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7.014 Introductory Biology, Spring 2005
Transcript – Lecture 8

Let's get started. So I'm going to finish up energy today. And then we're going to begin sort of section more or less we'll call it molecular biology but it's sort of dealing with the issues that revolve around the discovery that DNA was the genetic material and then working through how people understood how information got from the DNA into everything else, how things were regulated. There are an incredibly large number of important discoveries that form the foundation of how we think about biology that are going to come out in this next section, but before I do that I just want to finish up this section that I talked to you about, about energy.

And I hope as we go along here you're going to see how some of these sort of disparate parts of the course begin to come together. Almost everything we're going to be talking about now is going to be needing energy such as replicating DNA or making proteins and all sorts of things. And those are driven ultimately by ATP. And what I've been trying to talk to about for the last lecture or two is how the cell gets the ATP, the energy money that it needs to make things.

We talked through glycolysis, this ancient, ancient way of getting a couple of ATPs out of a molecule of sugar so well-imbedded in our genetic makeup it's in almost all organisms. And then I talked last lecture about this other principle which must have come up very, very early in evolution. Again, it's used by all organisms. And that's the principle of capturing the energy that's inherent in a proton gradient across a membrane.

And I talked to you then about the idea then the way it worked was that the cell would have something in its membrane that would be a proton pump and it would pump the proton from one side of the membrane to the other. So it's working against the gradient. So it's doing energy. So there are a couple of different ways energy needs to be provided. It could be provided by some kind of light energy, and that's what drives photosynthesis.

I'll say a few words about that. Or in the case of respiration with the oxidative phosphorylation, I showed you how it was the electrons sort of descend in stepwise fashion down from one state to another. There's energy given off, free energy is available, and that can be used to power the pump. And once the proton gradient is made then the cells can turn it around and use the energy that's in that proton gradient to make ATP.

So in respiration remember the trick was then to take those two pyruvates, burn them all the way down to carbon dioxide and water, make as many ATPs and NADHs as you could, then take the NADHs, use them to make a proton gradient and eventually, if you will, convert everything into ATP so you've got it as energy. Our cells do it. That part, respiration and the oxidative phosphorylation is done in mitochondria, which I said sort of came from bacteria that were captured at some point.

Here's a picture of a mitochondrion. It still looks more or less like a bacterium. And I showed you the little parts that are in there. It was funny. Right after lecture I went back to my lab. I picked up a recent issue of Science. And I opened up to a page that said something about rats that had been bred to be very poor at aerobic exercise.

And it went on to talk about the health problems they had. And there was a sentence in there that they think the underlying cause is by breeding these rats and selection for rats that are poor at doing aerobic exercise. What they think it all stems from is having very inefficient mitochondria that don't work nearly as well. And that would make a lot of sense. I was going to scan that article but we had some technical issues this morning.

Maybe I can show it to you next lecture. OK. So the one last thing then that I want to do is I want to say a few words about photosynthesis because that actually preceded respiration. Respiration couldn't evolve until there was oxygen in the atmosphere. So probably the first use or certainly one of the first uses of the proton gradient happened in this scale of evolution and put here somewhere maybe 3.

4 billion years ago or so when what I had called photosynthesis -- -- release I on day one in the sort of trivial fashion. This is known as cyclic -- -- photo phosphorylation. And the principle is relatively simple. It's to capture the energy in sunlight -- -- to make a proton gradient. And that then can be used, as you now know, to make ATP. So in order to capture energy from sunlight nature had to evolve molecules that are able to absorb in the appropriate wavelength range.

You know the names of those molecules. Chlorophyll come in two principle species. You don't have to remember the structure. What you can see is a lot of conjugated double-bonds. That's how you sort of tune the absorption of a molecule. If you want to make it absorb a longer and longer wavelength you start hooking together double bonds. And you can set it up sort of you can get a molecule to absorb at just about any maximum absorption, any wavelength you want.

So chlorophyll is able to absorb this energy. And the principle of this is what happens. You have this chlorophyll and it absorbs a photon. And an electron gets excited so it basically moves to another orbital. It's farther away from the nucleus. It's easier now for that electron to get lost than it was before. Now, if nothing was happening that electron would eventually just fall down to its ground state and you'd lose all the energy as heat.

So what happens in photosynthesis, though, is that the electron falls back down to the ground state again in a series of steps. And how this happens, electrons are basically getting passed from one carrier to another. And the same principle as we saw in respiration applies in that at each phase in here a proton is pumped. Now, the out and the in are reversed from what it says in respiration.

