

DISCOVERING THE HELICAL STAIRCASE

ROHINI CHINTHA

Mittu is smitten by a photograph of what looks like an 'X' in his grandpa's scrapbook. In response to his questions, Grandpa narrates a story – that of the discovery of the 'molecule of life'. Does Mittu succeed in his quest to understand the mystery of 'X'? Let's find out.

Mittu came down from the attic bursting with curiosity. His project on 'how grandparents spend their holidays without gadgets' was about to take off. Mittu had just found a sketch of a mysterious black and white photograph of what looked like an X in Grandpa's scrapbook, and couldn't wait to ask Grandpa about it.

Grandpa was out in the garden, reading his newspaper. Mittu rushed to Grandpa, showed him the 'X' and said, "Let's start here."

Grandpa looked at the photograph gravely. "This is a copy of the famous Photograph 51. The most crucial evidence in the discovery of the **molecule of life** – deoxyribonucleic acid or DNA."

"DNA is the molecule of life? How?"

"Tell me what you know about cells? The ones that make up plants and animals?" Grandpa questioned.

"A cell..." Mittu tried to recollect, "...is the basic unit of life. It is made up of a protective outer covering called the plasma membrane, and a jelly-like substance called

the cytoplasm. The cytoplasm has many organelles which help the cell survive?"

"Go on," encouraged Grandpa.

"A cell's nucleus has DNA..." Mittu paused.

Grandpa patted Mittu. "Well, you've learnt your lesson well. Do you know that DNA codes for amino acids?"

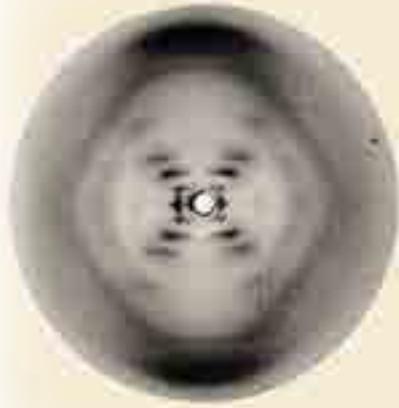
"I know amino acids!" Mittu looked excited. "Amino acids make up proteins. Proteins make up the cell and, the whole organism."

Grandpa smiled. "Yes. And some proteins act as enzymes that help in the formation of carbohydrates and lipids. Carbohydrates, lipids and proteins together make up life structures. This is why DNA is popularly called the '**molecule of life**'."

"DNA," Mittu added brightly, "passes characters (~traits) from parents to children."

"Yes! So it is also the '**molecule of heredity**' – the genetic material." Grandpa was silent for a minute and then sprang a question at Mittu. "But, Mittu, have you heard the story of how we know all this about DNA?"

Mittu shook his head.



The mysterious photograph.

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*Franz's
Pencil
Sketch
Type II*

"The quest to understand heredity began centuries ago," Grandpa explained. "People like Pythagoras, Empidocles, Hippocrates, Aristotle, Leonardo-da-Vinci and Maupertuis came up with many ways of explaining it. But, the first real breakthrough came in 1866, with Gregor Johann Mendel's principles of heredity. Mendel, an Austrian monk with an interest in plant variations, had been conducting experiments to understand transmission of characters in the edible pea plant. Based on the results of these experiments, he proposed that parents pass on their characters to their

offspring (~children)."

"Mendel knew about DNA in 1866 then?" Mittu asked, surprised.

"No," Grandpa smiled, "Mendel used the term '**factors**' to refer to the units of transmission of characters or traits from parents to their children. According to him, factors were of two types. Some, which he called **recessive**, were associated with traits that were not seen in every generation. Others, that he called **dominant**, were associated with traits seen in all generations."

"Your sharp nose is a recessive character, right, Grandpa?" Mittu said eagerly

"Because dad (your first generation child) missed it, but I (your second generation child) got it?"

"Yes", Grandpa smiled. "But, of course, not all characters can be categorized as recessive or dominant. Some show intermediate features too."

