

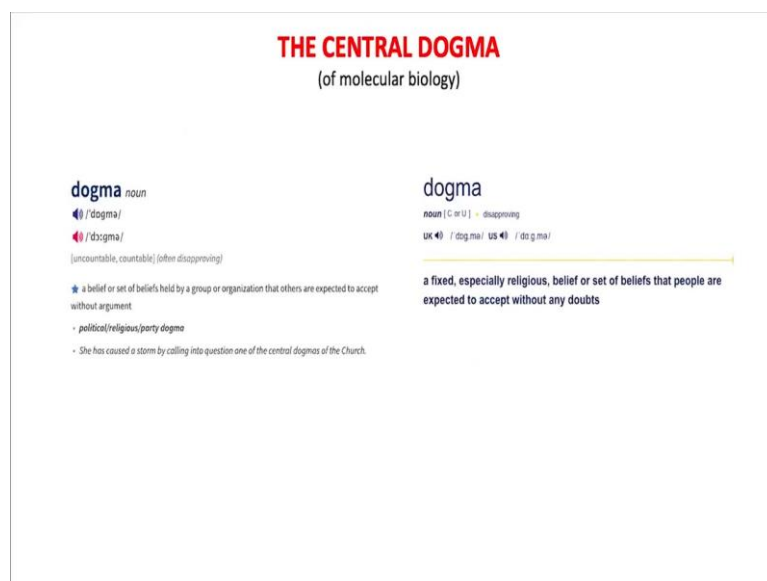
**Introduction to Cell Biology**  
**Professor Girish Ratnaparkhi**  
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**Indian Institutes of Science Education and Research Pune**  
**An Overview of Central Dogma of Molecular Biology - Part 1**

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So, I am a geneticist and developmental biologist and I have been in IISER, for about 10 to 12 years. I work on this animal called as the fruit fly, which you can see on the left-hand side. And I basically model human disease and do genetic experiments using this model organism.

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Now, as I said, I would like to start with something which is part of the molecular biology module of what I am supposed to teach you. And what I would like to start with is what is called as the central dogma of molecular biology. Now, the central dogma of molecular biology was proposed, as I will show you in the early 1950s, which is pretty much almost 70 years ago.

And there are issues with calling the central dogma, the central dogma, which is again, something I will come to, but I will use this as the centerpiece of whatever I am going to teach you over the next 5 to 7 lectures. So, whenever I talk to you about, for example, biomolecules, I will refer to the central dogma, whenever we talk about cell biology and refer to the central dogma.

And the central dogma will be sort of the bones of the flesh, which I will be talking about. Now, a dogma is supposed to be a belief or a set of beliefs, which are held by a group or organization that others are expected to accept, without argument. So, it is a hard and fast set of beliefs, which cannot be changed. And as you will realize, when I talk to you about the central dogma, that is not what the central dogma is.

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**The Central Dogma**  
(Francis Crick)

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have

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graph LR; DNA --> RNA; RNA --> Protein; RNA --> DNA; Protein --> RNA; Protein --> Protein; DNA --> DNA; RNA --> RNA; Protein --> Protein;
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but never

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graph LR; Protein --> RNA; RNA --> DNA; DNA --> DNA; RNA --> RNA; Protein --> Protein;
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where the arrows show the transfer of information.

Notes: Late 1950's

Cold Spring Harbor Meeting  
(1967)

Now, the history of the central dogma goes all the way back to the 1950s. And what you the person you see here, on the right-hand side, is a gentleman called Francis Crick and he is giving a lecture in 1967, in New York State in a university called the Cold Spring Harbor Laboratory, or CSHL.

Now, in this meeting, as you can see in the Blackboard behind, he is drawing a simple schematic, which today we know as the central dogma, and the origins of the central dogma as it is drawn over here goes all the way back to the late 40s to the early 50s. And here is a snapshot of a document which Francis Crick wrote in the late 1950s, where he talks about the central dogma and what the central dogma pertains to is basically the flow of information and these are molecules you have, at least those of you who have done a little bit of biology till 10th or 12th standard have been exposed to, you know what DNA is, you know what RNA is, and you know what protein is.

So, what this central dogma or which we should actually call the central hypothesis, as you will realize, pertains to the flow of information. And what it basically says is that information is stored in a molecule called DNA. And in the 1950s, it was not very clear where information was stored, and till the early 1930s, and even in the 1950s, there were a set of people who believed that proteins were the repository of information. Today, we know that information is genetic and it is stored in DNA. We will come back to this era again and again in the next few lectures.

So, DNA as we know today is the repository of information. From DNA information is transferred to protein. And at that time, it was not very clear how DNA and this was a hypothesis, it was something which was proposed, it was not clearly proven, it was not clear if at all information would flow from DNA to protein, which was the execute molecule within the cell, how this would flow. And the proposal here was it could flow directly from DNA to protein, there could be an RNA intermediate and RNA intermediate could also transfer information to protein.

And what Crick proposed at that time, that never could protein transfer information to protein, never could protein go back in time and transfer information to RNA and never could protein transfer information back to DNA. So, this basically the central dogma as it was proposed, related to the transfer of information and various possibilities were discussed in the top part and in the bottom part, what they thought at that point was not possible.

And this dotted line over here, even in the 1950s, there was a possibility that RNA could transfer information to DNA. And this was based on viral experiments, experiments on viruses which were carried out. Now those people of your generation will see something very strange over here, they will see that the type part in black is, basically is DNA, RNA and

protein. But for some reason, the arrows are not in black. And that was because this was typed on paper with a typewriter and in the 1950s, technology to use paintbrush or any other software to actually draw arrows was not there. So, things were typed first, and the arrows had to be drawn by hand.

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**The Central Dogma**  
(aka the 'Central hypothesis')

"One gene made one enzyme" - Beadle ~1950 1950 to 1960; The decade of the great leap

1958

*My mind was, that a dogma was an idea for which there was no reasonable evidence...I just didn't know what dogma meant. And I could just as well have called it the Central Hypothesis...Dogma was just a catch phrase. And of course one has paid for this terribly, because people have resented the use of the term dogma, you see, and if it had been Central Hypothesis nobody would have turned a hair<sup>14</sup>.*

--Francis Crick

40 years under the Central Dogma. TIGS, 1948

**THE CENTRAL DOGMA**  
(of molecular biology)

**dogma** *noun*

🔊 /ˈdɒɡmə/

🔊 /ˈdɔːɡmə/

[uncountable, countable] (often disapproving)

★ a belief or set of beliefs held by a group or organization that others are expected to accept without argument

- political/religious/party dogma
- She has caused a storm by calling into question one of the central dogmas of the Church.

**dogma**

noun [C or U] - disapproving

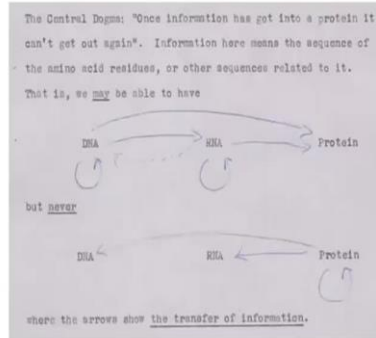
UK 🇬🇧 /ˈdɒɡ.mə/ US 🇺🇸 /ˈdɒɡ.mə/

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a fixed, especially religious, belief or set of beliefs that people are expected to accept without any doubts

## The Central Dogma

(Francis Crick)



Cold Spring Harbor Meeting  
(1967)

Now, the central dogma, even though Francis Crick called it the central dogma, and we today know it as textbook material, as a central dogma, was not really a dogma, as it is defined by the Oxford dictionary on the left and the Cambridge dictionary on the right. It was not a fixed set of beliefs. It was a hypothesis.

