Sage - Spring 2023

Welcome to

our last session of

"Genes for Very Smart but Ignorant People"

Sage - Spring 2023
Course Outline

1. *Gregor Mendel: How a monk came to discover the rules of inheritance*
2. *Genes and chromosomes - the fly in the ointment*
3. *Microbiologists discover that most genes are made of DNA*
5. *How two amateurs beat the A team to solve the structure of DNA*
6. *Proteins and the genetic code. Again an obscure team of players beats the pros.*

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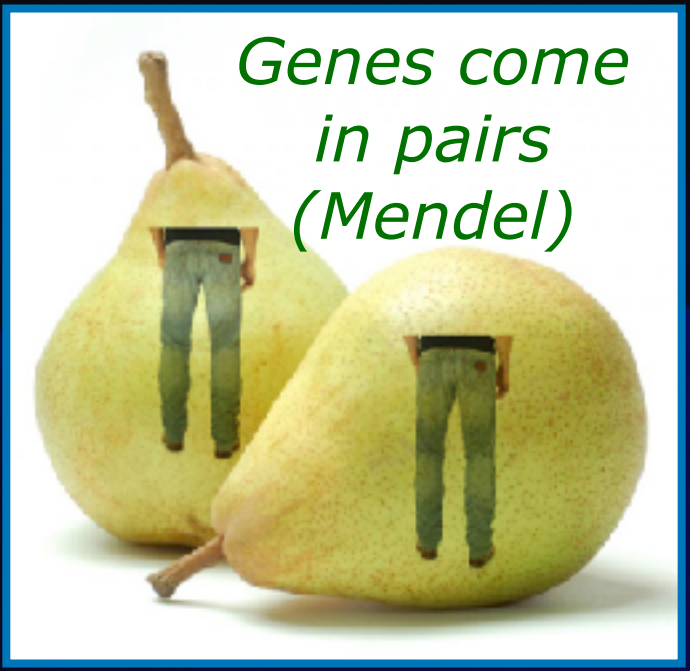
Grand Summary

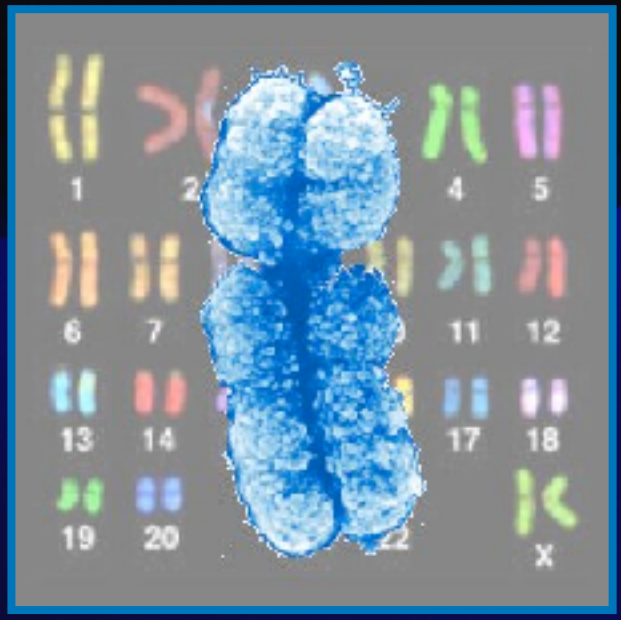
Let me remind you of the key concepts that I've asked you to retain from the previous sessions of this seminar.

1



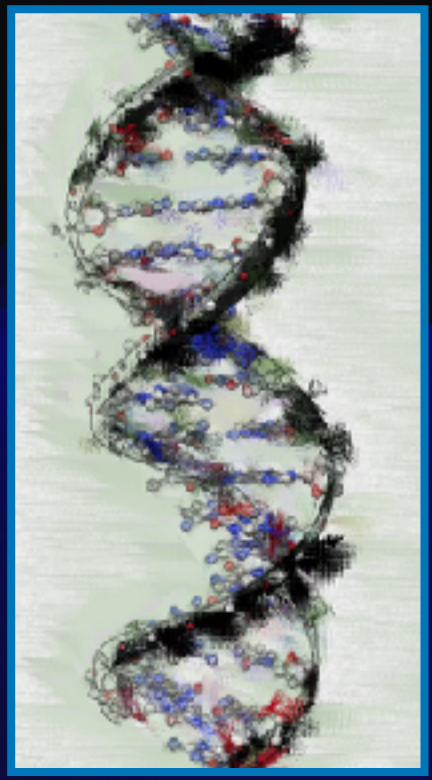
2

Genes are located on chromosomes that also come in pairs (Morgan)



3

Genes are made of DNA and specify the sequence of proteins



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The three major molecules of life (DNA, RNA, and proteins) are all polymers