Grandpa removed his spectacles and wiped them. Mittu pulled out a cobweb stuck on Grandpa's scrapbook and asked, "So, where does this photograph of X come in?"

"Not so fast," cautioned Grandpa. "That comes nearly a century after Mendel. To continue with our story, the next big discovery happened in 1869. A Swiss biologist called Friedrich Meischer happened to accidentally discover a new molecule while studying the proteins present in the white blood cells of pus. He knew this molecule was different from a protein because it formed a precipitate with acids, dissolved in alkaline solutions, and could not be digested by proteases (enzymes that digest proteins). Assuming it came from the nucleus of the cells he was studying, Meischer named this new molecule '**nuclein**.'"

"How is nuclein related to Mendel's factor?" Mittu inquired.

Grandpa explained, "While Meischer was exploring the chemical nature or structure of nuclein, or what it looked like; Mendel had looked at the functions of nuclein, or how it passed on characters from parents to children."

"Oh!" Mittu pretended to understand.

Grandpa went on. "It was nearly a decade later that Albrecht Kossel, a German biochemist, discovered that Meischer's nuclein was, in fact, made up of 5 molecules – Adenine (A), Guanine (G), Cytosine (C), Thyamine (T) and Uracil (U). He called these sub-molecules '**nucleobases**'. Kossel was awarded the Nobel prize in Medicine in 1910 for his discovery."

Beginning to piece things together, Mittu wondered aloud, "So, nuclein is made up of nucleobases?"



Gregor Mendel is known as the 'Father of Modern Genetics'.

Credits: Uploaded by Dominikmatus, Wikimedia Commons. URL: https://en.wikipedia.org/wiki/File:Gregor_Mendel_2.jpg. License: CC-BY.



Friedrich Miescher discovered 'nuclein'.

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Nodding to show that Mittu was on the right path, Grandpa continued, "Nuclein is also called nucleic acid, chromatin, chromosome, or DNA."

Mittu added energetically. "Aha! Meischer was the first to observe DNA!"

Grandpa resumed his story. "Going back a bit, in 1900, three scientists – Hugo de Vries, Carl Erich Correns and Erich Tschermak Von Seysenegg, had independently confirmed Mendel's experiments. Hugo De Vries called Mendel's factors, pangenes. Today, we know pangenes as 'genes'. So, genes are nothing but Mendel's factors."

"Cool."

"Then, in 1902, the German biologist Theodore Boveri, suggested that chromosomes or nuclein carried genes or factors."

"Great!" Mittu was enthusiastic. "So, Boveri combined Mendel's work on factors of heredity with Meischer's work on molecules. Genes on chromosomes or DNA pass characters from parent to child through the nucleobases A, T, G and C!"

"Brilliant theory!" said Grandpa, patting Mittu.

Mittu looked pleased. "And, is this correct?"



Albrecht Kossel was awarded the Nobel Prize in Medicine in 1910 for his discovery of nucleobases.

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"It is. And this was confirmed by Fredrick Griffith in 1928; Avery, Mcleod and McCarty in 1944; and Hershey and Chase in 1952!"

"Oh," said Mittu interrupting Grandpa. "A little slow please".

"Sure. Let us begin with 1928."

Three scientists independently confirmed Mendel's experiments:



(a) Hugo de Vries.