You have notes on respiration, or should anyway. But the in and the out, as you'll see, it's sort of an arbitrary. You sort of take a frame of reference and then something's in and something's out. The point is that in both of them protons go from one side of the membrane to the other and you get more on one side, you pump them in one direction and they flow back in the other.

And the in and the out is sort of an arbitrary way of describing what's happening, but in both cases the key thing is that you're pumping electrons out. And then these can

be used to make ATP, as we talked about with ATP synthesis. In this case the electrons eventually end up back on the chlorophyll. And so that's why it's called cyclic phosphorylation.

What you get out of this, as you can see, is ATP. So this was probably a really big deal in evolution because the current thinking is perhaps there was an RNA world that's still sort of being debated. At some point it's clear that somewhere around 3.8 billion years or so something that looks sort of like a present-day bacterium arose, probably ate molecules that had already been made in the sort of primordial soup, but when those started to run out then it needed other ways of making energy.

It needed other ways of making carbon. Here's a way of getting energy, but what's available to make more organic molecules is only carbon dioxide. And if you remember that little thing I showed you of if we're going from a methyl to a hydroxyl to an aldehyde to an acid -- -- to CO2, that direction is oxidation and that direction is reduction. So if we go in that direction and we end up generating NADH because we're taking electrons and giving them to something else, if we want to go the other way if we're starting with C02 what we need to do is we need to have a supply of reducing power so we can take the C02 and get it down to all the less-oxidized states that are necessary for building all the molecules that we've been talking about.

So making ATP was a great idea, but the cell still needed to have some form of reducing agent. And what they used was they used hydrogen sulfide. This is at least one of the major ways that it was done. And so there is a very slight twist here. This is NADP. It's the same molecule as NAD except there's an extra phosphorylation. And the one with the phosphate on it tends to be used in biosynthetic reactions, but otherwise it's exactly the same thing.

It's an electron banking thing. And what this gave was NADPH plus sulfur plus a hydrogen. So sulfur is a waste product. Here's the reducing power. Here's the ATP. That's what those organisms need to be able to synthesize new organic material without having to have pre-made molecules. A really big deal in evolution. And the idea for making ATP is based on this use of establishing a proton gradient, the same principle we've seen again.

Now, there's another possible source of reducing power, and that would be to use water as the source of the reducing power. But in order to do that you've got to put more energy into it. And this system wasn't able to handle it. But that happened soon enough with the development of what I called on the first day photosynthesis release II, which is technically known as noncyclic photophosphorylation.

Again, it uses the energy of sunlight. But the twist this time, it not only makes ATP, it also makes NADPH, it makes reducing power at the same time. So you can see that is a really major advance. If you can use sunlight to make both of them now you're really efficient. So this is how this one works. It's related to the other one. And the first part is more or less the same idea.

A photon is absorbed by a molecule of chlorophyll. It kicks the chlorophyll up to an activated state where the electrons are at a higher orbital far away. It wants to come back down. Energy is going to be released. So electrons gets passed, protons get pumped from one side of a membrane to another. Except this time, instead of coming back this lands in a different chlorophyll that has just recently lost a pair of electrons.

But there's a new energy input here that kicks this chlorophyll up to an even higher energy state than this one. And as these electrons start to come down the energy hill there's enough energy here to take a molecule of NADP+ plus a hydrogen ion and give NADPH. There's one thing that this isn't going to work like a cycle or a machine yet. Anybody see what hasn't been taken care of yet? Say again.

Send the electrons back to this chlorophyll, exactly. However, the way the energetics are structured now the cells were able to take reducing power from here and generate 2H+ plus a half of an oxygen molecule. And this would really be two waters giving four hydrogens and one oxygen molecule. So what you can see here now, there are a couple of really important things about this.

It needs more energy. It makes ATP and NADPH which leaves the cell able to carry out biosynthesis. And the third thing, which is an incredible influence on our planet, it started to generate oxygen as a waste product. And it's really a mixed blessing. I mean oxygen is very reactive. It damages our DNA. It damages our proteins. We have an amazing number of defenses against oxygen. But, on the other hand, as it accumulated in the atmosphere and organisms slowly over evolutionary time learned to deal with it, it then set us up for the possibility of respiration which, as you can see, is 18 times more efficient than in that ancient way of using glycolysis to make energy out of sugars.

So that's more or less the story. This part is called photosystem II. This assembly of stuff is photosystem I. And I just wanted to show you this next slide because chlorophyll isn't just floating around like this. As you might guess, it's bound into proteins and things. And someone has figured out the structure of photosystem I. It consists of 12 proteins, 96 chlorophylls and about 30 other molecules.