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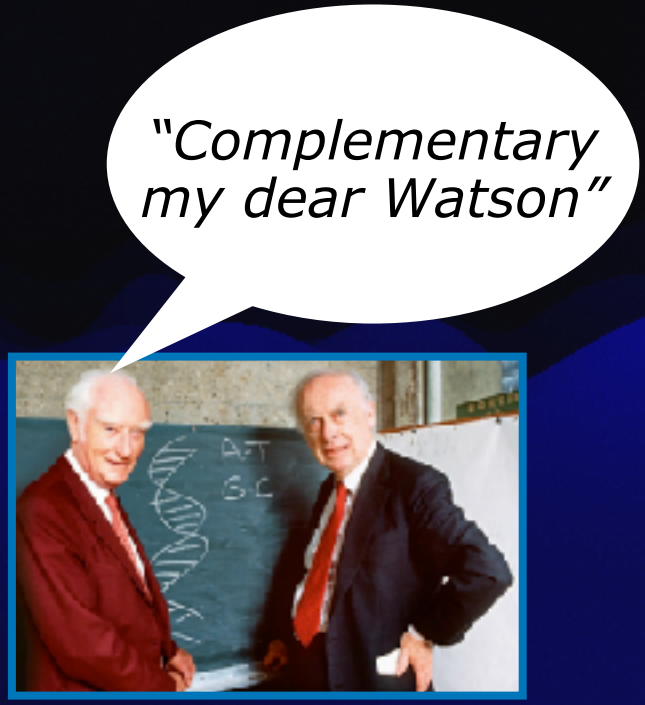
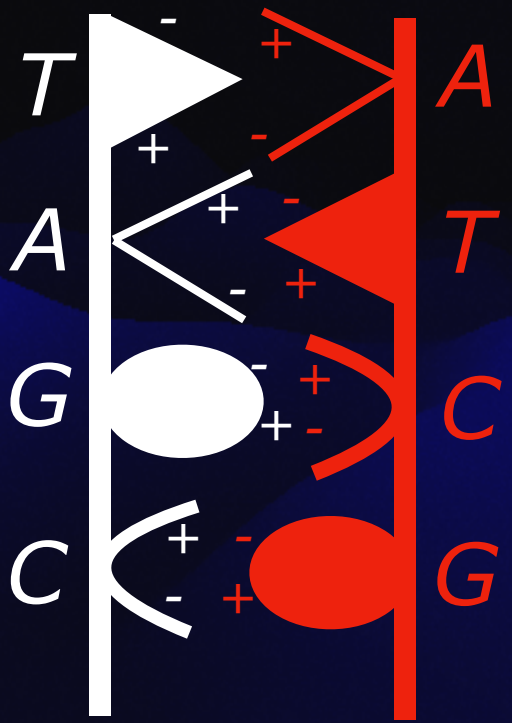
DNA consists of two polymer chains that are complementary to each other.





