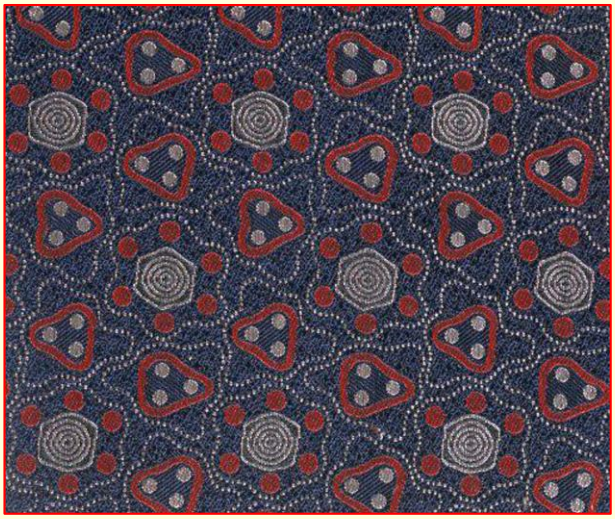


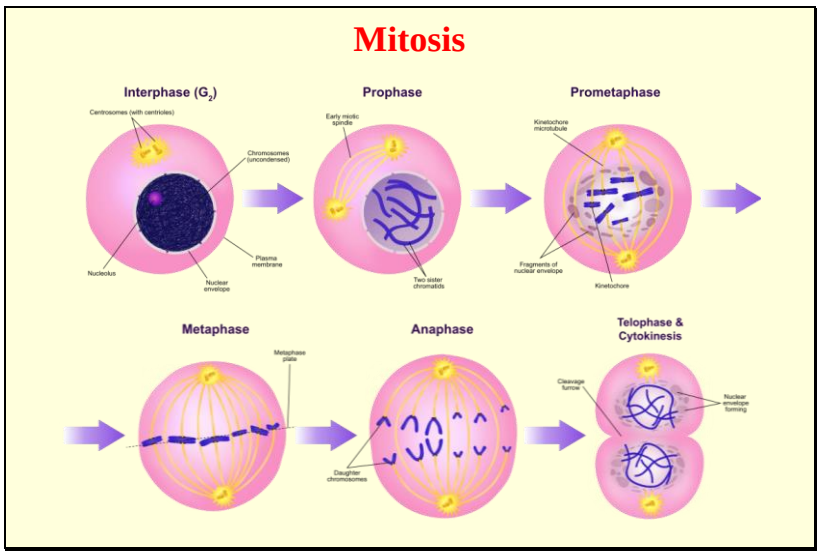
Life

Hemoglobin
Textile Pattern designed for Festival of Britain by Bernard Rowland, 1951

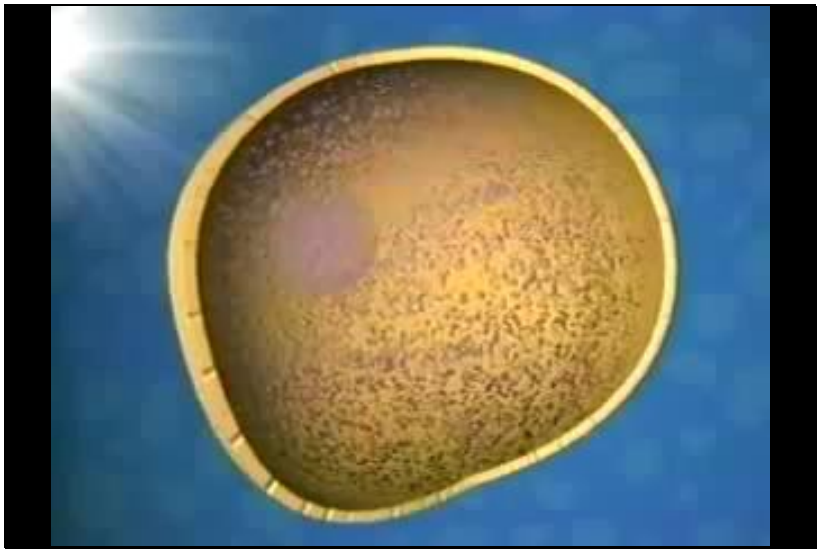
This silk pattern was derived from crystallographic studies of the molecular structure of hemoglobin. It was created for the Festival of Britain in 1951. It celebrated the centennial of the Great Exhibition of 1851 (the one famous for the Crystal Palace), though the contributors to the 1951 exhibition were completely British. It was meant to give the British people a feeling that they had successfully recovered from the war. It focused on science technology design architecture and the arts. It was a triumphant success. Exhibitions were given in many different cities but the most prominent venue was the new South Bank Centre in London.

Britain was home to the greatest achievement of molecular biology – the idea of the double helix published in Nature in 1953 by James Watson and Francis Crick.

The illustration portrays the beauty of the molecules that underlie life. The textile pattern is more abstract than real. One can perhaps imagine the heme rings and the oxygen, but this is a far cry from the actual structure that we discussed in an earlier presentation (“metabolism”). The structure of hemoglobin was finally worked out by Max Perutz (1914-2002) in 1959. He had come from Austria to England just before the beginning of World War II, and did his molecular biology at the Cavendish Laboratory in Cambridge. He was awarded the 1962 Nobel Prize for Chemistry



Life is based on reproduction. The basic processes of cell reproduction were observed in the late 19th century. Histological studies had demonstrated the process of cell mitosis. During this process the material in the nucleus condensed into thread-like chromosomes. The word mitosis comes from the Greek *mitos* thread. Close examination showed that these became formed of two chromatids joined at the centromere. The chromatids were pulled apart to form separate sets of chromosomes in the nuclei of the two daughter cells.



video is from
https://www.youtube.com/watch?v=AhgRhXl7w_g

The video presents the process in terms of what we know now, i.e. about DNA. At the beginning of the 20th Century, all that was known was that the chromosomes replicated and divided during mitosis.

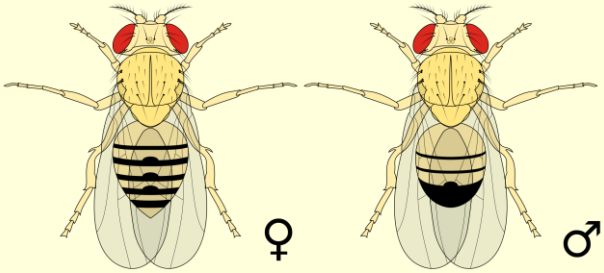
Walter Stanborough Sutton
(1877–1916)

The Chromosome Theory of Inheritance

As a graduate student in zoology at Columbia University, Sutton proposed in 1902 and 1903 that the chromosomes could be the biological basis for the Mendelian laws of inheritance. He later studied medicine and became a surgeon. A German biologist Theodor Boveri proposed similar principles, and their ideas are the foundations of the Sutton-Boveri theory that states that the chromosomes are the carriers of the genetic material.

