So in the last lecture I spent quite a while trying to convey a sense of how the structure of DNA was discovered. The crystallographic data that led to it, as I said, was collected by Roslyn Franklin. And I saw there was some confusion about this picture that I showed you next. This is not a photograph of a double helix. This is what happened when she bounced the x-ray off the crystal of DNA. This is the diffraction pattern that she saw. And then one works backwards from that trying to figure out what kind of structure it was that would have caused that diffraction pattern. And you have to be a pretty good x-ray crystallographer to draw any kind of inferences from that.

And there people, including Francis Crick, who saw the implications of it right away. But the point was she collected the data and then two people that I told you about then whose name you know so well, Jim Watson and Francis Crick, were the two individuals that came up with the model that explained the diffraction pattern.

And therefore we learned the structure of DNA as a double-stranded helix. I also tried to make the case that it wasn't two geniuses who sat down in the room, took a look at this and popped up with the model. It was a story of real people with misadventures and mistakes and recovery from mistakes and so on getting it. It was also a very small group. And I'm going to take just a very small minute at the beginning of the class because I have a colleague, Vernon Ingram who's sitting down here in the front, who was a member of this very small group with Jim Watson and Francis Crick. So here was there where all this happened. And almost nobody in the world has had a chance in your generation to hear directly from somebody who was there when it happened. So asked Vernon if he would come and just talk to you for a little bit just what it was like to be there.

Well, thanks, Graham. You seem to be at a very exciting state in 7.014. This structure of the secret of life, no less. And it's interesting that immediately when Watson and Crick put together a model of the DNA molecule that fit the x-ray data, that was the point, how do you know a model is correct?

Because there are certain distances in the model, and those have to correlate exactly with the distances of the x-ray spots in the diffraction pattern that you saw. That's how you know that a model that you've built to certain specifications corresponds to what the molecule of itself in the crystal that you're examining actually is composed of. It was by sheer accident that I happened to be working as a biochemist in the MRC, The Medical Research Council lab at the Cavendish Laboratory where Watson and Crick were working. Sheer accident. It was a very crowded lab, as Graham said. And that's something that you should remember. When you're choosing a lab to work in, always go to a lab that's overcrowded. Never go to a lab where there's lots of space because a really successful lab attracts so many coworkers, visitors that it rapidly gets overcrowded. And that was the case in this laboratory. The director was Max Perutz. Co-director John Kendrew doing x-ray crystallography of proteins for almost the first time, and solving the protein structure. Francis Crick was a graduate student of Max Perutz's doing his PhD work. And the first thing I remember about Francis was when I went there as a biochemist to work with Max Perutz, when I went there, there was this tall gangling guy constantly circulating between the top floor of the building, his office in the middle and the x-ray machines at the bottom. He was constantly going up and down. And

in those days the buildings didn't have an elevators or lifts as the English called them.

So he was in excellent physical shape. Very crowded, a very modest lab. And what's usually forgotten is a key member of that group, an engineer, Tony Broad, key person because he invented what was then the world's best and most efficient x-ray machine, a rotating anode x-ray machine.

And because to the x-ray crystallographers in that group this machine was available, because of that they were the preeminent x-ray structure group in the world. My job was as a biochemist protein biochemistry putting a heavy atom, mercury, very heavy atom into Max Parutz's hemoglobin crystals in specific places. That has a predictable effect on the x-ray pattern and that enables the Fourier diagram to be constructed with real phase values for the x-ray diffractions, for the physicists among you here. Are there any physicists here?

Yeah, I thought so. That was a big step forward and that was also a big step in figuring out the structure of the DNA samples semi-crystals that Professor Walker just referred to.

All dependent on the engineer Tony Broad who is never mentioned in any of these histories, but without him this would not have happened. So it was an exciting place to work in, very exciting. We were all young in those days. And living the lives of young men and young women with all the complications that arise when you put a whole bunch of very energetic young men, very energetic young women together. And by that I mean the interpersonal relationships which when you're in a crowded, very active situation can sometimes interfere. And always very entertaining, I can tell you that. I could give you chapter and verse.