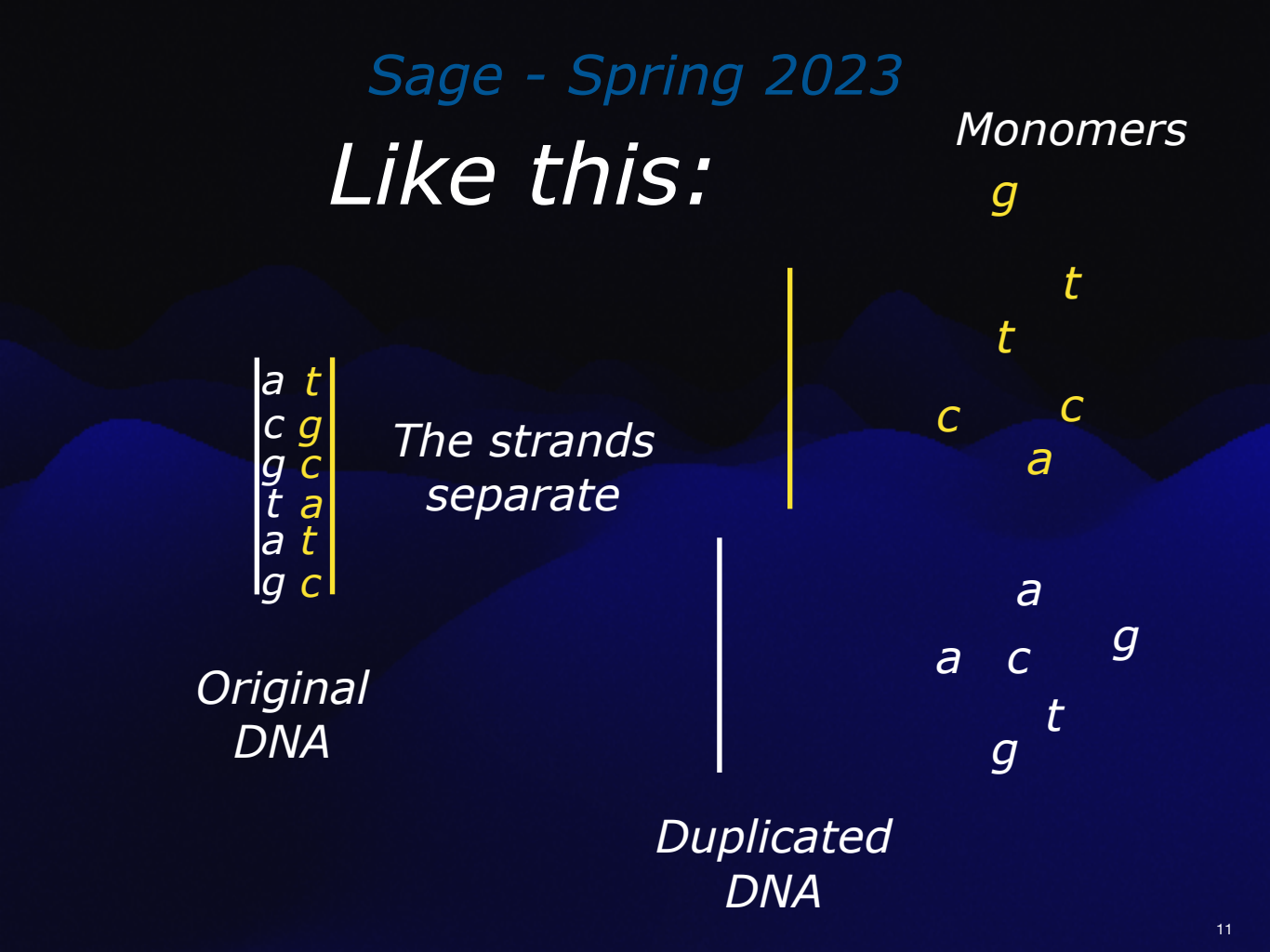
Complementation illustrated graphically.

Notice that both shape and charge are complementary.

The complementary character of DNA allows for the sequence of bases to be passed accurately from one generation to another.

It's one of the secrets of life.

Like this:


Monomers
g
t
t
c
c
a
a t
c g
g c
t a
a t
g c
The strands separate
Original DNA
a
a c
g
t
g
Duplicated DNA

6

Today's take home:

The Central Dogma

Information flows from DNA to RNA to Protein.

DNA → RNA → Protein

6

Dog Ma

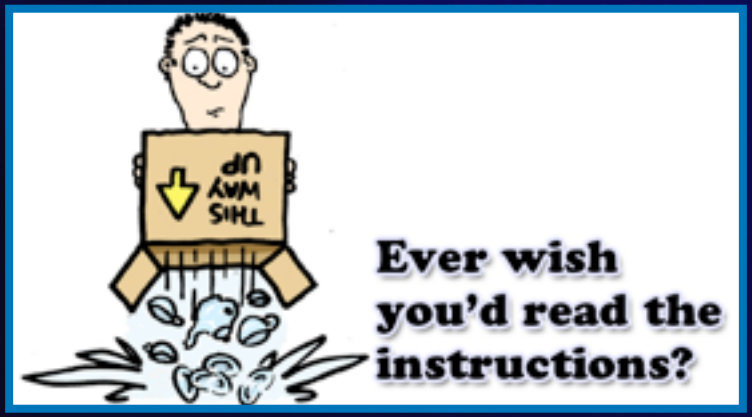
Here's the idea:

The monomers of DNA act as symbols.

In sequence, they can be used as a text and can serve to provide instructions.

It's the second secret of life.

The sequence of bases in DNA acts as instructions.



Instructions to do what?

That's where another polymer comes in.

Proteins

What's a protein?

What do proteins do?

DNA and proteins are both polymers, but they are very different.

If DNA is the recipe, proteins are the cooks.

If DNA is a musical score, proteins are the musicians.

*In a word, proteins **do** things. They are miniature machines.*

*Remember, DNA doesn't actually **do** anything. It's function is to provide instructions.*

Proteins are polymers that assume their structure from DNA's instructions.

Their subunits are called

amino acids

There are 20 different amino acids in proteins


Like these...

The parts are strung together in a polymer so that they don't go flying off in all directions.

Together, when arranged in a specific sequence, the amino acids can form a molecular machine, a device for carrying out a specific job.

There are about 100,000 different proteins in humans.

Each protein has a different sequence of amino acids.

Each gene is responsible for determining the sequence of each of these proteins.

Together, this assemblage of proteins, carries out almost all the activities necessary for life.

Let me emphasize:

sequence is all important.