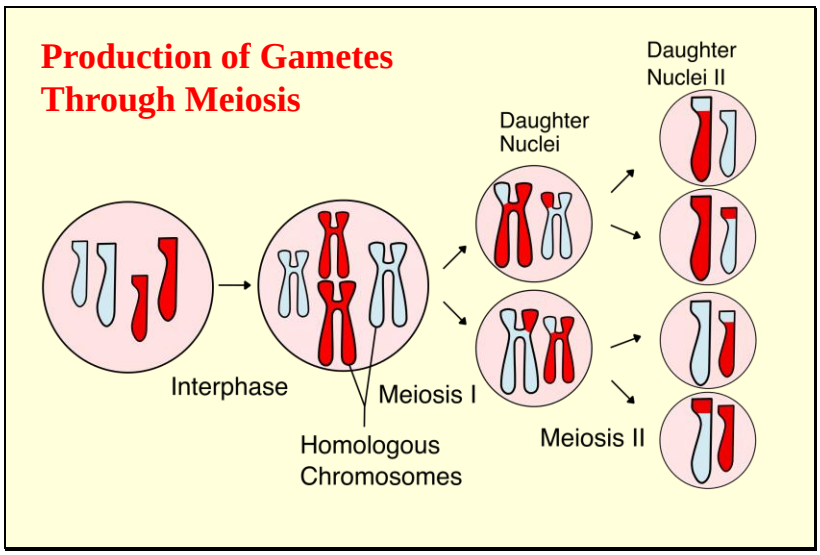
Walter Sutton was never really recognized for his insight.

Drosophila melanogaster



In 1908, Thomas Hunt Morgan (1866-1945) at Columbia University began to study the inheritance of different traits in the fruit fly. He examined the patterns of inheritance for mutations such as white eyes, and related them to the chromosomes. He demonstrated the “crossing over” of chromosomal sections during meiosis and noted how this provided genetic variation.

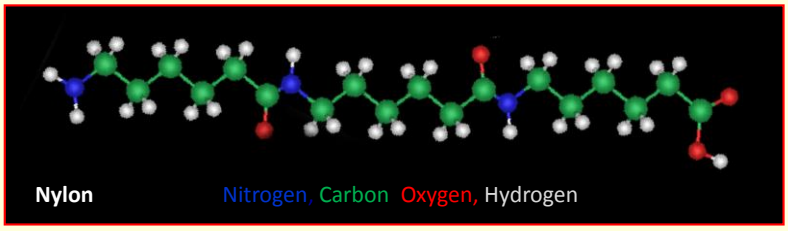
Drosophilia melanogaster means dew-loving and black-bellied.



Meiosis (from the Greek *meion*, less) is a specialized type of cell division that occurs in all sexually reproducing organism during the production of gametes (from the Greek *gamein*, marry) – sperm cells or ova. Meiosis reduces halves the number of chromosomes creating four haploid (rather than diploid) cells, each genetically distinct from the parent cell that gave rise to them. During the early phases of meiosis chromosomes exchange DNA regions (homologous recombination). This explains why the chromosomes in the sperm or the egg are different from those of either the mother or father chromosomes.

When the sperm and the egg (each obtaining one sample of each chromosome) fuse they each contribute their chromosomes to the zygote. The zygote then contains two samples of each chromosome.

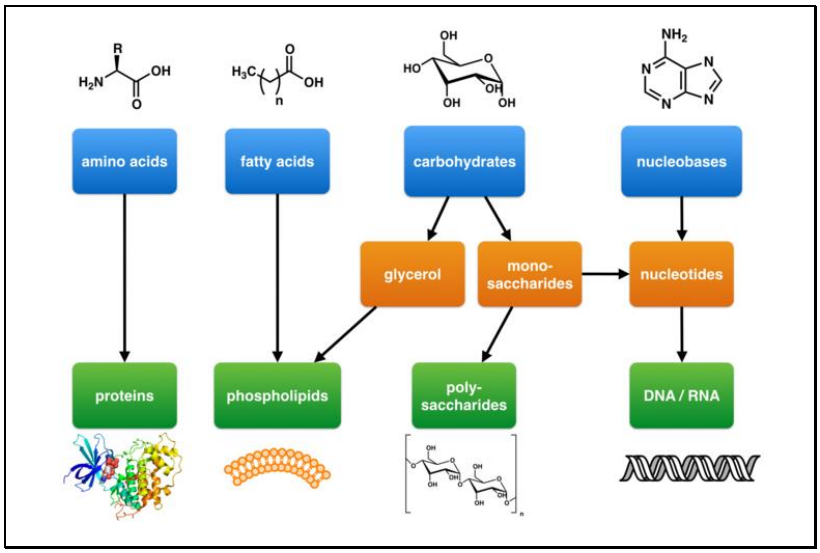
Macromolecules



In the early 20th Century, scientists considered all molecules to be composed of a small number of atoms. The material inside biological cells was though of as a colloidal suspension of small molecules. In 1920, Hermann Staudinger (1881-1965) reported that many different compounds such as rubber and proteins were "macromolecules" – long chains of molecular units linked together by covalent bonds. Ultracentrifuge studies of Theodor Svedberg (1884-1971) and his student Arne Tiselius (1902-1971) confirmed the large size of molecules such as hemoglobin and serum proteins.

Colloidal chemistry, though interesting. has little relevance for biology. It was one of the great "false paths" of biochemical research.

Staudinger's work led to the later industrial development of polymers such as nylon (illustrated). Staudinger was awarded the Nobel Prized for Chemistry in 1963. Svedberg received the Nobel Prize in 1926 but this was awarded for his earlier and much less significant work on Brownian motion. Tiselius received the Nobel Prize in 1948.



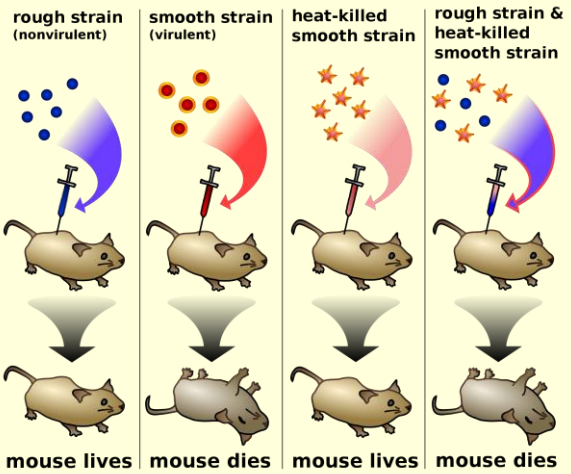
This illustration shows the different kinds of biological macromolecules. Each kind is based on repeating units linked together to from long chains or other complex structures. Proteins form both the building blocks of the body and the enzymes that facilitate chemical reactions. Fatty acids are linked into fats and the phospholipids essential for cell membranes. Monosaccharides combine to form polysaccharide, and nucleotides form the nucleic acids.