And this hypothesis, basically, was changed and is changing over time. And much of what we know about molecular biology can be understood by just each time you study something new, you imagine the central dogma in front of you. And then you ask yourself, how are things changing how have we learned more and more about biology from the 1950s to the year 2000.

Now on the left, you see the sort of timeline, which starts from 1900. And this is a very important year in biology, especially from the view of molecular biology and genetics. 1900, as we will go into and you have learned in your school, was the year of Mendelian genetics was rediscovered after almost 20 years by the Western world.

And the rediscovery of Mendelian genetics, along with merging the Mendelian genetics with the evolutionary hypothesis, which happened in the 1930s, which is somewhere over here led to a deeper understanding of biology. And the 1940s 50s 60s 70s, which is all these range over here was what we know as the golden years of molecular biology, spectacular discoveries were made in this time. And in my class, I will touch upon about a few of them probably 5 or 10 percent which is why over here in 1950 to 60s, I call the decade of the Great Leap, and you will understand what I mean.

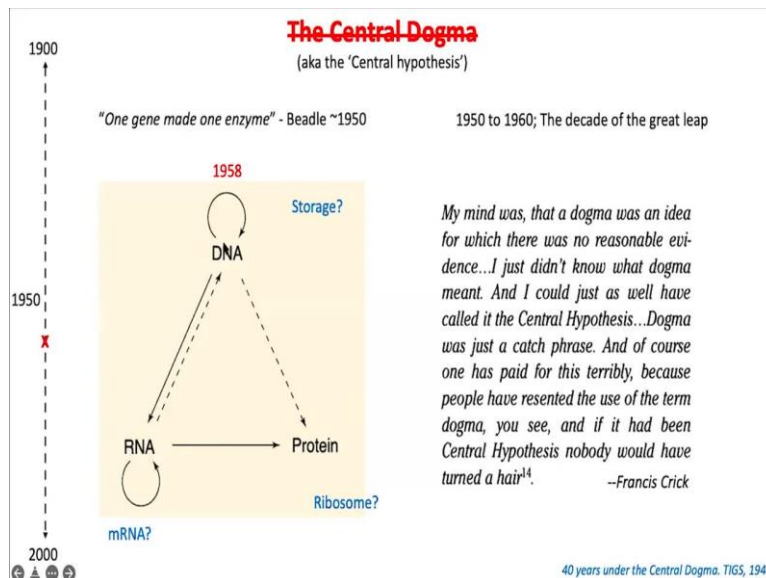
Now, from the 1900s to 1950s, the theories of Mendel were incorporated into the mainstream of biology, evolutionary theory was incorporated into the mainstream of biology. And genetics was due to being done very, very routinely in universities and research centers all over the world. By the 1950s, Beadle would get a Nobel Prize, George Beadle later on made this very famous statement, which again, you have learned in textbooks that “One gene made one enzyme”.

So, there was a relationship between genetic material and the making of an enzyme, which at that time was supposed to be completely proteins. And even though this much was known, even though we knew what amino acids were, it was not completely clear whether what the genetic material looked like, and many people did not believe that DNA was the genetic material, though, by the 1950s. Especially when you will see in this lecture from, from the 1950s to 1960s. This was something which was completely proven, and nobody went back to question that pretty much ever again. Now, as I said, the central theme of today's lecture is the central dogma. And this is the redrawing of the central dogma, which you saw in this old typewritten note, in a more modern arrangement.

Well, not really modern, but about 10 years later by Francis Crick, in a review, and again, this redrawing which is from 1958 talks about DNA, the flow of information from DNA to RNA, information flow from RNA to protein, and the possibility of information flow from DNA to protein. And the dotted lines where less possible events in terms of flow of information and unbroken arrows where the more probable events, there were questions being raised about DNA being the repository of information where all the information was stored. And this would be something which would be underscored and deeply believed in the 1950s.

It was not particularly clear that RNA was indeed, the intermediate and information from RNA came from DNA and it was then translated into protein. But this was something which was let us call it as an emerging idea and people started to believe this and the formation of protein itself, ribosomes had been discovered, and it was believed that these were potential protein factories. But proving all of this happened in the 1950s 1960. And you can read about this in an article which I will upload, which talks about the 40 years under the central dogma. It is a review from the late 1980s, the year is kind of wrong over here.

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Now, a very interesting set of events were happening in the 1940s 50s and 60s, including the definition of the central dogma, the understanding of DNA replication, the understanding of transcription, which is the formation of RNA from DNA, the understanding of translation, which is the formation of protein from RNA.

And molecular biology was a very exciting thing in those times. And a group of friends, led by George Gamow and Jim Watson, who shown over here decided to do something a little strange, they decided to form a club. And the members of this club came from different countries, though many of them were based in the UK and the US.

And these people were very excited about all the events all the new information, which is coming about molecular biology, and all the mysteries which surrounded molecular biology.

So, Gamow proposed that a group of people would form what would be called as the RNA tie lab. And each member would be given a code-name, which was basically related to an amino acid. And they knew that amino acids were strung together to make polypeptides. This was pretty much well defined by the 1950s. But the clear mechanistic link between DNA and RNA was not very clear. So, George Gamow and Jim Watson got together they started meeting like-minded people like Alex Rich, Leslie Orgel, over here. And remember, the members of this club did not all stay in a single location. They were from different places, they would write letters to each other, meet each other in meetings, and discuss the latest, which was happening in biology, molecular biology at that time. And gamma basically made these ties for everybody.

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In 1954, James Watson and George Gamow formed a "gentleman's club" to "solve the riddle of the RNA structure and to understand how it built proteins." There were 20 members, each of whom was designated by an amino acid:

Member	Training	Tie Designation
George Gamow	Physicist	ALA
Alexander Rich	Biochemist	ARG
Paul Doty	Physical Chemist	ASP
Robert Ledley	Mathematical Biophysicist	ASN
Martynas Ycas	Biochemist	CYS
Robley Williams	Electron Microscopist	GLU
Alexander Dounce	Biochemist	GLN
Richard Feynman	Theoretical Physicist	GLY
Melvin Calvin	Chemist	HIS
Norman Simons	Biochemist	ISO
Edward Teller	Physicist	LEU
Erwin Chargaff	Biochemist	LYS
Nicholas Metropolis	Physicist, Mathematician	MET
Gunther Stent	Physical Chemist	PHE
James Watson	Biologist	PRO
Harold Gordon	Biologist	SER
Leslie Orgel	Theoretical Chemist	THR
Max Delbrück	Theoretical Physicist	TRY
Francis Crick	Biologist	TYR
Sydney Brenner	Biologist	VAL

*"If I have seen further, it is by standing on the shoulders of giants" Isaac Newton in 1675, writing to Robert Hooke.*

George Gamow  
(Student of Neils Bohr)  
A cosmologist

Alpher-Bethe-Gamow paper, or  $\alpha\beta\gamma$  paper.

"The Origin of Chemical Elements", Alpher, Bethe and Gamow. Physical Review, 1948

### The RNA tie Club



Francis Crick

Jim Watson



George Gamow





And each member, and these are the members of the club, shown over here, got tie designation, and which was basically an amino acid and there were 20 members and as you know, there are 20 amino acids. So, each member got basically an amino acid designation with a tie, a tie of different colors. Now, when you look at these names, which are members of the RNA tie Club, you will realize that many of them are very famous scientists.