But it isn't really so very different from people your age now, right? I mean I'm not saying it interferes with you, sometimes it might. But it was an exciting lab, an exciting time to be there because we were not the only group trying to figure out the structure of DNA. A huge competitor was Linus Pauling at Caltech who had beaten that same group once before, quite recently, over the alpha helix, the crucial component of protein structure. He got the right answer first, 1.5 angstrom reflection, the alpha helix. And our group, Max Parutz and our group had been wrong. So the group was smarting under that kind of defeat, if you like.

And competition is a wonderful spur, as long as you don't let it get out of hand. Well, needless to say we didn't, but the competition with the Pauling lab was certainly so severe that we awaited the next letter. You see, in those days new scientific information arrived not by publications, that too much too long, but by personal letter. And, in fact, the NIH has put together all these various letters in the Francis Crick collection. And when you have time you should look at those. They're quite interesting because they tell you in a way a scientific paper does not tell you.

What I feel about my experiment results. What she feels about her experiment results. What it means to me as a person, to her as a person, to him as a person. So we were constantly watching the mail and discussing the news

as it came in, mostly over a beer at the pub next door. It was very conveniently located. But being a small group crowded together made communication within our group very easy indeed.

And we had fights. I don't mean physical fights.

We had scientific fights. And as a biochemist I was able to settle a crucial fight among the crystallographers Crick and Watson who were building the model. Because, quite frankly, they didn't know much chemistry. And were trying to build a model with the wrong confirmation of the peptide bond. They didn't realize that the peptide bond has two possible confirmations.

And they had at one point a terrible time trying to fit everything together because they were using the wrong confirmation.

I'm talking about lactam-lactim for those of you who are organic chemists and it means something, a confirmation. And once they got the first confirmation then the model clicked into place.

So we all helped, that's what I'm trying to say.

We all helped with one great aim in mind. It was clear.

And you know from what Professor Walker said, that the DNA structure, in its structure held the clue to crucial physiological behavior of DNA. And Crick and Watson said this in their first paper, the structure itself because of its complimentarity gives you an immediate clue as to how it replicates. And replication of DNA structure from generation to generation is, of course, the crucial thing about DNA. The copying, the precise copying from generation to generation. And that fell out the of x-ray structure. That's why the x-ray structure was so very important, because it gave you an immediate understanding of the role of DNA in modern biology. So that's what we did.

And eventually the people in the group, the group got so overcrowded they built a huge lab that was beautiful, like any new lab is.

But the thing I remember most of all was the atmosphere in that place.

So remember, when you go and choose a lab, choose one that's overcrowded.

It will pay off. [APPLAUSE] Thank you so much. That was really wonderful.

Thank you.

I don't know if some of you realized quite how rare that was, this discovery of the structure of DNA. As I said,

probably one of the big discoveries of mankind. Because, as Vernon said, you could see so many of the secrets of life as soon as you saw that structure. Very few people have ever heard from someone who was there at the time. Maybe you'll forget a bunch of stuff down the line, but I hope you'll remember you heard somebody who was there when Wesson and Crick were there and maybe his extra piece of advice about choosing a lab.

To say one thing quickly, some of you I think understood what I've been trying to do. I spent quite a bit of time talking about science being done by real people doing real experiments.

Thanks for your comments. A few of you have gone out of your way to say that this was a total waste of time and you didn't understand why I didn't teach you something instead of doing something on the test.

Well, I'm making up the test. And if you don't think there'll be something on scientific process on the second exam you'll be surprised. So I'm spending a lot of time on this, and the reason is because you are MIT student.

You know, you can go many places in the country to many high school biology courses and you can memorize, someone will tell you to memorize everything that's in the book, and you'll get tested whether you can memorize it. You guys are at MIT because you have the potential to be leaders in whatever you do.

I've made the transition from being an undergrad sort of trying to memorize stuff in a textbook to working on a cutting-edge.

I've made some reasonably significant discoveries in science, as have my other colleagues in the department, some of them making greater than I. But nevertheless if you're on the cutting-edge then you're dealing with all the stuff I'm trying to tell you about in this thing. You're working as a part of a group.

There's competition. There are interpersonal relationships. You make mistakes.

You recover from them. You're making inferences.

You're testing models. This is a very complex, very real, very dynamic, very human interaction. I hope you got a little bit of whiff of that from Vernon. And I wouldn't be, I'm quite capable of reproducing diagrams from the textbook without trying to give you a deeper understanding, and that's what I'm trying to do here. And I hope if it hasn't made sense to you by the end that at least a few more of you will get it.