Nikolai Koltsov (1872-1940)

Koltsov, a Russian biologist and geneticist, was long persecuted for promoting bourgeois science in opposition to the proletarian theories of Trofim Lysenko who claimed that learned characteristics could be inherited. In 1927 Koltsov proposed that each chromatid consisted of one giant hereditary molecule made up of two mirror strands that would replicate in a semi-conservative fashion using each strand as a template

Ultimately Koltsov was murdered by the Russian Secret Police NKVD. Koltsov's theories are remarkably prescient of the double helix theory of DNA that was presented by Watson and Crick in 1953. Watson and Crick were unaware of Koltsov.

Bacterial Trans-formation



Evidence for DNA as the transmitting factor for heredity came from studies of bacterial infections. Pneumococcus can exist in two forms – a nonvirulent unencapsulated strain (rough) and a virulent encapsulated strain (smooth). The capsule around the smooth strain prevents the bacteria from being engulfed by the neutrophils and macrophages. In 1928 Frederick Griffith (1879–1941), an American bacteriologist, reported that something available from dead virulent bacteria could "transform" nonvirulent bacteria into virulent bacteria.

Photograph from 1944

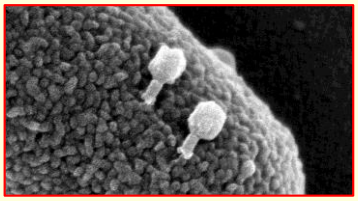
Oswald Avery (1877-1955)

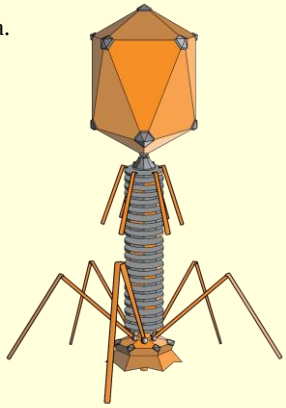
Avery was born in Halifax and moved with his family to New York when he was 10 yr. After training in medicine he worked at the Rockefeller University Hospital. He carefully analyzed the nature of the transforming factor that had mediated the effects reported by Griffith. By treating it with protease he demonstrated that the transformation was not due to a protein, which had been the initial hypothesis. The transforming factor was nullified after treatment with deoxyribonuclease, indicating that it was DNA – deoxyribonucleaic acid.

The paper was published in 1944 with Colin MacLeod and Maclyn McCarty. At the time Avery was a professor emeritus.

Bacteriophages

Bacteriophages are viruses that infect bacteria and then replicate themselves within the bacteria. In 1952 Alfred Hershey and Martha Chase demonstrated that the material that the phages injected into the bacteria (and which led to their replication) was DNA. This confirmed the work of Oswald Avery and his colleagues.



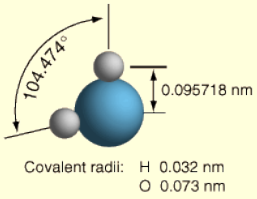


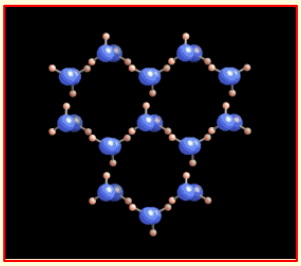
The illustration on the right shows the structure of a myovirus bacteriophage. The lower left shows bacteriophages attached to an Escherichia coli bacterium.

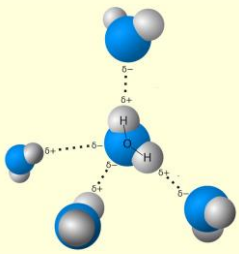
These experiments confirmed that DNA was the molecule that instantiated the process of inheritance but how was this done? To understand this process the structure of the DNA molecule had to be determined. Crucial information came from studies of crystals.

Water Crystals

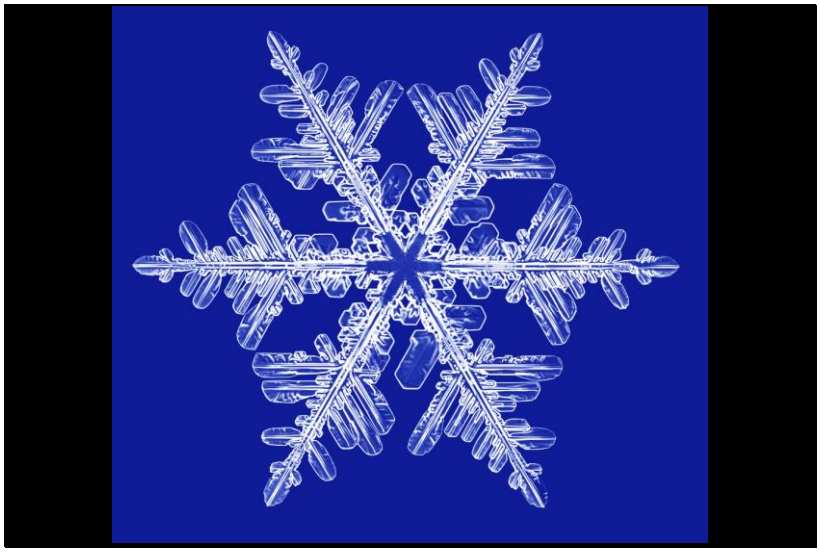
Molecules can bind together to form repeating geometric structures called crystals. Examining these crystals can thus tell us much about molecules. The distances between atoms in a crystal are of the same order as the wavelength of x-rays: 0.01-10 nm.