And these are names you should know about. So, for example, Alexander Rich went on to do very interesting things with DNA structure, and with collagen structure. Erwin Chargaff, I hope some of you have heard about, he basically found the equivalents of ratios between AT and GC nucleotides. Jim Watson and Francis Crick, of course, we will talk about. Many of you have heard of Richard Feynman, who was at Caltech, and Sydney Brenner is somebody you will hear about Max Delbruck, Melvin Calvin also.

So many of these went forward to become Nobel laureates. So, this was a set of very, very smart people who were communicating with each other, and who were basically involved in trying to understand the wonders of what was coming out of many experimental labs in the 1940s 50s and 60s.

Now, Isaac Newton has famously said in a letter in 1675, to Robert Hooke, that if I have seen further, it is by standing on the shoulders of giants, and these people became giants of their fields. And in order to become giants, they are dependent on work done by other giants so as to speak, in the 1920s in the 1930s. And we can go all the way back to the theory of evolution, we can go back to Mendelian genetics.

So much of progress in science is basically done by breakthroughs, which are made in earlier generations. And these very famous people were dependent on researchers before them. And researchers today depend on the science done by these people. Now, George Gamow himself was a very interesting chap. And if you look over here, you will realize that George camel was actually a physicist. He was actually a cosmologist, and he was the student of Niels Bohr. And you will also notice that not everybody over here is a biologist.

There are many chemists, because biochemistry is in those days was the purview of the Chemist if not only the biologist, you will notice that there is a theoretical chemist for example, Leslie Orgel, Delbruck was a theoretical physicist who went completely and totally into molecular biology specially, phages, bacteriophages, you will see physicists here and you will also see theoretical people who do math who are mathematicians.

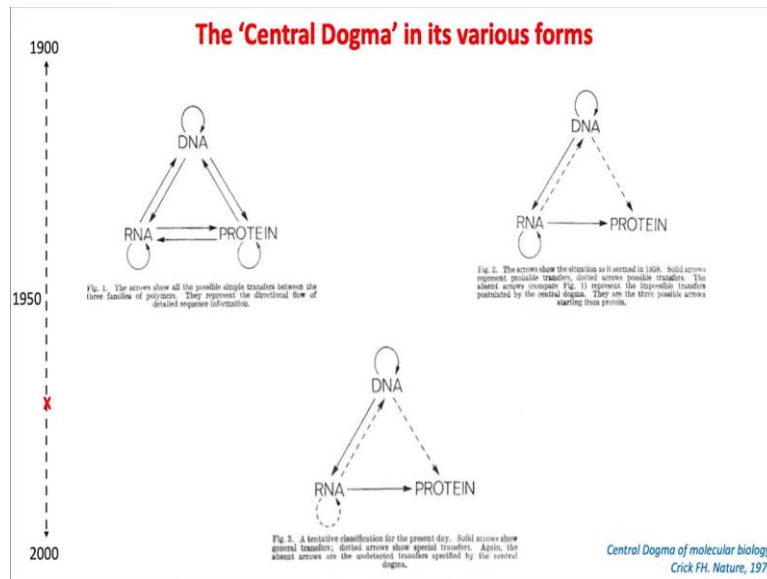
Now, Gamow, particularly someday I will focus on for a few minutes though each one of these people is interesting, because Gamow, in spite of being a cosmologist, and working in the area related to the origin of the universe, especially the big bang, also had a broad interest in science, and generally did all kinds of interesting things apart from just working on cosmology.

Gamow was also known today amongst the physicists for his very famous paper, which related to the big bang called the origin of chemical elements, which is called as alpha-beta-gamma paper and the reason it is called the alpha-beta-gamma paper is because it, of course, is a very interesting breakthrough paper. But it also has his authors, Alpher, Bethe, and Gamow.

So, these were the 3 authors of the paper. And it turns out that when Gamow did this work, he did it with a graduate student who is Alpher. And when he was, when the final draft of the paper was ready, and he was sending it out to publication, he decided that that paper would look so much better if there was a beta in between Alpher and Gamow.

And he basically added Hans Bethe as an author to this paper, even though Hans Bethe had not contributed at all to any of the work just for fun. And this just for fun is another reason why you realize why George Gamow created this club called the RNA tie club, it was a means to bring fun into science. And it was also a means by which a group of very interesting people stayed in touch by writing letters meeting each other in meetings and forwarding the idea of molecular Biology.

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### The Central Dogma (Francis Crick)

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have

but never

where the arrows show the transfer of information.

Notes: Late 1950's

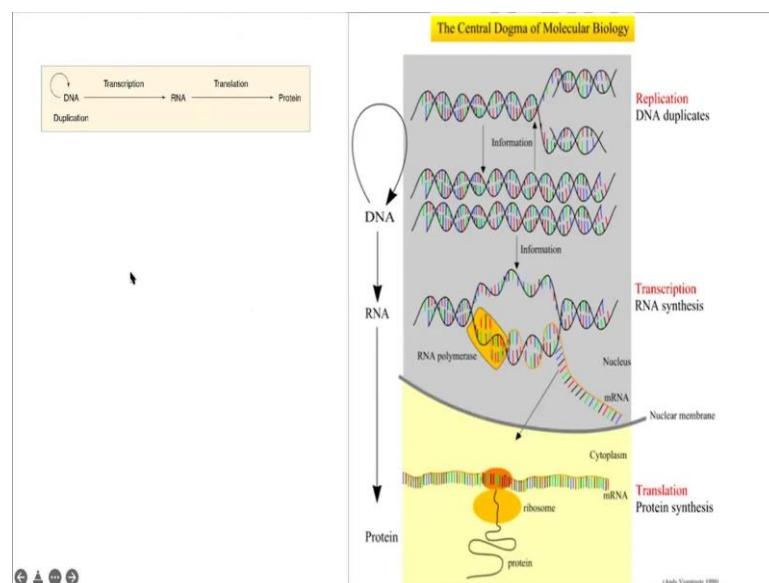
Cold Spring Harbor Meeting  
(1967)

So, this is where we basically were in the 1950s there was a relationship in terms of information flow between the 3 major macromolecules which is DNA, RNA, and also protein. And what was not very clear at that time, and this is a paper written by Francis Crick in nature in 1970, as to and the crossover here marks the time period, what we are talking about is what was the relationship between them in terms of flow of information.

I know students are taught in high school about DNA makes RNA and RNA makes protein. But the central dogma was not about what makes what, the central dogma was, what is the storage area for information, this information is used to build life. And how does this information flow and figure one over here talks about all the possibilities of flow of information, DNA to protein, protein to DNA, protein, makes protein, and so on and so forth.

Figure 2 is the figure you saw earlier, which was crawled in the late 1950s by Francis Crick, which was a possibility of DNA also allowing flow of information to protein. And this thing has changed a little bit. And the DNA to protein flow of information has never really been proved. But what was very clear as early as the 1950s, was that absolutely Crick believed that protein information from protein could not be transferred back to DNA, or to RNA. And this seems to be fairly clear, though there are many modifications on the central Dogma.