And those of you who I think saw what I was doing I appreciate your telling me that in the things. These are anonymous so I don't know, but a couple of you are certainly trying to make it clear that you didn't think it was worth your time coming to lecture.

I'm trying to tell you why I'm trying to do it.

I'm trying to teach you in a deeper way. And this is a required course.

It's important for your life. I hope some of you will see that or if you don't see it now you'll see it later in your career.

OK. Now, we're going to talk about DNA replication.

I'm going to start to drive into some of the details that maybe are more the kind of things you're expecting. I just want to make one quick point here. I've talked about cell division and we saw this, how cells come from other cells going to make more cells.

I showed you this little movie you've seen a few times of a yeast cell dividing, but all cells divide.

Here's a cancer cell dividing. If you get a cancer it's a cell that's forgotten how to stop dividing and is growing to make a tumor. There's this cancer cell dividing. It looks not unlike a yeast on a molecular level, very, very similar. But there's another point. I told you how the structure of DNA with the complimentary strands with G pairing with C and A pairing with T immediately gave rise to an insight as to how the genetic material could be replicated. And you guys know that it's held together by hydrogen bonds between base pairs which are about one-twentieth the strength of the covalent bonds.

So you're able to peel the strands apart without breaking the covalent bonds. And then by pairing A with T and G with C and doing that on both strands then you can end up with two identical copies.

And so if you do two identical copies and you do it again you get eight. One of the things we've realized over the last two or three years in looking through the exams is somehow, at least some of the class, didn't connect the business about cells coming from other cells and DNA duplicating to give daughter DNA. And I'm just trying to hammer home the point that these are related. Every time a cell divides it has to duplicate its genetic information.

That's why I'm going to be telling you about DNA replication.

Here's a picture of that same cancer cell, but watch over here.

This is the DNA. And you see it's doubled. And see how the DNA, which is the chromosomes, has pulled apart so that at the end you now have two cells and you've got identical copies of DNA.

So if you're studying cancer, for example, this sort of thing is relevant to you. OK. So the issue of how -- Well, before I do that, I'm sorry. Just a couple of things about DNA replication before I dive into this. So we all started out as a single cell. I've got a lot more obviously because I'm made up of a lot of cells. If I took all the DNA in my

body and I wind up all the molecules in it, do you guys have any idea how long that would be? Who thinks it would reach let's say across the room? OK. Across campus?

Across Cambridge? Around the world? To the moon? Anybody left?

To the sun? I've got ten to the fourteenth cells.

There's about a meter or two in each cell. 10 to 20 billion miles of DNA in each of our bodies, human DNA.

They would go back and forth to the sun multiple times.

So that much DNA had to get replicated in order for the fertilized egg we all started out as to become you.

Another thing, the accuracy of replication is about ten to the minus tenth. Most people, including myself, don't have a very good feel for exponents. So that's one mistake in 10 billion. You know, it could be one mistake in 10 to the ninety-ninth. Well, what is one mistake in 10 billion mean? So let's relate it to something we know.

If I was typing let's say an eight letter word, 60 words a minute, 24 hours a day, 7 days a week, and I was as good as DNA replication, how often would I make a mistake? So you can each think of how long you think that is. But if I was good on average, I would make a mistake once every 38 years.

So I'm about to tell you about a process that's absolutely astonishing in terms of how fast and how much you can do and with an accuracy that goes beyond what we're used to in our ordinary life.

So how does it do this? It has to be more than just pulling the strands apart. And there's been some confusion as to why I'm emphasizing 5 prime and 3 prime.

Well, each of these subunits, each nucleotide, this is a 3 prime hydroxyl and this is the 5 prime position. If we were joining together subunits that had a hook and an eye it would make a difference because it's not the same on both ends. If we're going to start hooking together it's exactly the same thing when we get to a biochemical level, the 5 prime end is not the same as hydroxyl at the 3 prime end because the whole thing is asymmetric.

So the enzymes that copy DNA are known as DNA polymerases.

