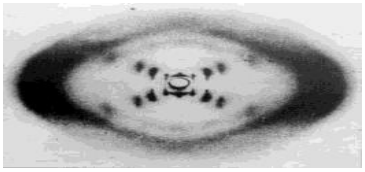
1984

The possibility that DNA could be used for human identity and relationship testing had been discussed from the time that DNA was first revealed as the molecule which makes people unique, however, it wasn't until the discovery of the first VNTR (Variable Number Tandem Repeats) probe by Prof. Alec Jeffreys (now Sir Alec) of Leicester University in 1984 when the first practical testing system became available. The first use of DNA testing for human identification anywhere in the world was in the UK as part of a non-criminal case in 1985, Sarbah vs. The Home Office, 1985 (the Ghana immigration case). In this case DNA testing was used to prove the mother-son relationship between Christiana Sarbah and her son Andrew

Milestones in DNA History

1869 Johann Friedrich Miescher identifies a weakly acidic substance of unknown function in the nuclei of human white blood cells. This substance will later be called deoxyribonucleic acid, or DNA.

1912 Physicist Sir William Henry Bragg, and his son, Sir William Lawrence Bragg, discover that theycan deduce the atomic structure of crystals from their X-ray diffraction patterns. This scientiFic tool will be key in helping Watson and Crick determine DNA's structure.



Pholo courtesy of Cold Spring Harhor Lahoratory Archives.

1924 Microscope studies using stains for DNA and protein show that both substances are present in chromosomes.

1928 Franklin Griffith, a British medical officer, discovers that genetic information can be transferred from heat-killed bacteria cells to live ones. This phenomenon, called transformation, provides the first evidence that the genetic material is a heat-stable chemical.

1944 Oswald Avery, and his colleagues Maclyn McCarty and Colin MacLeod, identify Griffith's transforming agent as DNA. However, their discovery is greeted with skepticism, in part because many scientists still believe that DNA is too simple a molecule to be the genetic material.

1949 Erwin Chargaff, a biochemist, reports that DNA composition is speciesspecific; that is, that the amount of DNA and its nitrogenous bases varies from one species to another. In addition, Chargaff finds that the amount of adenine equals the amount of thymine, and the amount of guanine equals the amount of cytosine in DNA from every species.

1953 James Watson and Francis Crick discover the molecular structure of DNA.

Photo by A.C. Barrington Brown, courtesy of Cold Spring Harbor Laboratory Archives.

1962 Francis Crick, James Watson, and Maurice Wilkins receive the Nobel Prize for determining the molecular structure of DNA.

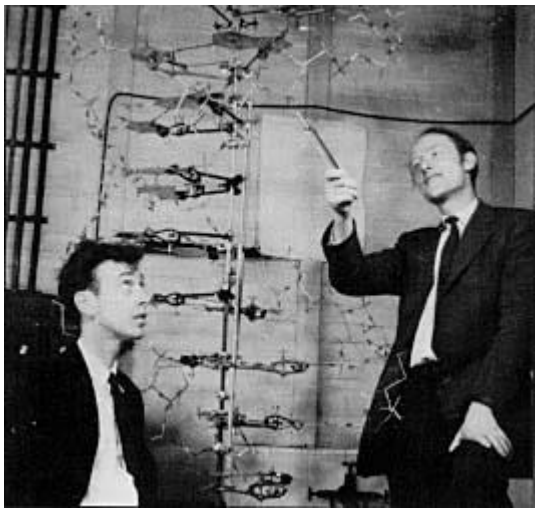


figure 9

Milestones in Biotechnology

1909 British physician Archibald Garrod first proposes the relationship between genes and proteins. He hypothesizes that genes might be involved in creating the proteins that carry out the chemical reactions of metabolism.

1930s Through experimentation with mutant strains of Neurospora bread mold, George Beadle and Edward Tatum support Garrod's hypothesis. This evidence will give rise to the "one gene-one proteinH hypothesis," that each protein in a cell results from the expression of a single gene.

1957 During a dysentery epidemic in Japan, biologists discover that some strains of bacterium are resistant to antibiotics. Later scientists will find that this resistance is transferred by olasmids.

1961 Sidney Brenner and Francis Crick establish that groups of three nucleotide bases, or codons, are used to specify individual amino acids.

Pholo courtesy of Huntington Potter and David Dressler.

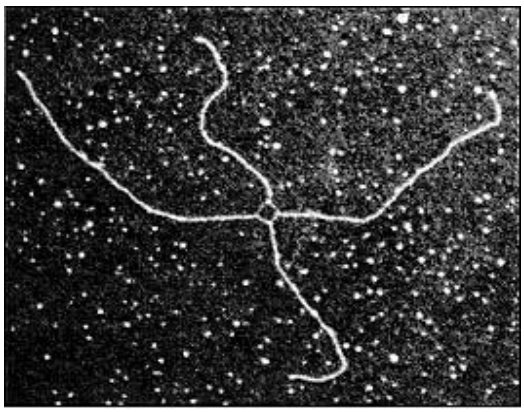


figure 10

1966 The genetic code is deciphered when biochemical analysis reveals which codons determine which amino acids.

1970 Hamilton Smith, at Johns Hopkins Medical School, isolates the first restriction enzyme, an enzyme that cuts DNA at a very specific nucleotide sequence. Over the next few years, several more restriction enzymes will be isolated.

1972 Stanley Cohen and Herbert Boyer combine their efforts to create recombinant DNA. This technology will be the beginning of the biotechnology industry.



figure 11

• • • • • •

Sources:

http://www.blc.arizona.edu/molecular_graphics/dna_structure/dna_tutorial.html

http://nobelprize.org/medicine/laureates/1962/index.html

http://www.genomenewsnetwork.org/resources/whats_a_genome/Chp1_1_1.shtml

http://www.sciencephotogallery.co.uk/articles/DNA_50yearsArticle.php

http://www.cshl.org/public/SCIENCE/Watson.html

http://www.wellcome.ac.uk/en/genome/geneticsandsociety/hg13b001.html

http://eurofinsforensics.co.uk

www.GenomeNewsNetwork.org