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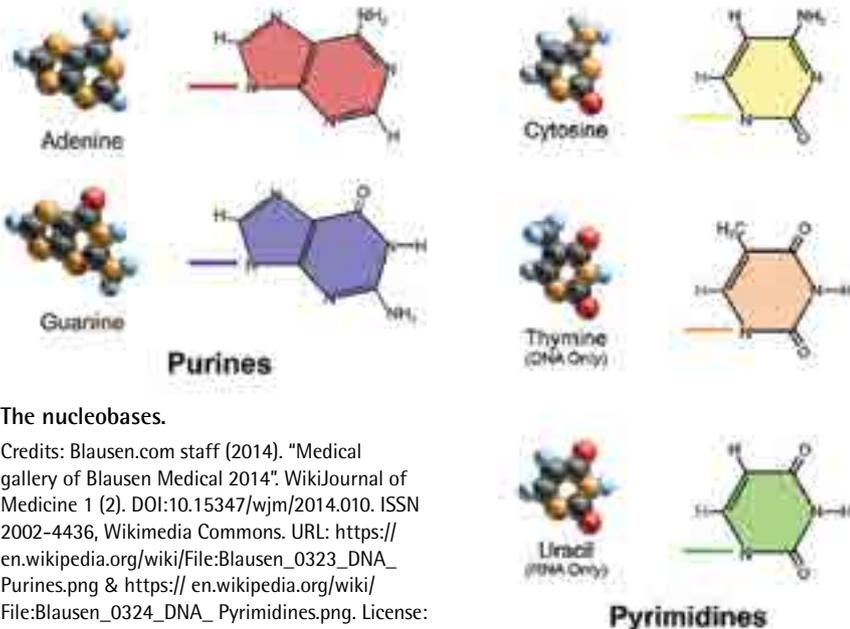
(b) Erich Correns.

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(c) Erich Tschermak Von Seysenegg.

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The nucleobases.

Credits: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436, Wikimedia Commons. URL: https://en.wikipedia.org/wiki/File:Blausen_0323_DNA_Purines.png & https://en.wikipedia.org/wiki/File:Blausen_0324_DNA_Pyrimidines.png. License: CC-BY.



Theodor Boveri suggested that chromosomes or nuclein carried genes.

Credits: Theodor Boveri. In: Hugo Freund und Alexander Berg (Hrsg.): Geschichte der Mikroskopie. Leben und Werk großer Forscher. Bd. 1, Biologie, Umschau Verlag, Frankfurt am Main 1963, S. 121-132, Wikimedia Commons. URL: https://commons.wikimedia.org/wiki/File:Theodor_Boveri_high_res-2.jpg. License: CC-BY.

"But Grandpa, did nothing important happen between 1902 and 1928?" Mittu inquired.

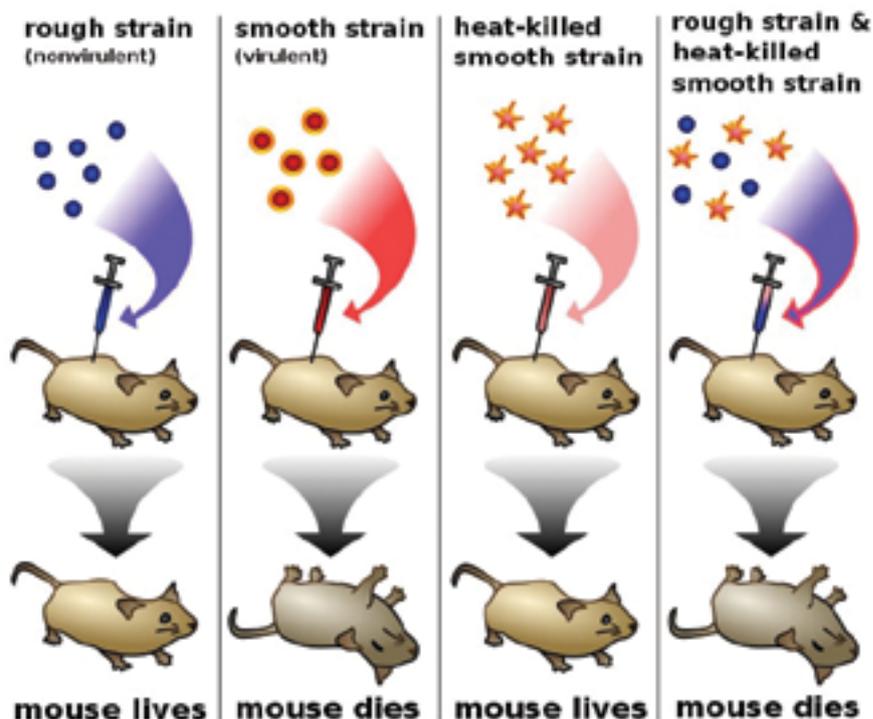
"Well, between 1902 and 1910, mutations were identified. Mutations are improper combinations of A, T, G and C, leading to wrong amino acids."