And it was a very difficult challenge to figure out how they operated, but Arthur Kornberg was the first person to solve this problem. He was an extraordinarily gifted biochemist. He's still at Stanford. And what he found was if we have a 5 prime end this would then be the 3 prime end, and there's a 3 prime hydroxyl which is this one right here. And this was paired, say, with a C and A paired with a T. And let's say a G paired with a C here. And let's say the next template base was, let's make it a T. What Arthur Kornberg was able to find was an enzyme activity

that catalyzed a template-dependent replication of DNA. That was critical because he had to find, if you broke the cells open, somewhere in that gamish of enzymes and things from inside a cell. There had to be something that was able to copy DNA. So in order to do that he had to work out an assay. And he also had to have some kind of guess as to what the cell would be using in order to carry out the synthesis. But one thing that was sort of obvious was a DNA template because that was being copies. But the other part was you had to have energy to form a covalent bond.

So somehow there had to be something that was sort of activated with the energy built into the molecule so that thermodynamically the whole thing would slide downhill when you made a bond. And he knew that the cell had triphosphates, just the same type that we talked about when we talked about ATP.

So this would be a deoxyribonucleotide triphosphate.

And he was able to make a guess, because he had to try things until he found something that would work, that this was what's used in DNA synthesis. So this hydroxyl ultimately attacks this phosphate here. And these two other phosphates then come off as a leaving group. So if we thought of it as a pea like this with two more peas here, these two come off and you get a new bond formed to the phosphate. And so what Kornberg then was able to find by using a DNA template that had this sort of structure and [TTATA?] like this, that he was now able to get an A added here. This hydroxyl here became the new hydroxyl.

And so the direction of synthesis, this strand is the other way, so the direction of synthesis of a DNA polymerase, it's polymerizing in the 5 prime to two 3 prime direction. This was again an amazing discovery because it was the first time that anyone had found an enzyme that could copy DNA. Arthur Kornberg got a Nobel Prize for it. But at this point actually genetics came in because there was a scientist John Cairns who was at that point down at Cold Spring Harbor, as I told you the other day. And John, in spite of the fact that Arthur had found a DNA polymerase that had all the properties that you would expect for copying DNA, didn't think that was the one that actually copied the DNA necessary for cellular replication.

So he reasoned if he was right he'd be able to find a mutation that would eliminate the activity of that enzyme and the cell would still live.

And so they did a screening, and it was a lot of work, but they eventually found a mutant of E. coli that lacked this DNA polymerase that Arthur Kornberg had discovered. And the cell was still alive and was still replicating its DNA. So it told both John and then Arthur there must be another enzyme in the cell.

And so Arthur went back. And now working in a mutant that was missing this first polymerase he discovered he found the one that really replicates the DNA. The first one is important, too. It's needed for DNA repair. I'm going

to talk to you about that in next lecture, but it's not absolutely crucial for life. And there's an interplay of genetics and biochemistry.

And you'll see I'm just sort of foreshadowing what we're going to get to when we talk about the genetics of this.

And I know a couple of you clearly were frustrated about me showing you pictures of the people who did this, but nevertheless since this was such a historic event a couple of years ago at Cold Spring Harbor.

This you see the helix model down there. There was Jim Watson opening the symposium. When I got up to talk I said, well, I told my students that I'd let them know what it was like when I was there, so I took out a camera and I took a picture of the audience.

And so there are a bunch of Nobel Laureates and types here who were sitting there smiling for you guys in the class. And there was Arthur Kornberg giving his talk. Now, these DNA polymerases are incredible protein machines. The crystal structures of DNA polymerases operating their template have been solved.

And you can solve, depending on how many diffractions you can get, you can get a model that's more and more detailed.

And there have been very high resolution models of DNA polymerases.

This blue and white stuff is the surface of the protein, and this is sort of a template and the various parts.

Just to give you an idea here are these tracings of the shapes of the electron density. You can see how the crystallographers have fit the nucleotides right in the crystal into these electron densities. And here putting it together a bit in the blue is the secondary structure of the protein and the templates and whatnot. And I don't expect you to see very much in that, but the point is I wanted to sort of just set you up to show you this little movie. Because DNA polymerases are incredible machines. They copy at about a thousand nucleotides a second and their accuracy is really amazing.

And I'll tell you all the tricks to the accuracy in the next lecture, but I want to show you this little movie because this is sort of a simulation of what must happen every time a nucleotide is added.

Now, we'll see this over and over again so I'll take it in pieces.

The yellow and the orange are the secondary structures.

That's an alpha helix. And certainly one thing you can see is happening, as we're looking at this, is the parts of the protein are moving during this. So you can see this alpha helix that's sort of swinging up and swinging back down.