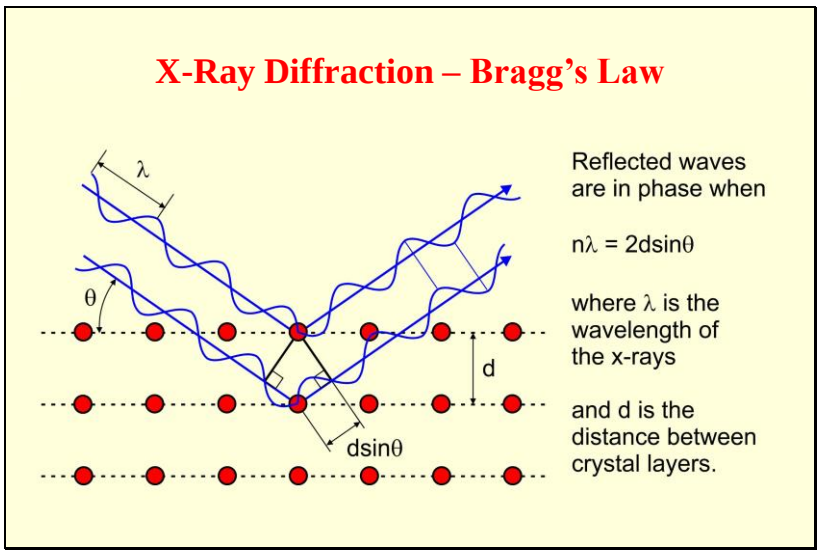


In order to find out how DNA worked we needed to determine its structure. The technique that was most helpful in this endeavor was crystallography.
The illustrations a molecule of water (upper right), the crystalline structure of ice (lower left) with its overriding hexagonal geometry. The water molecules in ice are held together by “hydrogen bonds” between the hydrogen atoms and the oxygen atoms (illustrated in the lower right).

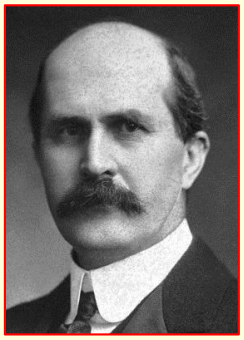


The hexagonal structure of the ice crystal determines the structure of snowflakes. Minor variations in temperature and wind cause variations in the basic structure, so that there are an infinite variety of snowflakes.

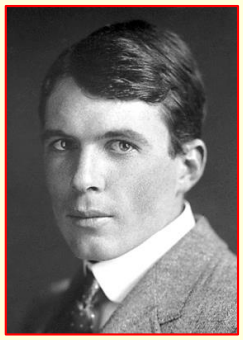
But we should return to how we might "look" at the crystal structure.
A beam of X-rays is delivered at a crystal and a detector measures the intensity of the rays scattered by the crystal.



When the x-rays scattered by the different layers of the crystal are in phase, the film in the detector is exposed and shows a dark spot. When the scattered rays are out-of-phase they cancel each other and do not expose the film.



William Bragg
(1862-1942)



Lawrence Bragg
(1890-1971)

Father and son were born and educated in Adelaide, Australia. They came to Britain in 1908 when William Bragg accepted a professorship at Leeds University, and began investigating the x-ray diffraction by crystals, which had just been reported by the German physicist Max von Laue (1879-1960). Lawrence Bragg proposed an equation to analyze the diffraction patterns. The 1915 Nobel Prize for Physics went to both William and Lawrence Bragg.

Von Laue received the Noble Prize for Physics in 1914.
The Braggs are the only father-son joint winners of the Nobel Prize, and Lawrence Bragg is the youngest ever Nobel recipient. Lawrence Bragg was 25 years old when he received the prize. He went on to become the director of the Cavendish Laboratory at Cambridge University (1938-1954). While there, he supervised Max Perutz (winner of the Nobel Prize in Chemistry in 1962), and he was the director when Watson and Crick did their 1953 work on DNA (Nobel Prize in Physiology or Medicine in 1962).

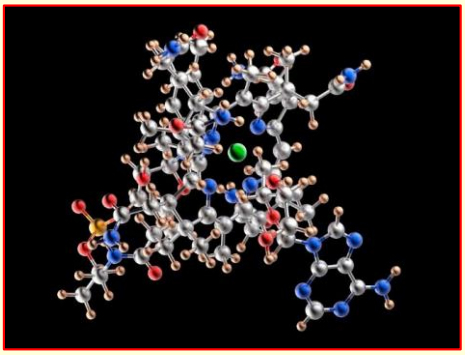
The early crystallographic research concerned the structure of various metallic crystals. It took a while before scientists could handle the crystallographic patterns produced by complex organic molecules.

Kathleen Lonsdale (1903-1971) was the first crystallographer to study organic molecules. In 1929 she showed the structure of the benzene ring. The photograph shows her in 1946 along with

many different molecular models. She was the one of the first two women elected to the British Royal Society in 1945. As well as being a productive scientist she was a Quaker and an ardent pacifist. She was imprisoned for her pacifism during World War II.

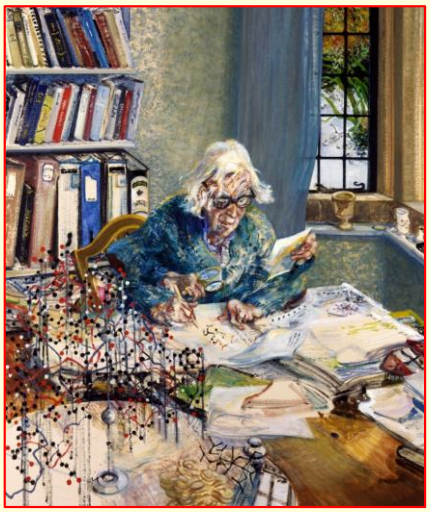
Dorothy Hodgkin (1910-1994)
photograph 1937

Using crystallography, Hodgkin was able to determine the molecular structure of numerous complex molecules such as cholesterol, penicillin and finally in 1948 vitamin B12:



Dorothy Hodkin was the second female crystallographer to contribute significantly to our understanding of molecular structure. She was awarded the 1955 Nobel Prize in Chemistry for her works. Why crystallography was popular with female scientists is not known. I think that it was because it was a new field in physics, one where there was not so much of an already established hierarchy.

The green atom in the vitamin B12 is cobalt. Also known as cobalamin, it is the most structurally complex of all the vitamins.



Dorothy Hodgkin
(1910-1994)

Insulin

Maggi Hambling, 1985

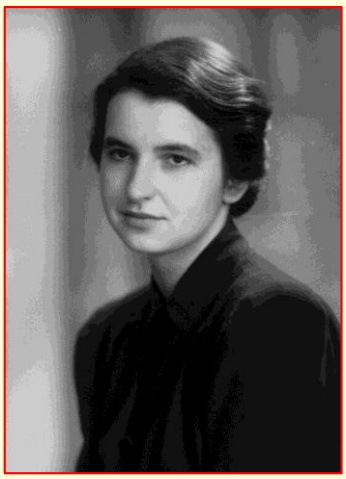
This is a later portrait of Dorothy Hodgkin from the National Portrait Gallery in London. It shows both the indefatigable energy (the hands cannot stop moving) and the rheumatoid arthritis.

The composition of insulin was worked out by Frederick Sanger in 1951. Its 3-D structure was discovered in Hodgkin's laboratory in 1969. The magenta sphere is a zinc ion.