"Like misspelt words?" Mittu was curious.

"Yes. Garrod identified that mutations in DNA led to functional defects and caused human diseases. Around the same time, T.H. Morgan identified the first mutant in the fruitfly *Drosophila*. Then, in 1928, Fredrick Griffith, a British bacteriologist, used experimental evidence to show that nucleic acids do indeed transfer characters from one individual to another, through a process called 'transformation'."

"How did he do that?"

"Griffith used two strains of the bacteria *Streptococcus pneumoniae*. One, called the S strain, caused disease in mice; while the other, called the R strain, did



Griffith's transformation. Griffith took two strains of the bacteria *Streptococcus pneumoniae* – the non-virulent Type II R (rough) strain and the disease-causing Type III S (smooth) strain. Panel 1: When Griffith injected the rough strain into mice, the mice lived. Panel 2: When he injected the smooth strain into mice, the mice died. Panel 3: When Griffith injected heat-killed cells of the smooth strain into mice, the mice lived. Panel 4: Surprisingly, when he injected a mixture of heat-killed cells of the smooth strain and live cells of rough strain, the mice died. Griffith proposed that the rough strain was 'transformed' into a virulent strain because it took in nucleic acids from the heat-killed smooth strain.

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not. When he used a mixture of heat-killed cells of the S strain, which he knew to be non-virulent, and live cells of the R strain to infect mice, the mice showed symptoms of disease. This led Griffith to postulate that the S strain passed on its disease-causing trait to the non-virulent R strain through its DNA." Grandpa paused.

"But how do we know that the disease-causing trait was passed on by DNA?"

"Because Avery-MacLeod-McCarty and Hershey-Chase used slightly altered versions of Griffith's experiment. Oswald Avery, Colin MacLeod and Maclyn McCarty, three American geneticists, showed that mixing the DNA of the S strain of *Streptococcus pneumoniae* with live cells of the R strain could transform the R strain to the disease-causing S type. Proteins

of the S strain were, however, unable to transform cells of the R strain in the same way. In a similar experiment, the two geneticists, Alfred Hershey and Martha Chase showed that radioactively labelled Phage DNA was capable of causing infection in bacterial cells by a process they called 'transduction'."

"Was photograph 51 the next clue?"

Grandpa laughed. "No. Next, we move back to discoveries around the chemical nature and structure of DNA."

"But why?" Mittu was impatient.

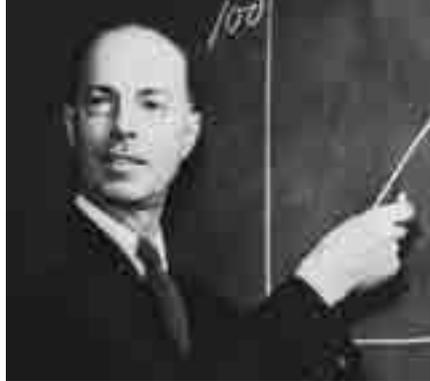
"Because Photograph 51 is an important clue to the chemical nature of DNA. So, moving on, in 1929, Phoebus Levene, an American biochemist, showed that in addition to Kossel's nucleobases, nuclein had a sugar molecule and a phosphate

Three scientists confirmed that Griffith's 'transforming molecule' was DNA



(a) Oswald Avery.