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So here is the central dogma as we know it DNA can replicate and this is shown in the right-hand side. This is where the genomic information is stored as ATGC as the ATGC code which you are aware of. DNA replication allows you to take information stored in DNA and make copies of it. And this is something you know happens in cell division during mitosis and also in meiosis, DNA is copied into 2 independent parts.

And both these independent parts basically will go into 2 different cells. So, the information is conserved from generation to generation, by DNA replication. Now inside a cell and this is a picture of a cell, information can be passed to RNA because it turns out that the way molecular biology and biochemistry have evolved in sense over the last few billion years, there appears to be a need for an intermediate and DNA cannot pass on its information directly to the executive molecule which is protein. The information is passed to RNA. RNA, then basically is decoded because RNA is there in a certain form, which is very similar to DNA. It is also a nucleic acid.

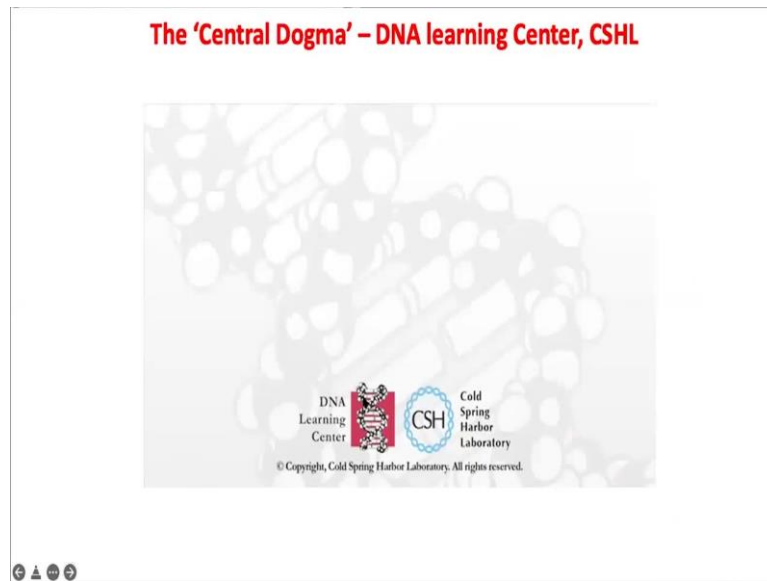
The process of making RNA from DNA is called transcription. And the molecule involved is RNA polymerase. And when transcription happens mRNA is created. And in eukaryotic cells mRNA is in a different compartment from where the ribosome is, therefore, it has to be transferred through nuclear pores to the cytoplasm, where the ribosomes are sitting.

The ribosomes will read the RNA, which we now call messenger RNA, and this RNA will now be converted into protein. And this is called as this process is called as translation. And just for nomenclature's sake, I am going to say a few write down a few things, which are sort of important in the future. So, I will call it machine and I am calling it a molecular machine, which does replication. So, this machine I am going to call DNA dependent DNA polymerase. So, replication is carried out by a polymerase, which can polymerize nucleotides, but it is dependent on DNA. So, it is a DNA dependent DNA polymerase and we call it we call it a molecular machine. Transcription is done by a protein called RNA polymerase. But its full name is a DNA dependent RNA polymerase.

Now, you know that RNA can also go back and form DNA. This is the process of reverse transcription, which we will talk about in the next lecture. And we will call that machine as the RNA dependent DNA polymerase, right. So, you can start with RNA and you can make DNA. And you can take RNA and you can make protein.

You know, the ribosome does it. But let us just give it a name. Let us call it a RNA dependent amino acid polymerase, where polymerase is not a great term, we will call it a RNA dependent amino acid, it cannot be a synthesis because it is not synthesizing amino acids. It is just stitching it together and that is what the ribosome does.

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So, I will now show you a movie which is a movie from the Cold Spring Harbor Laboratory, which is a famous laboratory in New York, where in the 1950s meetings were routinely held. And Jim Watson, who will talk about in the next few slides actually became for many years, the director of the Cold Spring Harbor Laboratory. All right, so let us see the movie.