It is the sequence of amino acids in a protein that determines what kind of machine it forms and therefore what job it performs.

Let's tackle another big question:

How exactly does DNA determine the sequence of machine parts in these proteins?

How is a sequence in DNA used to specify the sequence of a protein?

The first person to make a serious attempt at answering this question was a physicist:

George Gamow

George Gamow

Gamow, born in Odessa in 1904.

As a young adult in the 1930s, he became unhappy with how things were going in the USSR.

George Gamow

He and his wife decided to defect.

They tried to cross the Black Sea to Turkey (170 miles) by kayak?!

They got caught in a storm and had to turn back.

George Gamow

Then he tried to rent a sleigh from some Eskimos in an effort to escape via Finland.

But the authorities were already prepared for people escaping that way.

George Gamow

In the end, he tried to get away in a more conventional way: He was invited to speak at an International Conference in Belgium. He thought he would defect once he got there.

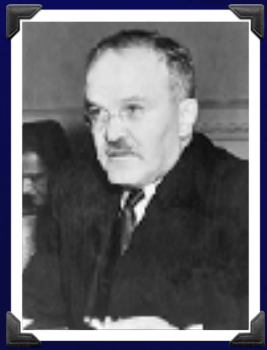
George Gamow

Alpher, Bethe, Gamow

But there was still a problem: his wife. How was he to get her out?

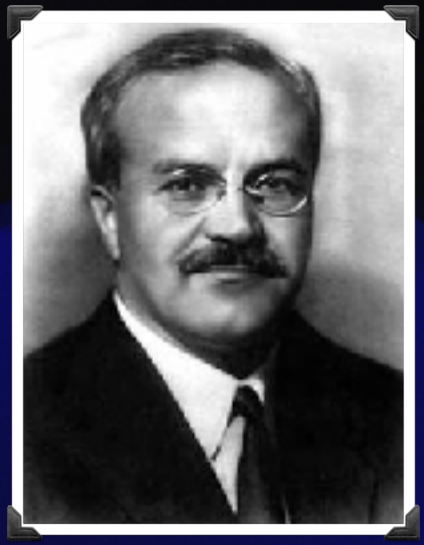
He knew one high official, Nikolai Bukharin, former member of the Politburo, Soviet Central Committee, and editor of Izvestia and Pravda. He appealed to him for help.

Bukharin got him an interview with Molotov, the number two man in the Soviet Union.



Molotov asked Gamow why he wanted to take his wife with him.

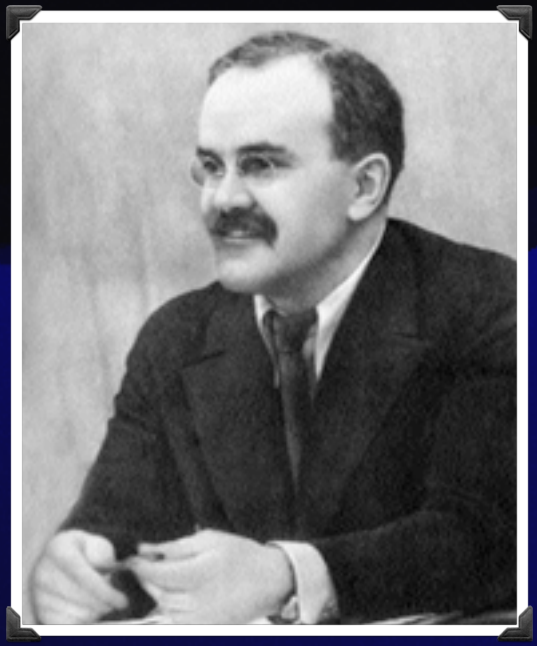
"I could tell you that my wife is a physicist.. and acts as my secretary, and I can't attend a big ... meeting without her help, taking notes ... but it is not true," Gamow responded



"I want to take her to France afterwards, show her Paris and buy her some clothes."

Molotov smiled.

"Well, there probably will be no difficulty."



Gamow defected and eventually ended up in Washington, DC at George Washington University as Professor of Physics.

He had a long career and made many contributions to physics.

In addition, he popularized science.

He had a whimsical sense of humor.

Alpher, Bethe, Gamow
"The Origin of Chemical Elements"

He heard about Watson and Crick's paper on the structure of DNA shortly after it was published.

He understood that DNA specifies the sequence of monomers in proteins.

But there's a problem.

Remember, DNA is a polymer consisting of 4 kinds of monomers.

Proteins have 20 different monomers.

How could a sequence of four symbols be used to specify something with 20 different monomers?

Gamow devised a way.

Can you think of how to do it?

Easy.

The symbols are treated as letters. You then group the letters to form words.