Now, what's over here is the template base.

That's the base that correspondents to the T that I was just showing you here. This is the incoming nucleotide.

There is the triphosphate coming down here. And, in fact, you just see those two phosphates going.

So what's happening here, this is going to be the end of the growing chain. It's going attack right there, join the phosphate and the pyrophosphate will leave.

And if you'll take a look, when you see this movement of this helix from the beginning state to up to here, you'll see what happens.

It's squeezing the template base and the incoming nucleotide together.

What it's really doing is testing for the correct shape.

Remember the shape of an A-T base pair and a G-C base pair is the same.

And if those of you who are confused about guanine and the keto-enol thing, try to draw hydrogen bonds with the enol form of guanine and see how you do. I think you'll begin to understand a bit. So at the heart of life is something that can copy DNA. And there are these exquisitely beautiful machines. The replica machine in E.

coli has 18 proteins and the ones in our bodies are even more sophisticated with even more parts. OK. But to replicate a DNA molecule there's another problem that comes up.

Because DNA polymerases copy -- -- and grow chains in a 5 prime to 3 prime direction.

And they need a 3 prime hydroxy terminus. So they won't work if you just gave it a single strand of DNA.

No DNA polymerase can handle that. It has to have something like this where there's a template strand -- -- and there's what's known as the primer strand.

So there has to be something that has the 3 prime hydroxyl and there has to be something that's going to provide the template that's going to be copied. So if we pull strands apart like this with 5 prime to 3 prime then they'll be 5 prime to 3 prime running in the opposite direction. If we have a template like this, this is OK because the strand here can be copied 5 prime to 3 prime.

This is the new strand being synthesized by the DNA polymerase.

But what about the other strand? The replication fork is moving in this direction, but if the -- So here is the 3 to 5

prime direction here. So if the DNA polymerase is going to be copying this strand it's going to be moving backwards to the direction of the replication fork. Now, I guess evolution and nature could have selected for two types of DNA polymerases, one that copies 5 prime to 3 prime and one that copies in the opposite direction. But it didn't. And there are a number of theoretical reasons that we could discuss in a more advanced course perhaps for why that is true. But, in fact, what it does is it uses the same polymerase. So as these things peel apart the polymerase works in the other direction, but there's another problem. If I just peel it apart like this there's no 3 prime hydroxyl. So it took people quite a few years to figure out the strategy that's used in nature. Nature has a special enzyme that makes a little piece of RNA. It's called an RNA primer. And what it does is it provides a 3 prime hydroxyl.

And once you have the 3 prime hydroxyl at the end of the little RNA chain then the DNA polymerase -- -- can be made 5 prime to 3 prime.

So as you peel open the replication fork then little pieces of RNA are used to make a new strand of DNA and it goes this way.

Now that obviously doesn't give you a new intact DNA strand.

And part of the clue to this working out what was going on at DNA This strand is pretty easy to do, but what the cells have to do now is replication was the recognition that newly synthesized DNA was made as they've got these little RNA primers. little pieces. And then later it got joined into

And then they remove the RNA by an longer pieces. And the person who discovered this was Okazaki. So these fragments of DNA that are synthesized initially are called Okazaki fragments, after the person who discovered this.

It was rather puzzling because when you tried to look at the synthesis of DNA you're looking at a long molecule, and you found some of the newly synthesized material was in short pieces. And as you watched over time it got longer. So the cell, I think you can sort of see from first principles what has to happen here then.

That in order to come and make -- enzyme that's capable of degrading the DNA or clipping it at the junction. And that then leaves the cell in this sort of situation where there are little tiny gaps in between these pieces of DNA. But at the end of each one of these is a 3 prime hydroxyl. So another polymerase or one or another polymerase in the cell can fill those little pieces of DNA out. And then there's one little nick that needs to be sealed. And so what you finally end up with is a 3 prime hydroxyl here, a 5 prime phosphate that's at the other end, and then these are joined together. This is one nucleotide here and the other here. These are then joined together to give the ordinary phosphodiester bond that links -- -- the two nucleotides together like that. And the enzyme that does that is an enzyme called DNA ligase.

You can almost think about it as DNA Scotch tape that will take a little nick in DNA, if we've got a phosphate and hydroxyl, and it will join them together.