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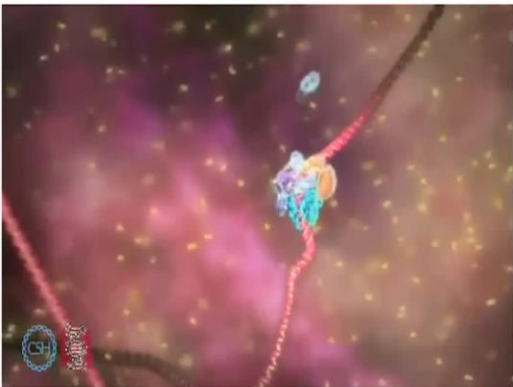
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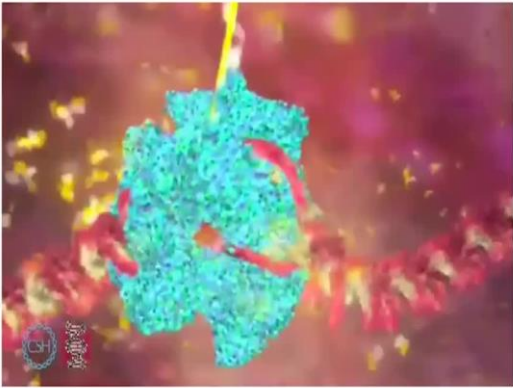
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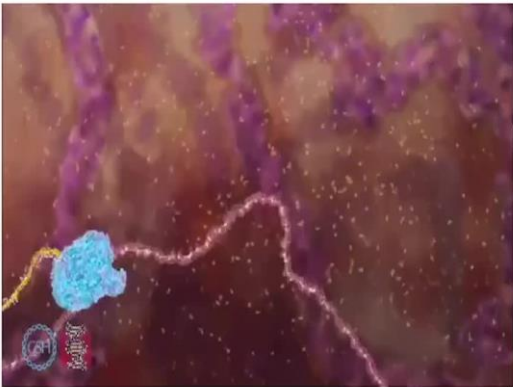
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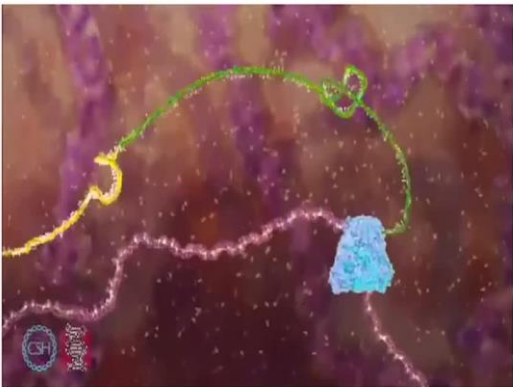
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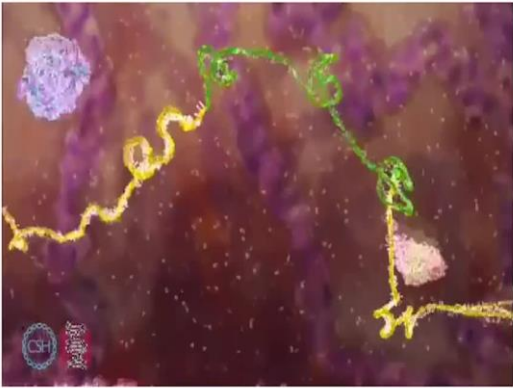
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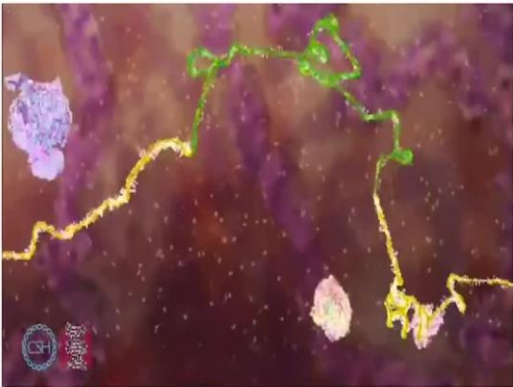
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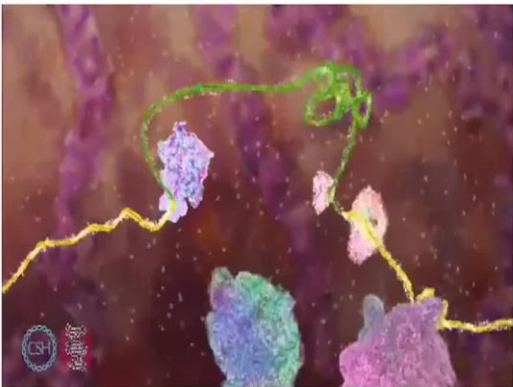
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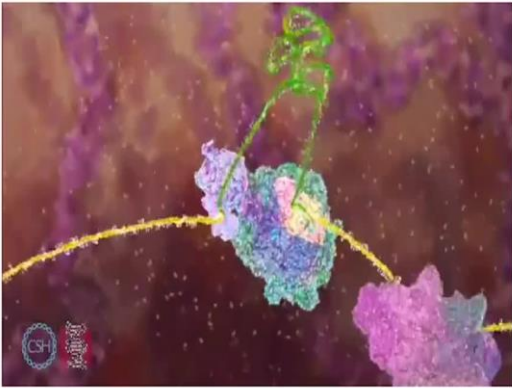
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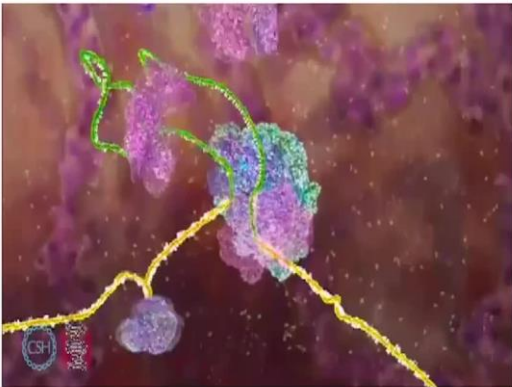
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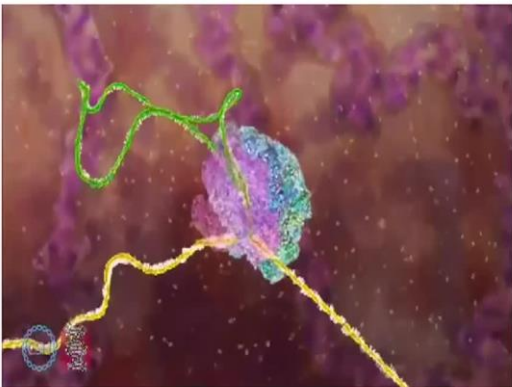
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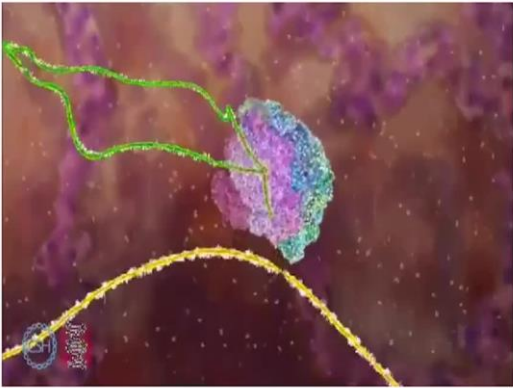
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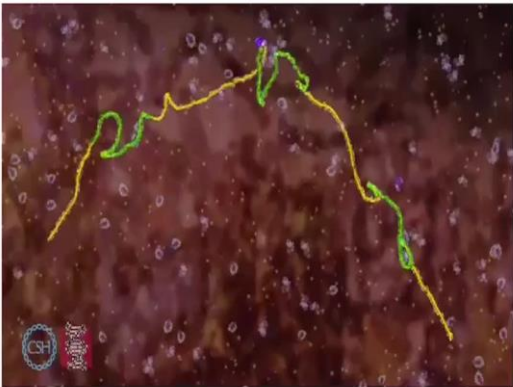
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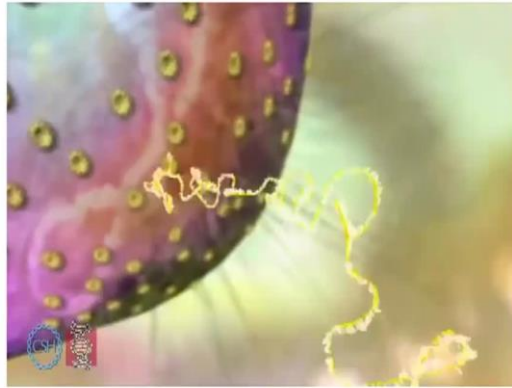
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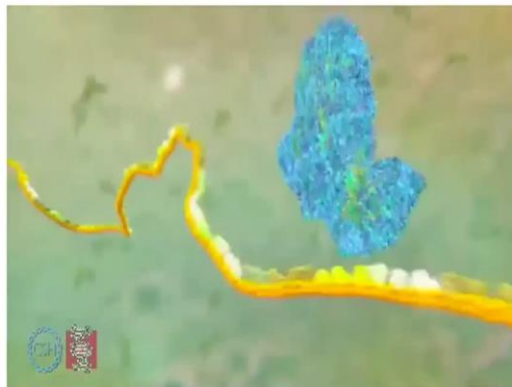
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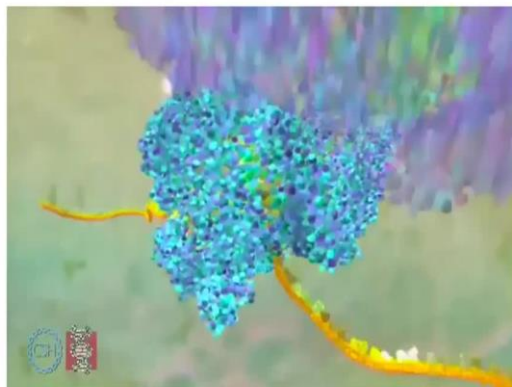
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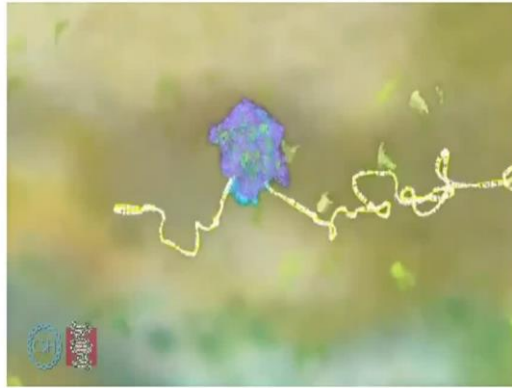
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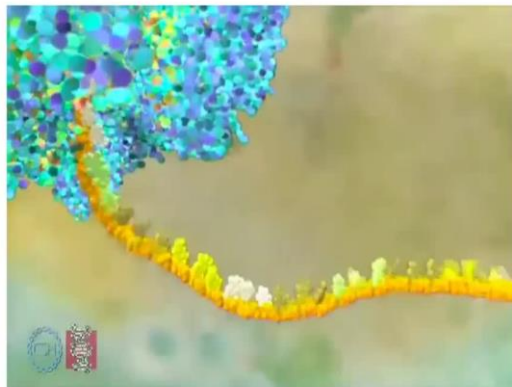
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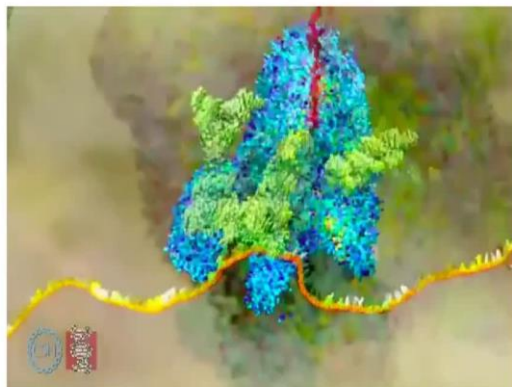
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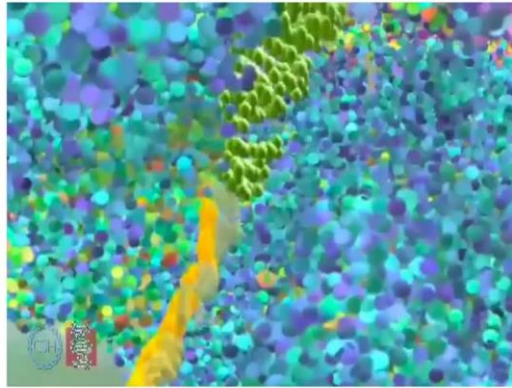
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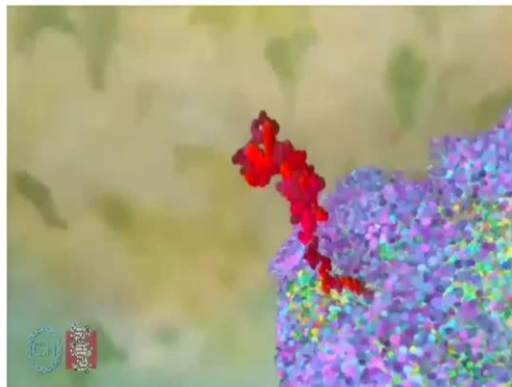
**The 'Central Dogma' – DNA learning Center, CSHL**