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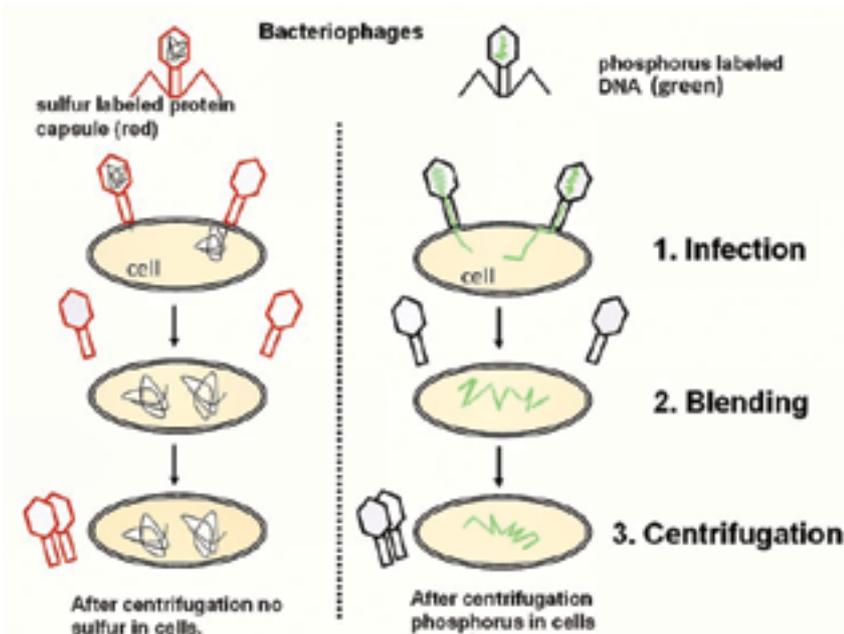
(b) Colin MacLeod.

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(c) Maclyn McCarty (to the extreme right).

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Hershey and Chase's transduction.

T2 phage is a virus that infects the bacteria, Escherichia coli (E.coli). To confirm that DNA was the transforming molecule in Griffith's experiment, Hershey and Chase labelled the DNA of a virus (T2 phage) with radioactive phosphorus and its protein capsid with radioactive sulphur. When the radioactively labeled virus was used to infect E.coli, Hershey and Chase found phosphorous labelled DNA in the infected cells. This confirmed that it was DNA, and not protein, that was the 'molecule of life'.

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group. He named this combination of a nucleobase, a sugar molecule, and phosphate, a 'nucleotide'. But, Levene didn't stop here. He went on to propose

that each DNA molecule had a tetra-nucleotide structure, or consisted of one set of A, T, G and C. Clear?" questioned Grandpa.

"Clear".

By 1934, two Swiss scientists, Torbjorn Caspersson and Einar Hammersten, showed that DNA was a polymeric molecule with long stretches of nucleotides that were not necessarily in multiples of four. So, of course, the tetra-nucleotide structure was rejected. Then, in 1937, William Astbury took the first photograph of DNA through X-ray crystallography, using a sample supplied by Caspersson."

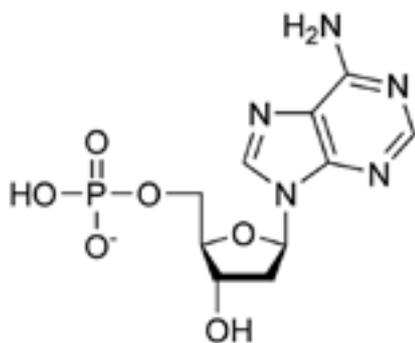
Mittu sighed. "Is photograph 51 next?"

Grandpa ignored the interruption. "In 1950, Erwin Chargaff discovered that the cells of all organisms showed a 1:1 ratio of purine (adenine and guanine) and pyrimidine (thymine and cytosine) bases. He also proved that A always pairs with T, and G always pairs with C."

"Why A-T and not A-C?"

"Stable hydrogen bonds can only be formed between A-T and G-C, but not otherwise. In 1951, Edward Ronin suggested that DNA may have phosphate groups at its centre and nucleobases jutting outwards. Then, came a discovery in 1952."