And what it really does is it functions as an antenna. Some of the other molecules can absorb it at wavelengths that are different from chlorophyll. And all the energy gets funneled into the chlorophyll and into this process. And you'll probably recognize by now that proteins here we're seeing alpha helices and beta sheets in here as part of this structure. So the first organisms that learned how to do this were organisms we now know as cyanobacteria.

They're a kind of bacteria that has two membranes like E. coli and like the other ones that we've talked about. You're familiar with these. There's the green scum you see on ponds. Here's a close-up. Sometimes they grow as filaments, the cells in a chain. You notice they're green. They're making chlorophyll. And what happened in plants was that apparently something probably related to the present-day cyanobacteria got trapped inside some early progenitor of what we now know as plants and green algae.

And this trapped bacterium became a chloroplast. And it had all the machinery necessary to carry out this noncyclic photophosphorylation. The structure of these things, there's an outer membrane. Just similar to what I told you for the mitochondria. There's an inner membrane. And what's special about the mitochondrion then, there's another membrane inside that's known as the thylocoid.

And that's where all the chlorophyll is. And the reason the out and the in is a little bit confusing in here is this part, which is probably the cytoplasm of the old bacterium, is pumped from what's known as the stroma of a chloroplast which is equivalent to

the cytoplasm of the original bacteria into the lumen. So the chlorophyll that's in this membrane absorbs the light, pumps protons into the lumen building up a proton gradient, and then they flow back out in the other direction and make ATP.

Here's a picture of a chloroplast once again. It looks an awful lot like the bacterium still that got captured. All this stuff on the inside, those are the thylocoid membranes that carry out this specialized stuff. So there you have it. That's how cells, the major ways that life has figured out how to make energy. When Penny Chisholm starts to talk to you she'll talk to you about how organisms adapt to various niches, things that live in the bottom of the ocean, things that live in various places.

They all have to make energy. Well, they all use some variation on these principles I've talked to you about. And she'll then show you how they're very clever at extracting energy out of all sorts of things by applying these principles in different ways. OK. So what we're going to start doing now is we're going to start talking about DNA. This is certainly a molecule that's fascinated me all my life. You should know from the first part that it's built up of units known as nucleotides that have a sugar.

It's a ribose sugar that's missing one hydroxyl so it's a deoxyribose. The sugars are numbered 1, 2, 3, 4, 5. I showed you that. There'll be a phosphate. And then one of these nucleic acid bases, either a pyrimidine or a purine. And in DNA you find the pyrimidine bases are cytosine and thymine. And in DNA the purine bases are adenine and guanine. And then these subunits are polymerized together.

In essence, splitting out water to give you a polymer. And I didn't emphasize this too strong the first time I showed it to you. It's going to become a very big deal over the next few lectures as we begin to consider how nature had to figure out how to replicate DNA and all sorts of implications to go along with this, but there's a polarity to a strand of DNA. This is what's called the 5 prime sugar.

The primes indicate the numbers referring to the sugar, and the ones without primes are referring to numbers of atoms that make up part of the nucleic acid base. So if we're looking at a chain, this is a 5 prime carbon of the sugar, that's the 3 prime. And so what you can see, this bond which is really a phosphodiester bond, the phosphate group has formed an ester with this hydroxyl and with the hydroxyl that used to be here.

So it's a phosphodiester bond and it's a 5 prime, 3 prime bond. It joins the 5 prime carbon to the 3 prime carbon up here. So that means if you're looking at a chain of DNA, if you come down this way you're coming in the 5 to 3 prime direction. If we come up the other way we're coming from the 3 prime end heading towards the 5 prime end.

So you'll see me saying 5 prime, 3 prime. Now, as I told you, the principle force that holds the strands of the DNA together are hydrogen bonds, three of them between a G and a C and two of them between an A and a T. And then they are a pair of strands. And they're actually running in opposite polarities. This is something to contend with when we think about replication. 5 prime to 3 prime in one direction and 5 prime to 3 prime going in the opposite way here.

And then, as you all know, it's called the double helix. So it's actually not flat like this in space. It's in a 3-dimensional twisted into a double helix and the base pairs are

held together by hydrogen bonds between the bases on the opposite strands down the middle of the molecule. And I like this little movie I showed you because you can see it pretty well. The nitrogens are blue.

It's easy to see the bases. And the hydrogen bonds are right in the middle. There's another force I didn't mention and it doesn't matter for this course, but when the bases sort of stack on top of each other there's actually a kind of extra stabilization that comes from that. It's a gorgeous molecule. You all know it encodes the genetic information. We're going to be talking about it a lot, but first thing, you know, I could just tell you it's the genetic information.