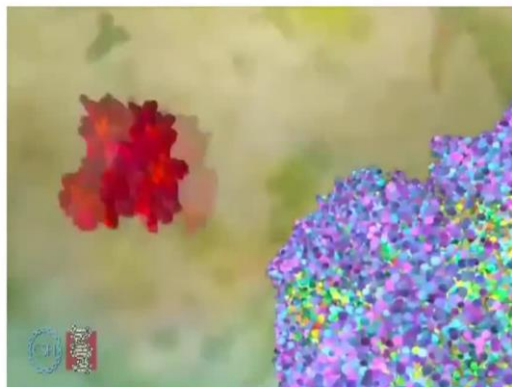
The 'Central Dogma' – DNA learning Center, CSHL



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The DNA double helix contains 2 linear sequences of the letters A, C, G and T, which carried coded instructions. Transcription of DNA begins with a bundle of factors assembling at the start of a gene to read off the information that will be needed to make a protein. The blue molecule is unzipping the double helix and copying one of the 2 strands.

The yellow chain sneaking at the top is a close chemical cousin of DNA called RNA. The building blocks to make the RNA enter through an intake hole, they are matched to the DNA letter by letter to copy the gene. At this point, the RNA needs to be edited before it can be translated into a protein. This editing process is called splicing, which involves removing the green non coding regions called introns, leaving only the yellow gene-coding exons.

Splicing begins with assembly of factors at the intron exon borders, which act as beacons to guide small proteins to form a splicing machine called the spliceosome. The animation is showing this happening in real time. The spliceosome then brings the exons on either side of the intron very close together ready to be cut, one end of the intron has cut and folded back on itself to join and form a loop.

The spliceosome then cuts the RNA to release the loop and join the 2 exons together. The edited RNA and intron are released and the spliceosome disassembles This process is repeated for every intron in the RNA. Numerous spliceosomes remove all introns so that the edited RNA contains only exons, which are the complete instructions for the protein.

Again, this is happening in real time. When the RNA copy is complete, it sneaks out into the outer part of the cell. Then all the components of a molecular factory called the ribosome locked together around the RNA. It translates the genetic information and the RNA into a string of amino acids that will become a protein.

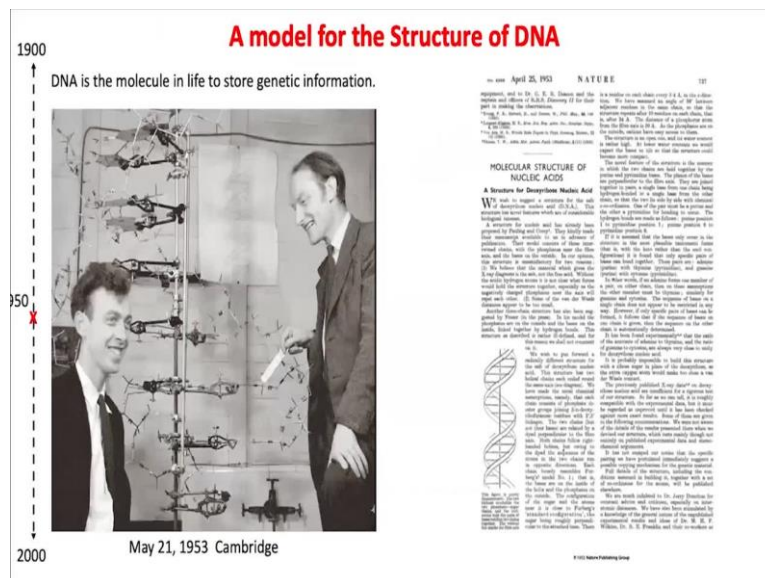
Special transfer molecules, the green triangles bring each amino acid to the ribosome. Inside the ribosomes the RNA is pulled through like a tape. There are different transfer molecules for each for 20 amino acids shown as small red tips, the code for each amino acid is read off the RNA, 3 letters at a time and matched 3 corresponding letters on the transfer molecules, the amino acid is added to the growing protein chain. And after a few seconds, the protein starts to emerge from the ribosome. Ribosomes can make many proteins; it just depends what genetic message you feed into the RNA.

Alright, so you saw an animation of what happens inside the nucleus, where the DNA dependent RNA polymerase sits on DNA, along with many, many transcription factors.

It copies all the information to a yellow nucleic acid strand, which is RNA, we will come to RNA splicing a little later, but RNA is edited. And I will explain why it is edited for those of you who have not done this earlier. And the edited RNA, which is the yellow strand comes out of the nucleus goes into the cytoplasm, finds the ribosome, and the ribosome reads the hidden code, the genetic code in the RNA, which originally is stored in DNA.

And then makes a protein, the protein which is a linear sequence of amino acids, then folds, and then it has an executive role. And this executive role is very important for life, per se. And unless you have all the information stored in DNA, you cannot go through the process of transcription translation, which is part of the central dogma as proposed by Crick and you cannot make proteins and if you do not have proteins, you basically cannot have life.