That's how Morse code works.

www.learnmorsecode.com

A ·−	I ··	Q −−·−	Y −·−−	1 ·−−−−	
B −···	J ·−−−	R ·−·	Z −−··	2 ··−−−	
C −·−·	K −·−	S ···	Period ·−·−·−	3 ···−−	
D −··	L ·−··	T −	Comma −−··−−	4 ····−	
E ·	M −−	U ··−	? ··−−··	5 ·····	
F ··−·	N −·	V ···−	/ −··−·	6 −····	
G −−·	O −−−	W ·−−	@ ·−−·−·	7 −−···	
H ····	P ·−−·	X −··−		8 −−−··	
				9 −−−−·	
				0 −−−−−	

Gamow came up with a scheme whereby the four bases in DNA could be used directly to specify the 20 amino acids in proteins.

It was completely wrong.

Nevertheless, Gamow tried to publish his idea. He was recently elected a member of the National Academy of Sciences (formed in 1863 by President Lincoln to "investigate, examine, experiment, and report upon any subject of science").

National Academy of Sciences building, located in Washington, D.C., on Constitution Avenue along the National Mall, just across from the Vietnam and Lincoln memorials; photograph by JD Talasek/National Academy of Sciences. Additional Information

As a member, his submissions did not have to be peer reviewed. He sent in a manuscript.

He shortly thereafter got a call requesting him to retract the paper.

The biologists were upset by it.

He asked that the manuscript be returned. He put it, without making any changes, into another envelope and sent it to the Danish Academy of Sciences, where he was also a member.

Then he sent reprints of the paper to every biologist at the US National Academy of Sciences.

He published another version of his paper in the journal "Nature".

It had a great impact.

Gamow was wrong.

But he had posed the problem correctly.

The DNA sequence somehow dictates the sequence of the monomers in proteins.

How?

The theoreticians had had their day.

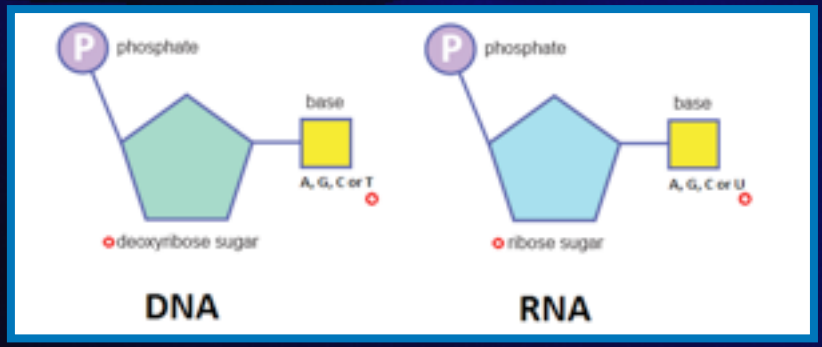
Now the experimentalists began producing data.

RNA was brought into the picture.

It turns out that DNA doesn't act directly to synthesize proteins.

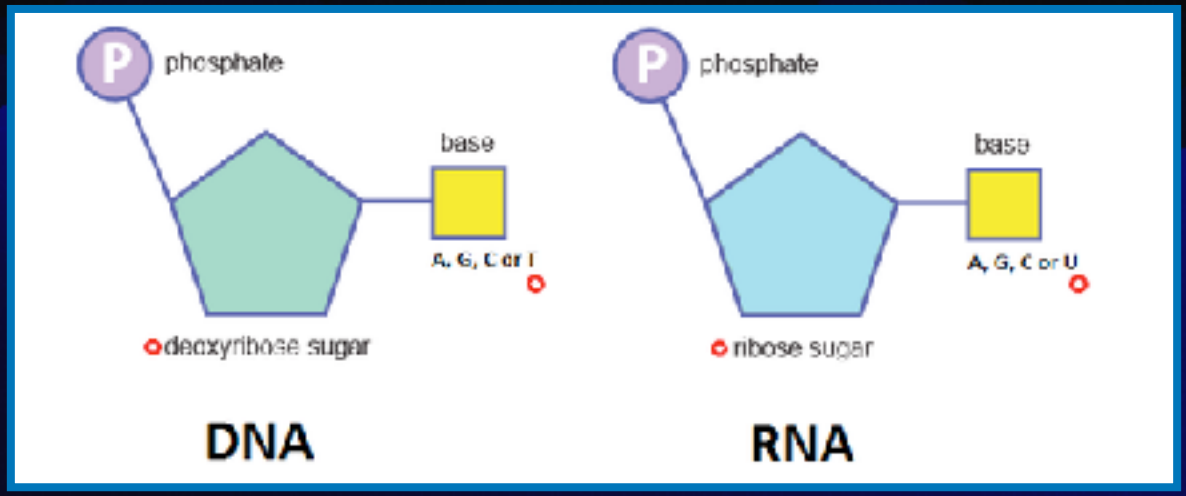
What's RNA?