And so we now come to our third female crystallographer.

Rosalind Franklin (1920-1958)

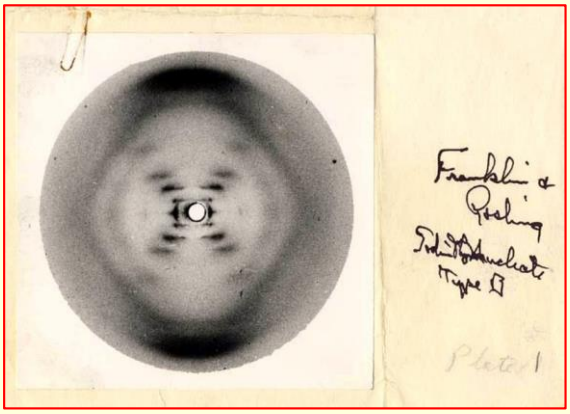
Born to a prominent Jewish family in London, Franklin obtained her doctorate at Cambridge University in Physical Chemistry in 1945. After postdoctoral work in Paris in x-ray crystallography, she joined King's College London in 1951. While there she began her studies of DNA using the nucleic acids isolated from calf thymus. Her results suggested that its molecular structure was helical in nature, but she was cautious about interpreting her results.



Photograph 1946

Rosalind Franklin was working together with Maurice Wilkins at King's College. The two scientists did not get along, and she left to take a position at Birkbeck College in 1953. There she used crystallography to study viruses. Aaron Klug who had just obtained his doctorate came to work with her at Birkbeck. He later was awarded the Nobel Prized in Chemistry in 1982 for his work on the structure of viruses.

Photo 51



In 1952 Rosalind Franklin and her student Raymond Gosling obtained a clear x-ray diffraction image of DNA from calf thymus ("sodium thymonucleate type B"). This was to prove crucial for the double helix model.

Francis Crick (1916-2004)

and

James Watson (1928-)

Francis Crick began his Ph.D. in London but his work was cut short by World War II, when he worked in the Admiralty Research Laboratory on mines and minesweepers. After the war he decided to study biology, focusing on DNA. In 1951 James Watson who had recently finished his Ph.D. at Indiana University came to Cambridge and they began to collaborate.

The photograph shows Crick and Watson walking in the Backs at Cambridge. King's College Chapel is in the background. Note that King's College Cambridge (founded by Henry VI in 1441) is quite independent of King's College London (founded by King George IV in 1829).

Crick finally obtained his Ph.D. from Cambridge in 1954 after his work on the double helix.

Cavendish Laboratory

Established in 1874 by the Duke of Devonshire to commemorate an Henry Cavendish, the laboratory was home to many important developments in physics and chemistry. In its first century it was directed by James Clerk Maxwell, Baron Rayleigh, J. J. Thomson, Ernest Rutherford and Lawrence Bragg. 29 Nobel Prize winners worked in the Laboratory. On the door is inscribed: *Magna opera Domini exquisita in omnes voluntates eius* (Psalms 111:2 Great are the works of the Lord, wherein all his meanings can be sought.)

Henry Cavendish (1731-1810), the man who weighed the world, was distantly but not directly related to the Duke of Devonshire.
My translation from the Latin differs from the usual.

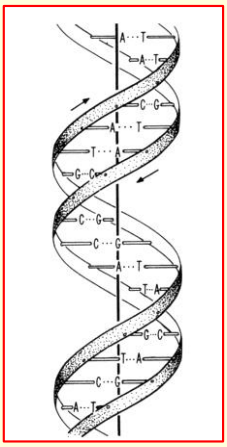
Crick and Watson began to study the molecular structure of DNA using scale models of the different components. They did not have their own crystallographic data, but had to use what they learned from the work of Maurice Wilkins and Rosalind Franklin in London. Unlike Franklin and Wilkins, Watson and Crick were far from cautious and worked by trial and error.

What exactly happened about Franklin's data is not known. Wilkins did obtain a copy of Photo 51 and did show it to Watson and Crick. Some have suggested that this was unethical, but Franklin likely transferred her data to Wilkins because she was moving to Birkbeck.

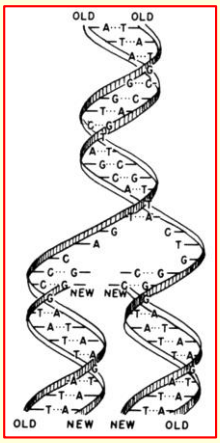
Many people were attempting to discover the structure of DNA. Linus Pauling had worked extensively on the structure of proteins and had demonstrated the alpha helix in myoglobin in 1951. He had considered a triple helix for DNA but this did not fit with the crystallographic data. The competition was intense.

Finally in April 1953 Watson and Crick (they had flipped a coin to determine the order of authorship) published their double helix model in Nature. It was followed by papers by Maurice Wilkins and his colleagues and by Franklin and Gosling.

A Structure for Deoxyribonucleic Acid
The Double Helix

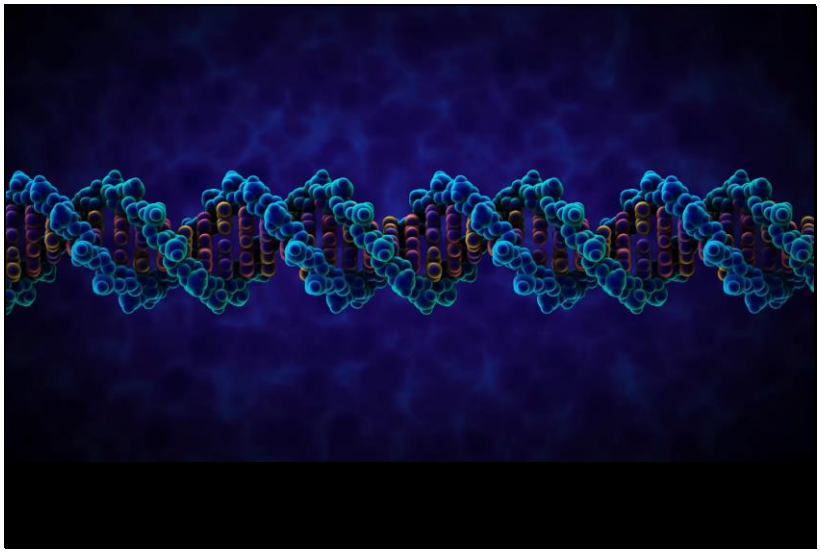


"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."



The illustration for the Nature article (similar to that on the left but without the base pairs) was made by Crick's wife Odile. The quoted comment by Watson and Crick near the end of their Nature paper is a marvel of scientific understatement.