"Too many details. Can we just skip all this?" Mittu snapped.



A nucleotide has a nucleobase (upper right), a sugar (centre) and a phosphate group (left).

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"Sure," said Grandpa innocently.

"Photograph 51 was taken in 1952. But let us skip that part."

Mittu growled.

Grandpa chuckled. "This photograph was taken by Rosalind Franklin using x-rays."

"A woman scientist in 1952?"

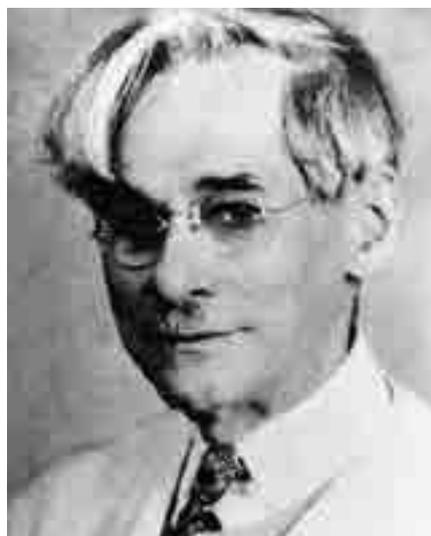
"Yes. A very accomplished yet under-recognized scientist."

"Under-recognized?"

"Yes. If you check your textbook, it's very likely that you'll find a copy of photograph 51, but without any mention of the fact that Franklin was responsible for taking it."

"But, why?"

"Because there were many scientists racing towards identifying the structure



Phoebus Levene identified the chemical structure of nucleotides.

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of DNA. Franklin was only one among them. In fact, it's likely that she had nearly cracked the structure of DNA with this Photograph. Looking at it, she had identified DNA to be a double helix – that's your mysterious X," said Grandpa.

"This is a photo of a DNA molecule?!" Mittu looked at the image again. Then, "what is a double helix, Grandpa?"

"Well, every molecule of DNA is composed of two strands of nucleotides that are anti-parallel to each other. Franklin was aware of Chargaff's rule. Based on the 'X' in this photo, she had, correctly, deduced that the nucleobases were on the inside of the helix and the

phosphate groups were on the outside (unlike earlier models). And, nucleobases on these strands were held together in pairs through hydrogen bonds. She is also supposed to have deduced that each base pair is 3.4 angstrom apart."

"Did she write about this?" asked Mittu.

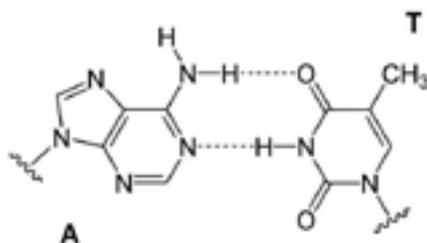
"She intended to, but wanted to wait till she had more evidence. In the meanwhile, she showed this photograph to a colleague, Maurice Wilkins. Wilkins was very keen on deducing the structure of DNA. So keen that his complaints had convinced Sir Braggs, head of the Molecular Biology Laboratory at Cambridge, to ask two scientists who worked there – James Watson and Francis Crick – to abandon their pursuit of the structure of DNA. Wilkins also turned down Linus Pauling's request to see Photograph 51. Pauling, a Nobel Laureate in protein chemistry, needed this evidence to confirm the 'triple helical' structure for DNA that he had proposed. Since Wilkins had declined his request, Pauling based his model on Astbury's images instead. The race got harder. Sir Braggs advised Watson and Crick to rejoin it. On a visit to King's college, Watson coaxed Wilkins into showing him Photograph 51. Wilkins



Rosalind Franklin used x-rays to photograph DNA.

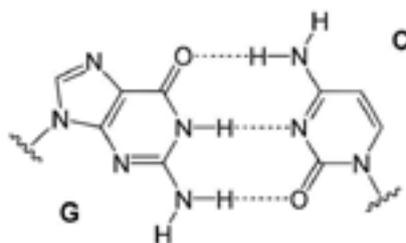
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Erwin Chargaff's base pairing.