RNA is a polymer that closely resembles DNA.



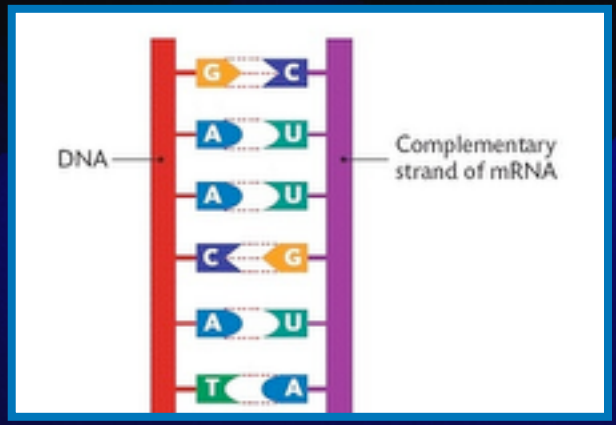
The monomers of DNA and RNA

It bears a slightly different sugar and the base U substitutes for T.



RNA's often are single stranded.

A chain of RNA can be complementary to one of the two chains of DNA.



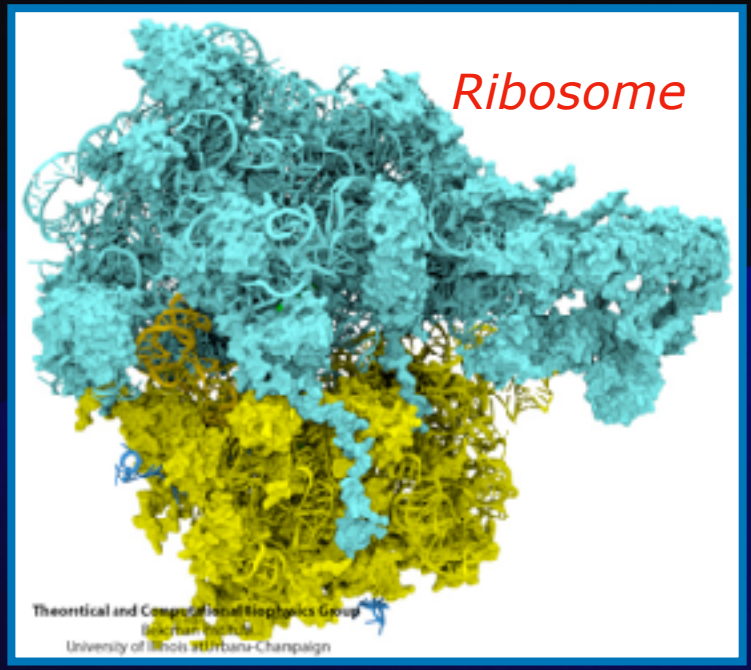
It was thought that stretches of DNA are copied into a single stranded complementary strand of RNA.

*These sequences of DNA that do this are called '*genes*'.*

RNA copies leave the DNA and travel to a master machine in the cell where they can be used to dictate the sequence of a protein.

These master machines are called

"ribosomes"



Ribosomes are complex generic protein building machines. Their specificity comes from RNA copies of a gene: mRNA

(messenger RNA).

mRNA's move away from their complementary DNA, attach to ribosomes, and specify specific proteins.

But how?

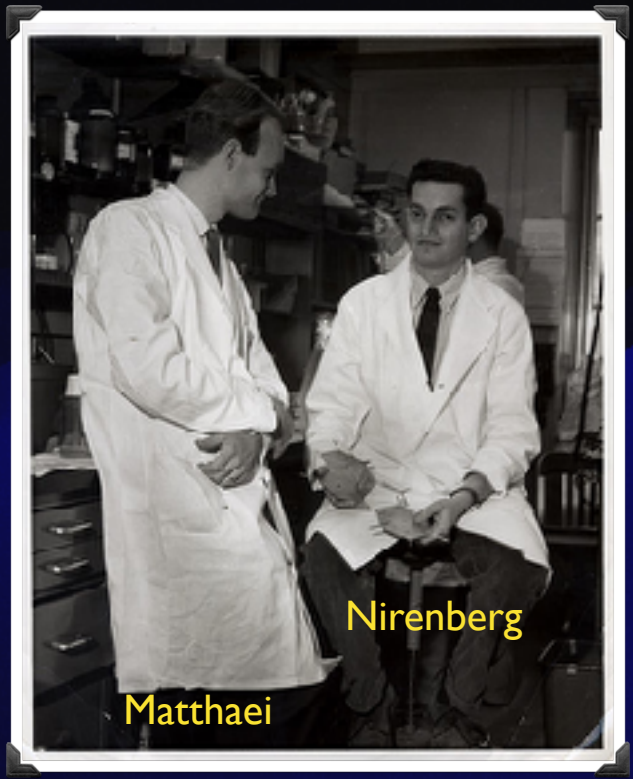
How are the four nucleotides of RNA translated into the 20 amino acids of proteins?