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So now that you have a visualization of how the different molecular mechanisms in the central dogma are happening, you have an idea about the flow of information. Let us now go back to 1953. And 1953, again is a very, very critical and major year in molecular biology. And one element of the central dogma is DNA and what we will do now is we will focus a little bit on DNA.

Now, what you see in the picture is a historic picture taken on May 21 1953, With the Watson on the left, Crick on the right, standing in front of their model of what a DNA structure

looked like. And they built this model and proposed this model in a very famous paper in Nature in 1953, which is shown on the right-hand side. It was basically a one-page paper which spilled over to the second page a little bit, a few 100 words.

And this paper today we know was very accurate about the structure of DNA. So, did they solve the structure of DNA? No, they did not. Were they the first to model DNA? They were not. They in fact, had modelled DNA multiple times, in the 2 years before this paper was published. And they had modeled it in different ways. It was just that this model to them made a lot of sense and they thought it was the correct model of DNA.

Had anybody else modeled DNA? Yes. Everybody, every chemist in the world had tried to model DNA. It was the Holy Grail of molecular biology. And everybody knew that modeling DNA would be a great discovery. So, what I will do in the next few slides is tell you the story, a little bit of the story of how DNA was modeled, and what is the background behind it.

So, the year is 1953, as shown on the timeline, these 2 people are very happy, because they think that their model is the model of DNA. And they are, they will be even more happier 9 years from this point, because 9 years from 1952 - 1953, which is 1962, they will receive the Nobel Prize for making this model. Now, let us learn a little bit about both these people Jim Watson and Francis Crick.

(Refer Slide Time: 29: 11)

Jim Watson, 23, Postdoctoral Fellow  
Francis Crick, 35, Ph.D. student, University of Cambridge

Cavendish Laboratory, University of Cambridge

Linus Pauling, California Institute of Technology (The Pauling-Corey model)  
Triple helix, bases facing outside

Maurice Wilkins  
Rosalind Franklin  
Kings College, London

How the two strands of DNA are connected. The authors state that a single base from one DNA strand attaches to a single base from the opposite DNA strand via hydrogen bonds. In DNA, hydrogen bonds occur between hydrogen atoms and oxygen or nitrogen atoms. While hydrogen bonds are weaker than the phosphate bonds connecting nucleotides together in each DNA strand, they are strong enough to hold the two helical strands together. Watson and Crick explain that for adequate hydrogen bonding to occur, within each pair of connected bases, one base must be a purine, a double ring, and one base must be a pyrimidine, a single ring.

Specific identity of each base in a base pair. The authors assume that each of the four bases can only pair with one other type of base. Adenine, a purine, can only pair with thymine, a pyrimidine. Guanine, a purine, can only pair with cytosine, a pyrimidine. Based on that logic, Watson and Crick explain that the sequence of bases along one DNA strand automatically determines the sequence of the other strand. Each base along a DNA strand pairs with its only viable counterpart on the opposite strand. To support their claim about specific base pairing, Watson and Crick cite experimental evidence. Erwin Chargaff at Columbia University in New York City, New York obtained that evidence. The authors explain that Chargaff determined that in DNA the ratio of adenine to thymine and guanine to cytosine is always roughly one-to-one. That means that the amount of adenine in DNA roughly equals the amount of thymine, and the amount of guanine roughly equals the amount of cytosine, which is the likely case if base pairing in DNA is specific.

X-ray crystallography evidence that they used to generate their model of DNA. Watson and Crick acknowledge that the x-ray crystallographic evidence of DNA published before they wrote their article could not confirm their model alone and there needs more experimental evidence to prove their model. Watson and Crick then postulate that the base pairing mechanism they proposed implied a possible DNA replication mechanism, though they do not describe that mechanism.

King's College London in London, UK. Rosalind Franklin, a chemist, and her graduate student, Raymond Gosling, collected the data. Watson and Crick acknowledged those individuals in their paper. From 1951 to 1953, Franklin and Gosling gathered x-ray diffraction pattern images of DNA, which they obtained from the x-rays of DNA crystals. When Watson and Crick wrote "A Structure for Deoxyribose Nucleic Acid," Franklin and Gosling had not published their most clear DNA diffraction images, despite those images having improvements over the published data at the time. In early 1953, without Franklin's knowledge, Maurice Wilkins a co-worker at King's College showed Watson one of Franklin's clear diffraction patterns of DNA. Later, Watson and Crick received a report Franklin wrote on her experimental findings. That report contained data Franklin presented at a colloquium at King's College in 1951. When developing their model of DNA, Watson and Crick drew conclusions from data contained within both Franklin's diffraction image and her report.

**A model for the Structure of DNA**

DNA is the molecule in life to store genetic information.

1900

May 21, 1953 Cambridge

2000

April 25, 1953 NATURE 137

**MOLECULAR STRUCTURE OF NUCLEIC ACIDS**

**A Structure for Desoxyribonucleic Acid**

WE wish to report a structure for the salt of desoxyribonucleic acid (DNA), the substance which carries the genetic information in living organisms.

A structure for nucleic acid has already been suggested by Hoogstraal and Hoogstraal<sup>1</sup>. Their model was based on the assumption that the phosphate groups and the bases are in the interior. In our opinion, the structure is unsatisfactory for several reasons. First, the model is not a double helix. Second, the model does not account for the fact that the distance between the phosphate groups is not constant. Third, the model does not account for the fact that the distance between the phosphate groups is not constant. Fourth, the model does not account for the fact that the distance between the phosphate groups is not constant.

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So, Jim Watson is 23 years of age, not too far away from your age, a few years older. He is done his PhD already. He is from the United States. And he is come to Cambridge to study in the Cavendish Laboratory. Francis Crick, at 35 years of age is a PhD student. And he is doing his PhD in the University of Cambridge. They are 10 years apart from each other.

They meet when Watson comes to Cambridge, they hang around together, eat lunch together and become friends. And they start taking interest in DNA per se, and also potential structure of DNA. Neither of them actually does any serious experimental work. They, in fact, go around looking at data which is already published and start trying to think about what DNA would look like in terms of its molecular structure.

In early 1953, the famous Linus Pauling, who is in the United States publishes DNA structure and this structure is coming out in nature. In that structure, there are three helices of DNA and all the nucleotide bases are actually facing outside. Now, Watson and Crick, are busy trying to build their own structure.

And what seems to be a very key point in their solution of the final structure is a visit to a nearby college called King's College in London, which is a few hours away from Cambridge. And there they meet Morris Wilkins, who is an experimentalist and who is doing an experiment which is called as fiber diffraction and what fiber diffraction is that you extract nucleic acid out from cells.

Nucleic acid in water is very viscous and if you put in a glass rod, inside the pure nucleic acid in solution, you can actually wind it out. Just like you can wind out a rope. And what

experimentalists in King's College are doing is they are pointing X rays at this fiber and getting what is known as fiber diffraction patterns, something I will show you in the next class.

And amongst the people working in King's College is a scientist called Rosalind Franklin and Rosalind Franklin has very good experimental skills. And early 1953 when Crick visits Maurice Wilkins, who is a friend of his, Maurice Wilkins shows him the data collected by Rosalind Franklin and that data is the cleanest fiber diffraction data which Francis Crick has seen in the last three to four years.