The bases that are attached to the long chain of DNA are cytosine, guanine, adenine and thymine. Their different sizes and structures allow them to pair and keep two strands of DNA in a double helix. A mnemonic for the base pairing is "Car in the garage, apple in the tree."



The structure of DNA is so important that we shall consider this video from MIT Office of Digital Learning even though it is longer than our usual videos – almost 6 minutes:

https://openlearning.mit.edu/news-events/blog/mit-biology-and-office-digital-learning-team-recognized-dna-video

Electron Microscopy

In 1905 Einstein proposed that light waves were also particles (photons). In 1924 Louis De Broglie claimed that particles could also act as waves. Thus they could be used in diffraction experiments and also in microscopy. Because of their wavelength was much shorter than that of light waves electron microscopy had much higher resolution.

Ernst Ruska (1906-1988), a German physicist, built the first electron microscope in 1933, using magnetic coils as "lenses." He received the Nobel Prize in Physics in 1968.

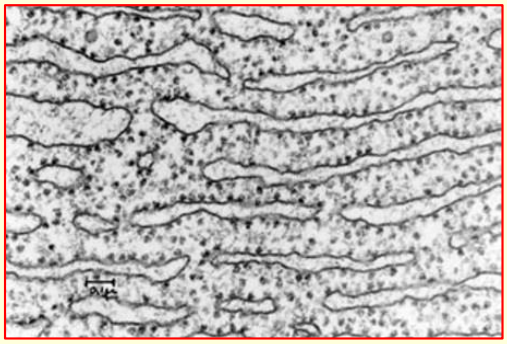
The Einstein equation for photons was $E = h\nu$ or hc/λ where h is Planck's constant.
De Broglie's equations for the particles was $\lambda = h/p$ where p is the electron's momentum.

The electron microscope can magnify up to 10 million times – compared to the 1000 times limit of the light microscope.

The first electron microscope in North America was built at the University of Toronto in 1938 by Professor Eli Burton and his students.

The microscopes were not used in science until after World War II. Then cell biologists began to see the organelles of the cell – endoplasmic reticulum (1945), the internal structure of the mitochondria (1952), and ribosomes (1955).

Ribosomes

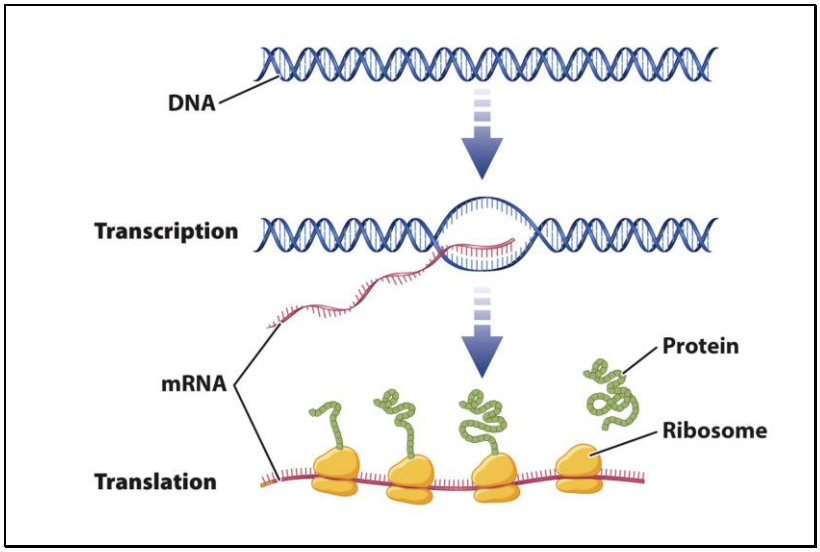


The electron microscope provided an unprecedented view of the internal structure of the cell. Among the most important new discovery were the tiny bodies call ribosomes, which George Emil Palade (1912-2008) first described in 1955. The structure and mechanisms of the ribosome were determined by Ada Yonath (1939-) in 2001.

Palade won the Nobel Prize in Physiology and Medicine in 1974, together with Albert Claude and Christian de Duve.

The Israeli Ada Yonath is our fourth great female crystallographer. She won the Nobel Prize in Chemistry in 2002, together with Venkatraman Ramakrishnan and Thomas Steitz.

Cell biologists could fractionate the different organelles in a cell using centrifuges. Then they could determine the chemical reactions that occurred in the different fractions. Ribosomes were involved in protein synthesis.

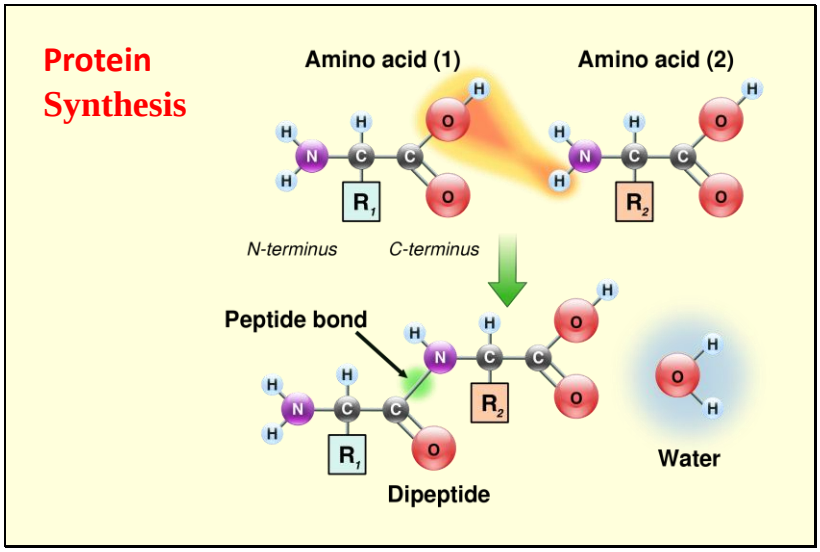


This is the Central Dogma of Molecular Biology. This theory of how the genetic information in the DNA brought about the traits that were inherited was first published by Francis Crick in 1958. The information in the DNA was transcribed to a "messenger RNA" molecule and the information in that molecule was translated into a sequence of amino acids in a protein by the ribosomes. RNA is similar to DNA but it uses uracil instead of thymine in its structure. The "code" in the RNA was thus composed of "letters" A, G, U, and C.

The ribosomes could thus manufacture enzymes that could generate energy and build cell components, or they could produce the specific proteins to carry oxygen, move muscles, transport neurotransmitters, etc.

The question now was how did the bases on the nucleic acids code for protein structure. A suggestion was that the code was based on triplets – like three-letter words (GUC, AGG, etc). This would give 64 possible codons (since there were 4 different bases and each could be used in any position in the code). This could then code for the 21 amino acids that composed proteins with some redundancy, and some coding for start and stop.