Which groups of nucleotides specify which amino acids?

Which word defines which amino acid?

The answer to this question came from an unexpected source.

Marshall Nirenberg and his associate, Heinrich Matthaei.



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Nirenberg was born in Brooklyn, NY (1927). He moved to Florida when he was 8 because his mother thought it would help his health.

He showed an early interest in nature.

He attended the University of Florida, then the University of Michigan. He earned a PhD.

He then took a job at the NIH, first as a postdoctoral fellow, and then as a junior staff member.

He was trained as a biochemist.

Biochemists take things apart in order to understand how they work.

His strategy was to try to make proteins in a test tube outside of living cells.

Once he succeeded he could manipulate the individual parts to find out what each component did.

Nirenberg and his wife (Perola) in 1968

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So he and his associate, Heinrich Matthaei, ground up some bacteria, and purified and parts involved in the synthesis of proteins.

mRNA, ribosomes, and other stuff

Nirenberg and Matthaei

If they knew the sequence of an added mRNA and the sequence of the protein that it specified, they could work out what nucleotides in the RNA specified which amino acids.

Nirenberg (1970)

Like this:

acggcugacgugcag… ← *RNA*

ala trp cys leu … ← *Protein*

Nirenberg (1970)

You need to know the sequence of both the RNA and the protein

Genes come in pairs

If you know the text and it meaning in another language, you can figure out what the symbols mean.

But they couldn't do that.

Unfortunately, no one had succeeded in purifying a specific mRNA at the time.

Nirenberg and Matthaei

So they decided to try the simplest RNA that they could think of. It was artificial. It consisted only of U's.

It was called "poly U".

Lo and behold, when poly U was added to his concoction, it directed the synthesis of a protein.

What protein did it make?

polyphenylalanine

That is, the synthetic RNA consisting of only U's directed the synthesis of a protein carrying a single amino acid

polyphenylalanine

They reasoned that a group of three U's specified the amino acid phenylalanine.

For a brief moment in 1961, Nirenberg and Matthaei were the only ones in the Universe who knew one of the "words" in the genetic dictionary.

UUU meant phenylalanine

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Now to announce it to the world.

But Nirenberg was unknown. He had been turned down in an effort to attend an important meeting at Cold Spring Harbor in NY.

Cold Spring Harbor Laboratory

But he was going to attend the International Congress of Biochemistry in Moscow in August.

He would announce his great discovery there.

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The International Congress had thousands of attendees and many speakers.

Speakers of lesser note were assigned 15 minutes in breakout sessions.

Nirenberg spoke to a virtually empty room.

His announcement was greeted with brief and polite applause.

No one seemed to recognize the importance of what he had said.

However, there was one person in attendance who understood the significance of Nirenberg's findings:

Matthew Meselson

Matthew Meselson

(1930 -)

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Meselson, a member of the inner circle, spoke to Crick of the talk he had just heard.

Crick talked with Nirenberg.

Soon Nirenberg was put on the agenda to speak to the entire conference.

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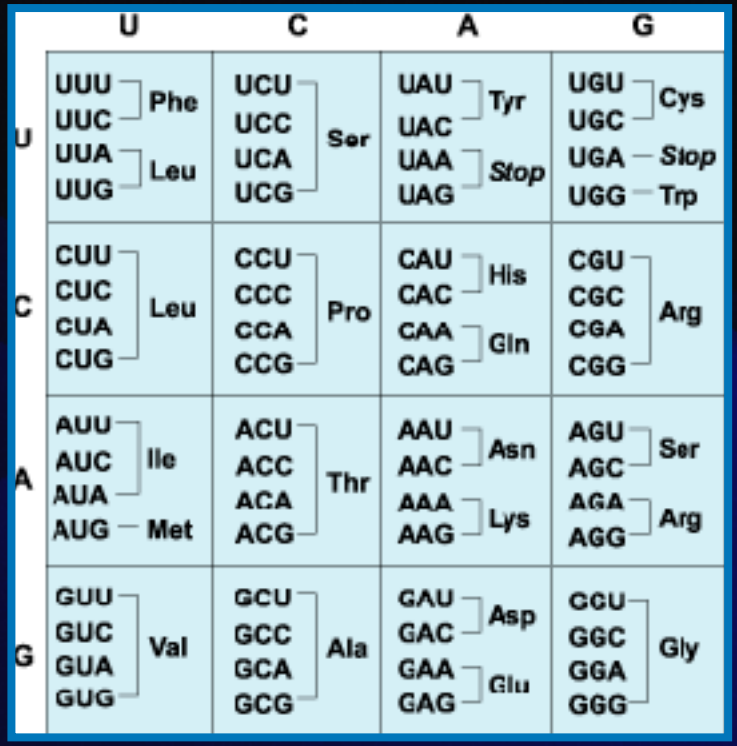
Nirenberg's announcement electrified the conference:

The first code word had been discovered.