So this process of replication, which can go at about a thousand nucleotides a second with this amazing degree of accuracy, uses two different DNA polymerases, both of which biochemically can only go in one direction. But you can see they have to be somehow oriented so that one of them is able to move in this direction and the other one is able to move in that direction.

The key part in this sort of the course is to try and understand this 5 to 3 prime and to get this basic idea that nature had to do something.

It was fairly easy to copy one strand because that was sort of the direction of the polymerase movement was the same as the replication for it movement, but the other strand had to have been much more a problem. And so when you get down to a biochemical level, though, it's very conceptually easy to say, oh, you've got complimentary strands so we just take it apart, we take the photograph and the negative and we make the opposite one and now we've got two copies. When you get down to the biochemical details there is this major biochemical issue of whether the polymerase can go in the 3 prime or the 5 prime direction.

And nature has chosen to do it all or has been selected to do it all somehow with a polymerase going in one direction.

There are many other aspects to DNA replication. And one of the tricks that I find most fascinating is that these polymerases, once they get on DNA they stay on. And that's part of the secret because it takes about a millisecond to add a nucleotide, but if it comes off the DNA it has to get back on. Then it takes about a minute. So the whole trick to being a very, very fast DNA polymerase is to somehow hang onto the DNA.

So what biochemists did was they purified the actual enzymatic activity that could carry out this process, and then they started to look for other protein factors that would help the process to work better. And they discovered something called a processivity factor which made the polymerase stay on the DNA.

And people wondered for a lot of years how that worked and why did this system work so well. And finally the crystal structure of the processivity factor was discovered. And if I go back to this sort of diagram where this is the piece of DNA that's copied, what it turned out was that the processivity factor is basically a doughnut that kind of gets clamped around the DNA like that.

So it's sort of like taking a washer with a place where you can pry it apart opening it up, putting it around the DNA like this.

And then the polymerase, more or less since this is topologically linked to the DNA, is like a washer sliding on a wire.

This DNA polymerase hangs onto that and it doesn't come off.

And I think there's a little picture of it.

Here's a little movie. There's the DNA going through and this is one of these clamps. It's virtually the same structure in a bacterium and inside of us. But, in fact, the amino acids are almost all different. But the underlying structure of the protein is almost identical. And there are special machines called clamp loaders that pry open this clamps, clamp them around DNA, and that's part of the secret to how these polymerases are able to polymerize DNA so fast. There are a lot of other pieces of this machinery. If you go on you'll hear more about them. I just want to give you one of the most recent insights.

I mean this, as you might guess, since DNA replication is at the heart of life it's been studied very, very hard, ever since the discovery of DNA helix. My colleague, Alan Grossman, made quite a discovery just probably three or four years ago.

He took that green fluorescent protein that we've seen a few times, and he actually joined the gene encoding green fluorescent protein to the backend of a piece of the DNA polymerase.

So wherever the DNA polymerase went now there was a little fluorescent molecule. And he looked to see where it was in the cell.

And I, like many other people, had for years taught, and this is why, you know, I have respect for the fact that I'm just teaching you the current model. For much of my career I taught, so DNA polymerase is sort of like a train going down the tracks a thousand molecules per second. And we're doing all this stuff with the leading and with the two strands. So let me just put those words up while I'm up there. This one is called, this strand that's easy to replicate is called the leading strand.

And this one where you have to do the primer and whatnot is called the lagging strand. In any case, what I had taught was that polymerase was like a train running on tracks.

You could calculate how fast it would move. What Alan, to his amazing I imagine, found was when he looked to see where the DNA polymerase was, it wasn't spread out all over the cell as if you thought it was a thing running on tracks.

In fact, it was in the center of the cell. And then late in cell division it split into two spots that went to the midpoints

of what would be the daughter cells. And so what he ended up realizing from that was that instead it was more as if the polymerase was a factory and it pulled the DNA through it rather than it traveling down the tracks of the DNA. And that was a very surprising discovery that went against all the dogma and all the pictures in the textbook. And it was a discovery at MIT.

That was published in, I think it was 2001, something like that, a very recent discovery. Things keep changing. That's again why I keep emphasizing I cannot teach you a fact in biology.

I can teach you the best understanding we have that explains the experiments to date. But somebody may make a discovery tomorrow. That means we'll have to change our understanding.

OK? So good luck on the exam. I'll see you on Monday, OK?