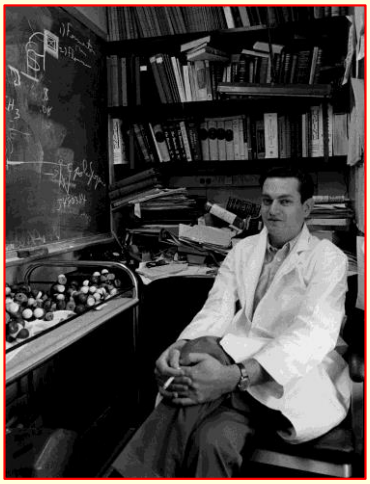
Video from the DNA Learning Center illustrating how ribosomes make proteins
https://www.youtube.com/watch?v=TfYf_rPWUdY



Proteins are formed by linking together amino acids. The carboxylic acid end of one amino acid links with the amine end of another acid. This linking forms a long chain, which then then coils on itself – the secondary structure. Finally there chains fold around each other – the tertiary structure.

Marshall Nirenberg (1927-2010)

At the NIH in Bethesda, Nirenberg studied the activity of RNA (riboneculeic acid) in solution with ribosomes and aminoacids. RNA is a nucleic acid that uses uracil instead of thymine. In 1961 Nirenberg and his post-doctoral fellow Heinrich Matthaei showed that an artificial RNA composed only of uracil - poly U - synthesized a protein chain composed only of the amino acid phenylalanine. Thus UUU coded for phenylalanine. Later work gave the complete code.



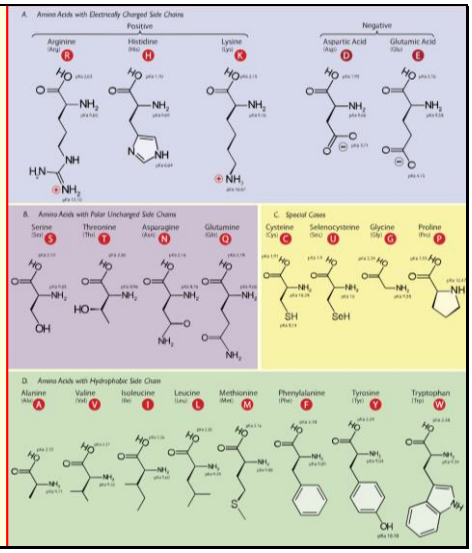
Photograph 1962

I like this photograph since it reminds me of my office when I was a scientist. Nirenberg received the 1968 Nobel Prize in Physiology or Medicine along with Gobind Khorana and Robert Holley.

Proteinogenic Amino Acids

21 different amino acids (right) can be linked together in protein chains.

Other amino acids such a gamma-amino butyric acid (GABA) and deoxy-phenylalanine (L-DOPA) serve as neuro-transmitters and others such as tri-iodothryronine serve as hormones.



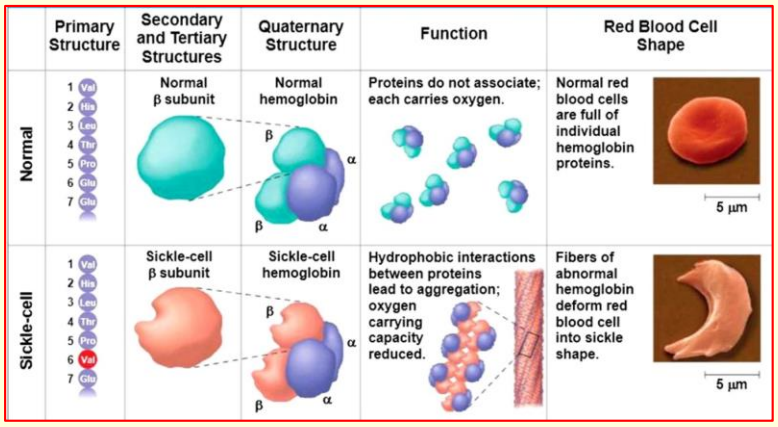
Genetic Code

Most amino acids are coded by several codons Only methionine and tryptophan are coded by a single codon.

The code also includes "start" and "stop" codons.

First Letter	Second Letter: U	C	A	G	Third Letter
U	Phenylalanine	Serine	Tyrosine	Cysteine	U
	Phenylalanine	Serine	Tyrosine	Cysteine	C
	Leucine	Serine	Stop	Stop	A
	Leucine	Serine	Stop	Tryptophan	G
C	Leucine	Proline	Histidine	Arginine	U
	Leucine	Proline	Histidine	Arginine	C
	Leucine	Proline	Glutamine	Arginine	A
	Leucine	Proline	Glutamine	Arginine	G
A	Isoleucine	Threonine	Asparagine	Serine	U
	Isoleucine	Threonine	Asparagine	Serine	C
	Isoleucine	Threonine	Lysine	Arginine	A
	Start Methionine	Threonine	Lysine	Arginine	G
G	Valine	Alanine	Aspartic acid	Glycine	U
	Valine	Alanine	Aspartic acid	Glycine	C
	Valine	Alanine	Glutamic acid	Glycine	A
	Valine	Alanine	Glutamic acid	Glycine	G

Sickle Cell Anemia

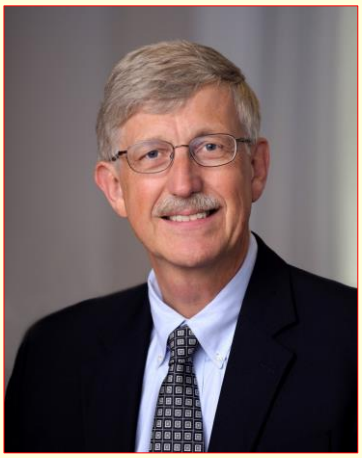


In 1948 Linus Pauling (1901-1994) had proposed that Sickle Cell Anemia was caused a genetically abnormal hemoglobin molecule. He demonstrated that the hemoglobin in patients with the disease was chemically different from normal hemoglobin. Sickle Cell Anemia is inherited as an autosomal recessive disease. Having one abnormal gene does not lead to the disease, but the mildly abnormal hemoglobin protects against malaria. This beneficial effect of the trait leads to the persistence of the gene in populations where malaria is endemic.

In 1956 Vernon Ingram (1924-2006) demonstrated that the disease is caused by a simple genetic defect that changes one amino acid in the DNA. GAG was changed to GUG. This tiny change altered the selected protein from valine to glutamic acid. This causes the structure of the molecule to change significantly. Since the three dimensional structure of a macromolecule is determined by the exact sequence of amino acids, the coiling and folding of the abnormal hemoglobin molecule would alter the structure of the red blood cell.