Soon Matthaei phoned to announce that he had found a second code word.

In relatively short order, over a number of years, the entire genetic code was worked out.



	U	C	A	G
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC UAA Stop UAG	UGU Cys UGC UGA Stop UGG Trp
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg
A	AUU AUC AUA Ile AUG Met	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG
G	GUU GUC GUA Val GUG	GCU GCC GCA Ala GCG	GAU Asp GAC GAA Glu GAG	GGU GGC GGA Gly GGG

Nirenberg (but not Matthaei) shared the Nobel Prize in Physiology or Medicine in 1968.

	U	C	A	G
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC UAA Stop UAG	UGU Cys UGC UGA Stop UGG Trp
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg
A	AUU AUC AUA Ile AUG Met	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG
G	GUU GUC GUA GUG Val	GCU GCC GCA GCG Ala	GAU Asp GAC GAA Glu GAG	GGU GGC GGA GGG Gly

The code is used, with a few exceptions, by all living organisms on earth.

	U	C	A	G
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC UAA Stop UAG	UGU Cys UGC UGA Stop UGG Trp
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg
A	AUU AUC AUA Ile AUG Met	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG
G	GUU GUC GUA GUG Val	GCU GCC GCA GCG Ala	GAU Asp GAC GAA Glu GAG	GGU GGC GGA GGG Gly

Nirenberg remained at the NIH for the remainder of his scientific career.

He abandoned investigating the code, and turned toward trying to understand the brain.

OK.

A grand summary

Genes come in pairs and are made of DNA.

They're passed on from one generation to another

The DNA sequence of a gene is copied into an intermediate molecule called RNA.

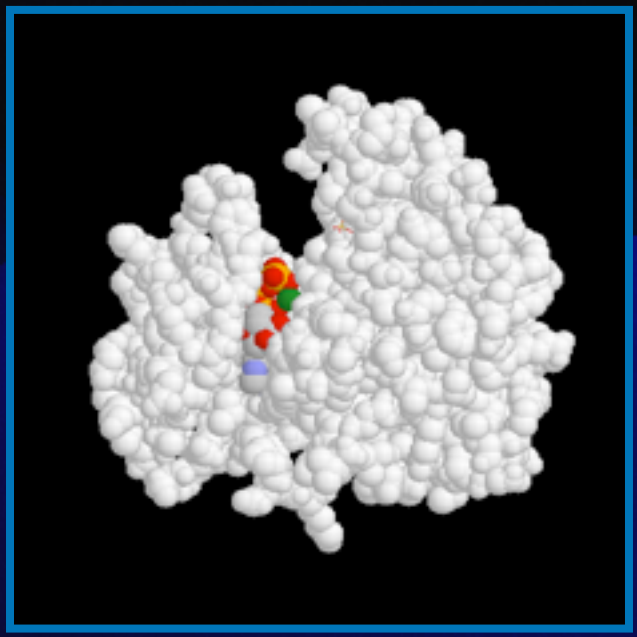
TACGTGGAAAGTGCA
AUGCACCUUUCACGU

This RNA sequence is, in turn, translated into a protein sequence using a device called a ribosome.

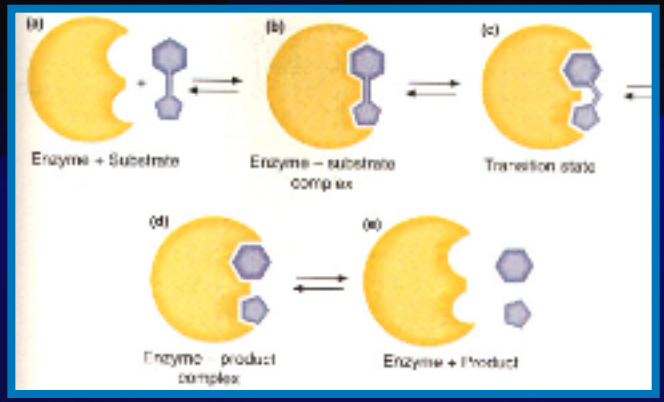
M H L S T

The RNA from each gene is translated into an individual protein with a specific sequence

The sequence of monomers in a protein determines its structure and thereby its function.



Proteins do the great bulk of the work in the cell. They act as tiny chemical and physical machines.



The secret of life is to make the right proteins, in the correct amounts, at the appropriate times and places.

That process is directed by instruction carried by DNA.

That's it.

That's the way life works.

Any questions?