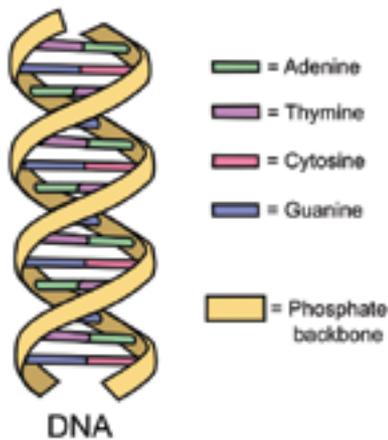
(a) Adenine-Thymine.

URL: https://en.wikipedia.org/wiki/File:Base_pair_AT.svg. Credits: Yikrazuul, Wikimedia Commons. License: CC-0.



(b) Guanine-Cytosine.

URL: https://en.wikipedia.org/wiki/File:Base_pair_GC.svg.



The double helix.

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 URL: https://pa.wikipedia.org/wiki/%E0%A4%E0%A8%B8%E0%A8%B5%E0%A9%80%E0%A8%B0:DNA_simple2.svg.
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did this without Franklin's knowledge or consent. As soon as he saw it, Watson recognized the significance of this photograph. Combining what they knew from the photograph and Pauling's protein structure, Watson and Crick built the first correct model of DNA in 1953. Watson, Crick and Wilkins were jointly awarded the Nobel Prize for Medicine in 1962 for this achievement."

"And, Rosalind Franklin?"

"She remained the 'Dark Lady of DNA.'"

Mittu looked at the photograph and sighed, "That is so unfair!"

Both remained silent for a while. Then, Mittu asked, "What is the point of all this discovery Grandpa?"

"Well, it helps us understand DNA replication, protein synthesis from DNA, DNAs role in disease, its use in treating diseases and also its application in solving crimes."

Mittu looked up at Grandpa questioningly.

"Francis Crick proposed the '**central dogma**' in 1957. Central dogma explains the flow of information from DNA to Proteins through RNA. According to it, DNA first passes on information to an intermediate molecule, RNA. RNA is then translated into the amino acids that make up proteins. Crick also proposed that the information for each amino acid was encoded in the sequence of three consecutive bases on each strand of DNA. This is called the '**genetic code**.'"

"And was this correct?"

"Yes." Grandpa replied. "The genetic code represents the words of DNA, made up of 3 nucleotides each (ATC, GAG, GTT, CCC...), which code for one amino acid each. It was discovered by Gamow in 1953, and Nirenberg, Khorana, Holley and Leder in 1965-68. So, you see, understanding DNA revolutionized science," Grandpa beamed.

"How?"

"Well, recombinant DNA technology (rDNA) was developed by Herbert Boyer in 1973. Using rDNA, we can mix DNA of different species, like plant and bacteria, human and bacteria or bacteria and viruses etc., to produce synthetic DNA of our choice."

"Like chimeras in Greek Mythology?" Mittu wondered.

"Something similar. rDNA is used to produce many new medicines and vaccines as well as control diseases like diabetes. For example, when the gene coding for human insulin is inserted into bacteria, large quantities of 'Humulin' can be produced to treat diabetes. Bacteria are easy to grow, and its products are simple to collect."

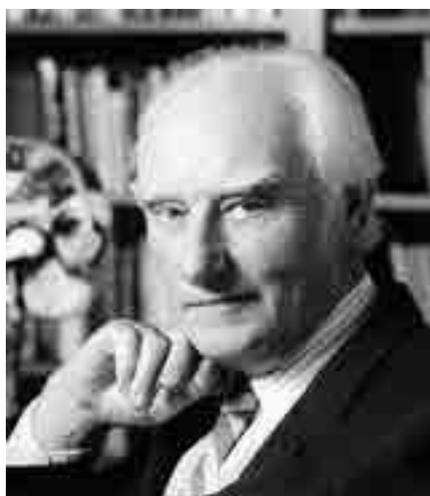
"How do you solve crimes using DNA?"