Human Genome Project

In 1993 an international research effort to sequence the entire human genome began under the overall supervision of Francis Collins at the US National Institutes of Health (NIH). In 1998 Craig Venter at Celera Genomics provided some privately funded competition, but ultimately the government funded project was successful and the full human genome was published in 2006.

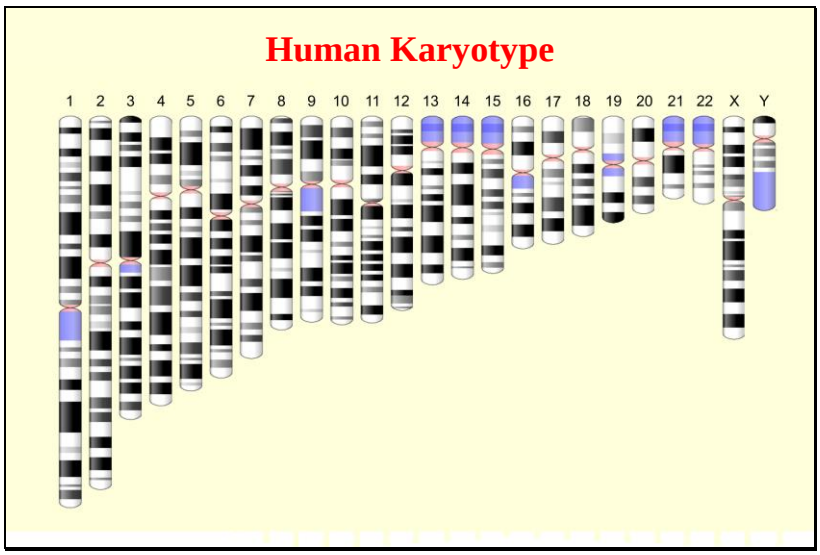


Francis Collins (1950-)

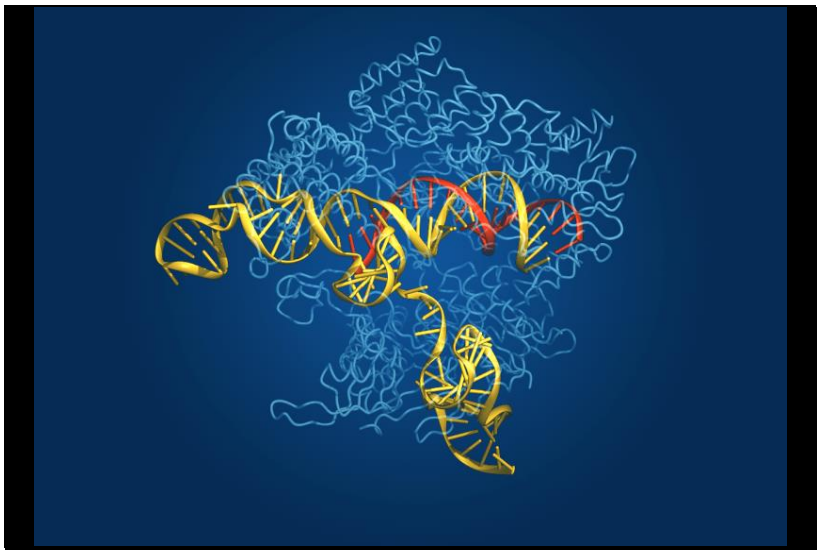
Collins led the Human Genome Project from 1993-2008 and has been head of the National Institutes of Health since 2009. He is a devout Christian. He promotes a fusion of Christianity and Biology in a movement called BioLogos:
http://biologos.org/about-us/

A quotation from his 2006 book *The Language of God*

> The God of the Bible is also the God of the genome. He can be worshipped in the cathedral or in the laboratory. His creation is majestic, awesome, intricate, and beautiful – and it cannot be at war with itself. Only we imperfect humans can start such battles. And only we can end them.



I cannot give the complete genome (from the Greek *gen* offspring) but we can consider the karyotype. The karyotype (from the Greek *karyon*, seed) is the number of chromosomes and the gene locations on these chromosomes. The human being has 22 pairs of autosomal chromosomes and 2 sex chromosomes. A person with both X and Y chromosome is typically male, and a person with two X chromosomes typically female. The diagram shows only one of each autosomal pair and one of each chromosomes. The karyotype provides the map of where genes are located.

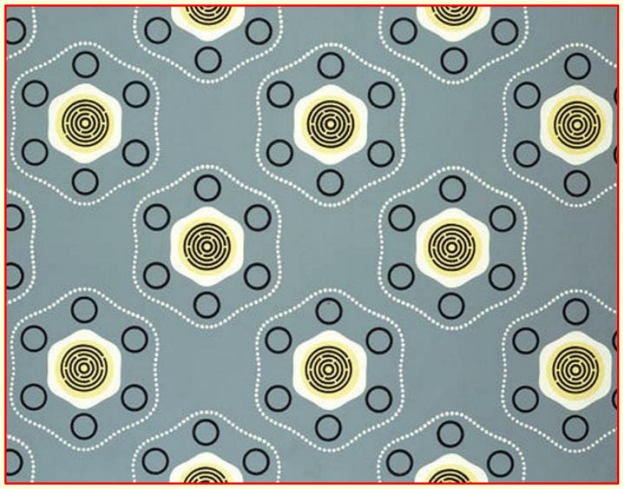


The image shows the structure of the Cas9 gene-editing enzyme (light blue) in complex with an RNA guide (red) and its target DNA (yellow). CRISPR (clustered regularly interspaced short palindromic repeats) are locations in the DNA molecule where the code repeats. These sequences are derived from DNA fragments from viruses that have during evolution infected inserted their DNA. These locations are part of the organism's immune response to the viruses. These locations

can also be used by special enzymes such as Cas-9 (Crispr-associated 9) to attach to and cleave the DNA molecule. The Cas9 approach to gene editing was developed by Jennifer Doudna (1964-) in Berkeley and Emmanuelle Charpentier (1968-) in Berlin.

In this way DNA can perhaps be edited. This brings up many ethical questions.

Life



Insulin Wallpaper Pattern designed for Festival of Britain by Robert Sevant 1951

We conclude with another design from the 1951 Festival of Britain. This is loosely based on the structure of insulin. The molecular structure of insulin was worked out by the British chemist Frederick Sanger in 1955. Sanger was awarded the Nobel Prize in Chemistry in 1958. He received a second Nobel Prize in 1980 for his work with DNA. Only 3 other people have received two Nobel Prizes: Marie Curie (Physics and Chemistry), John Bardeen (Physics), and Linus Pauling (Chemistry and Peace). Insulin's full 3-D structure was discovered by Dorothy Hodgkin's laboratory in 1969.