Because it is a very clean picture, immediately some things become obvious about the structure of DNA and Crick goes back and sits down with Watson and says that based on this picture that there are certain restraints and constraints which have to be in DNA and using that as the key breakthrough and please remember that , that is not the only reason, there are many other pieces of data out there and both Watson and Crick have been busy in these, they have been trying to model DNA for a significant amount of time.

But that seems to give them additional insight and they build a model of DNA within 3 months and they publish it by I think, May or June, around that time in nature. Now, this structure has certain key features, which I will not describe very clearly, very obviously there are two strands, which are anti-parallel, which most of you know by now.

The phosphate bonds are connecting the nucleotides together, I will show you pictures of nucleotides in a few slides. And they basically use Chargaff information to connect how AT and GC are hydrogen bonded together, again I'll show you this later, and very obviously, data collected by Rosalind Franklin and previously published data becomes fairly important for their discovery.

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Published: 25 April 1953

### Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid

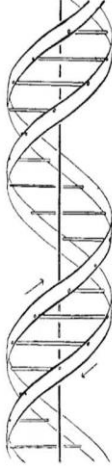
J. D. WATSON & F. H. C. CRICK

[Nature](#) 171, 737–738 (1953) | [Cite this article](#)

145k Accesses | 7927 Citations | 1631 Altmetric | [Metrics](#)

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey<sup>1</sup>. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.




So, this is the paper on 25th April 1953, in nature, and this is a schematic on the right-hand side showing the anti-parallel strands, 5 prime to 3 prime and 3 prime 5 prime. Again, these are concepts I will tell you for those of you who are not aware of them, and the strands, which you see over here, these are basically the bases which are finding, which are forming hydrogen bonds.

So, this is a simplistic representation of the double helix, which we know fairly well. And this is how their paper starts, “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”. And they basically rebut the Pauling and Corey structure which has just come out 2 months ago in nature and they say that, that is completely wrong.

And the next 10 years especially data collected by crystallography, not just on fiber diffraction, but also an actual crystals of DNA confirms that this form of DNA which we now today known as the B form of DNA, is actually an accurate model of what will be confirmed later as the correct model of DNA.

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**The three papers published back to back in Nature (1953)**

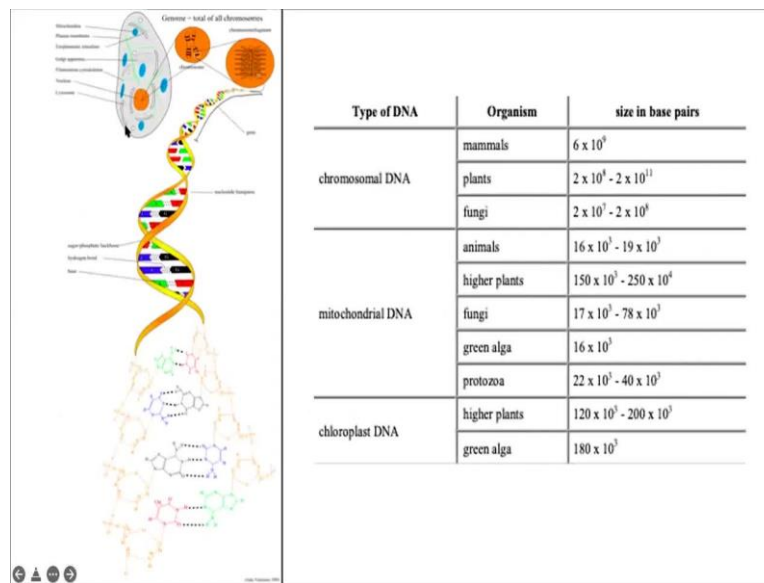


1. Watson JD, Crick FH. A structure for deoxyribose nucleic acid. *Nature* 1953;171:737-738. Also available from: <http://www.nature.com/genomics/human/watson-crick/>  
[Crossref](#), [Medline](#), [Google Scholar](#)
2. Franklin RE, Gosling RG. Molecular configuration in sodium thymonucleate. *Nature* 1953;171:740-741.  
[Crossref](#), [Medline](#), [Google Scholar](#)
3. Wilkins MHF, Stokes AR, Wilson HR. Molecular structure of deoxypentose nucleic acids. *Nature* 1953;171:738-740.  
[Crossref](#), [Medline](#), [Google Scholar](#)

Now, many scientists forget that the 1953 issue of nature, which is the April 1953 issue, contains not 1 paper but 3 papers, 3 very important papers. The first paper is the easiest to read. It is the shortest and it very clearly and simply spells out what the model of the DNA is. Also, in the paper immediately following the Watson Crick paper is the Wilkin-Stokes paper which also talks about the molecular structure of DNA.

And which is followed by Rosalind Franklin's paper, which actually shows the fiber diffraction image which has become very, very famous. So, it is these 3 papers together, which form the central tenet of DNA structure, with the model proposed by Watson and Crick, which stands to this day, data collected by Rosalind Franklin and also other data collected by Maurice Wilkins.

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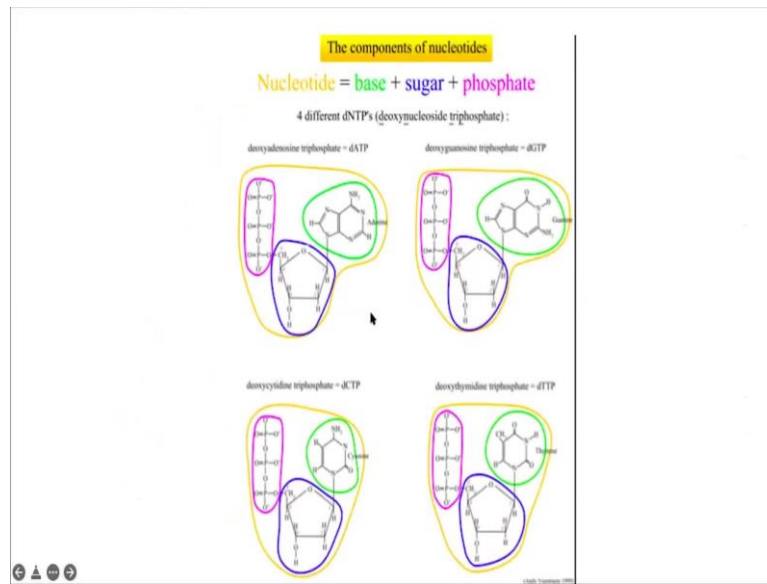


Now, on the left is a cell, and shown in orange is the nucleus and, as you know, the nucleus contains many, many chromosomes and these chromosomes when you unwind them, will basically have a single strand of DNA a single strand of double-stranded DNA with 2 strands running anti parallel to each other and connected by hydrogen bonding, which is shown over here. Now, there is a lot of DNA in cells, chromosomal DNA in mammals have about 10 raise to 9 base pairs, which is a lot of zeros, followed by 1.

Plants have even more DNA in the nucleus 10 raise to 11 base pairs, mitochondrial DNA is smaller, they are about 10 raise to 3 to 10 raise to 4 base pairs and chloroplast DNA is also not very long, it is about 10 raise to 3 and this is the central repository of all information and this information is transcribed and translated to make proteins and it is the proteins which do much of the work inside the cell.



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For those of you who have not seen the unit of DNA, it is basically a nucleotide it contains a base in green over here, sugar in blue, and the phosphate group and the connectivity between the phosphate groups with ATG and C, which is the 3 nucleotide triphosphates ATP GTP CTP and DTP is basically what makes up a strand of DNA.