Three scientists were jointly awarded the Nobel Prize in Medicine for the discovery of the structure of DNA



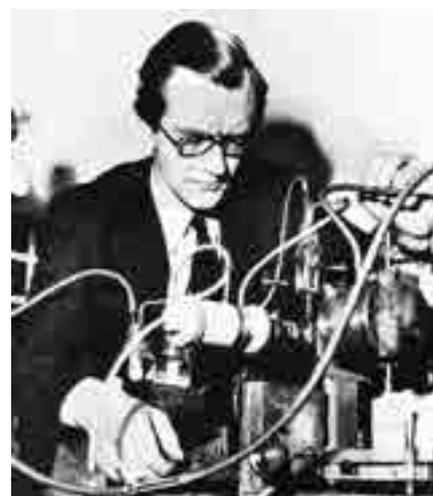
(a) James Watson.

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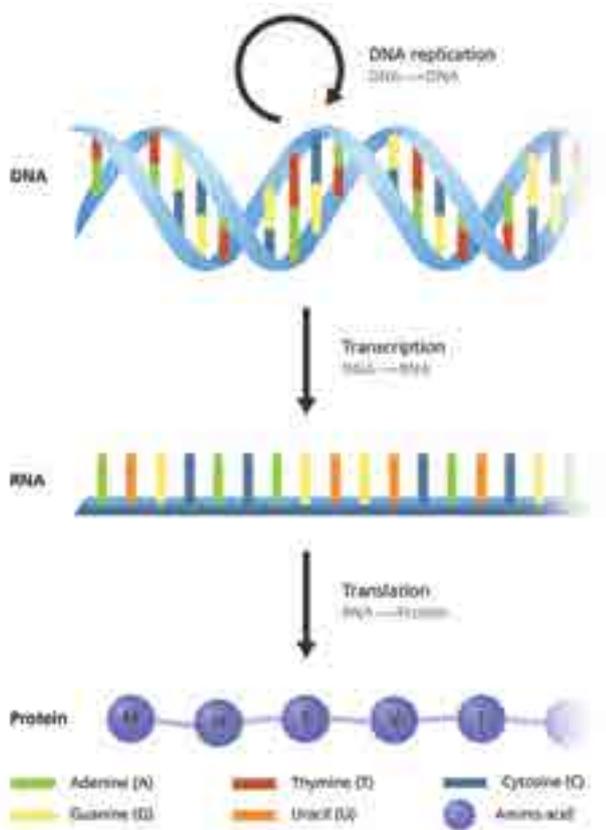
(b) Francis Crick.

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(c) Maurice Wilkins.

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The Central Dogma.

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Mittu asked eagerly.

"In 1977, Sanger Maxam and Gilbert developed a method to sequence DNA. Sequencing allows us to identify the order of nucleotides in each strand of DNA. In the same year, Alec Jeffrey developed a technique called 'DNA fingerprinting' and used it to solve crimes. This technique works on the principle that each individual has a unique order of nucleotides. Therefore, we can be identified by sequencing our DNA," explained Grandpa.

"So, Alec Jeffreys is the Sherlock Holmes of DNA science?"

Grandpa smiled and nodded.

"So, understanding DNA made life better?" Mittu expounded.

"Uh-huh."

"Okay!" Mittu remained thoughtful for a moment but sounded cheerful again. "So, you spent your holidays collecting stuff, right?"

"Who said so?" asked Grandpa.

"I thought your scrapbook was proof of that!" Mittu seemed perplexed.

"No," Grandpa laughed. "I just wanted to look up some old photographs. Thanks for bringing my scrapbook down from the attic. Now, if you are ready, let's begin the interview on 'how I spent my holidays back then without gadgets!'"

Mittu's jaw dropped. "Grrr...." He said pretending to bite Grandpa.



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