But one of the really big discoveries in biology was that DNA is the genetic information. And a point I'm trying to help you learn here, you know, I'm trying to teach you more than just facts. And I hope some of you at least will catch that. I'm trying to show you how biology is done. As an experimental scientist you don't sit down usually and figure it out. Instead you start doing experiments and you get all kinds of unexpected discoveries.

And, in general, as people work in these unexpected discoveries ultimately they come to these grand new insights that, you know, sometimes would have been very hard to forget. So the real question that people wondered for a long time, and we'll talk more about the history of genetics, but people knew we clearly had inheritable traits. You could see it in your kids.

People had been breeding plants and all sorts of things. Breeding domestic animals. They sort of understood the principle of inheritance. When I tell you about Mendel we'll begin to see how his thinking led to the idea that the inheritance wasn't just sort of like a liquid where everything mixed together. It came in units or particles which we know of as genes. And so the idea of genes had been accepted certainly by the beginning of this century anyway, but nobody knew what they were made of.

They were made of -- The major properties that they had was they clearly encoded information in some way. They must replicate because one cell could give two and on and on and on. So if you were going to pass it down in an inherited way they have to be replicated. And the third thing was that people knew somehow they could mutate or the information content that they encoded could be changed.

Again, you could see that, that you'd get something, an altered characteristic, and then it would be propagated down through that line. That was the principle of breeding that people had done for ages. And so they understood that. There was one other key thing they knew. They knew that these genes were in the nucleus. And I'll tell you the full story of how even that insight was arrived at.

But I'll just show you for the moment this little movie. This shows some chromosomes that are all bunched up and are just pulled apart at the time of the cell division. Those chromosomes, as we now know, are made of DNA. But in essence what people had seen through the microscope was these chromosomes or colored things that they could stain.

They could sort of see something had doubled. And just before the cell divided the two sets separated and each cell got a new set. So that's about what people knew. They had those properties. They're in the nucleus. They knew about as much as you do. They knew the major classes of biomolecules in a cell. So what do you think you

would need to do to show that DNA is the genetic material, encodes the genes? Find somebody near you.

I'll give you a minute or so. I'd like to hear what kind of ideas you come up with. Then I'll tell you how it happened. But I want to hear. Why don't you think about it and just see if you can come up with a couple ideas for me, what you'd need to figure out. Well, let's just see what kind of ideas anybody got. If you wanted to make me believe that DNA is doing that, or I think it's a protein for the moment, that's what I think is most likely, but what you do think? Anybody got an idea? Mess up the DNA and see if we can mess up the cell.

How are we going to do that? I can break a cell open and I guess I can purify DNA and I can analyze it. And it's got four bases in it and it's got sugars and phosphates. At that point nobody could sequence DNA. We didn't even know the structure. Yeah? Take it out of one cell and put it into another. And what would you expect to happen then? OK.

That's a really nice idea. Somehow if you took the DNA and moved it from one cell to another that the characteristic of this cell would be somehow carried over. OK. That's in fact the way it happened but not as simply as that, as I'll tell you, but that's exactly the essence of it. One little problem. Maybe we'll see if anybody has a thought on this. If I purify DNA, I mean nothing's ever really pure, right? You get it out and there's always little bits of stuff.

And someone can always argue, well, yeah, it's 99% DNA, but it's the other bits you cannot get rid of. Yeah? If you used radioactive material, how is that going to help us? It does contain nitrogen. Well, it gets a little complicated. Certainly nucleic acids have like phosphate in them, but so does RNA. That's going to be hard. Maybe if I had a mixture of things and I wanted to prove whether something was let's say DNA, a protein or something, you need some really specific way of saying I did something to the DNA and not to the protein or something like that.

Have you heard anything in this course that is really specific? Enzymes. Do you think that'd give you an idea of how you might do it? If I've got a tube and it's mostly DNA and maybe a bit of protein and something, and let's say his idea is working, that we can take the DNA from this cell and put it over into the second cell and see the characteristic change, if I wanted to do something to show that it was the DNA in the tube that was responsible, could you use an enzyme? And what kind of enzyme would you want? Well, what characteristics would you like it to have? Nature's probably made it for you already.

Something that synthesizes DNA? Something that breaks down DNA? Say I treated this tube with some kind of enzyme and then I wanted to see the outcome, what would we want, an enzyme that did what? Anybody else got an idea? You're asserting that it's the DNA in my prep, I like your idea, but I need to prove it so I need to do something to show that it's actually the DNA and not the other stuff.

So if I had an enzyme that did what to DNA? If I broke it down, yeah. We could treat it. And if your idea is right, we treat the stuff with something that specifically breaks down DNA it won't get transferred. Does that make sense? OK. I mean that's a way you could go at a proof of this. And, in fact, that's what happened. But I'm going to quickly tell you how it actually happened. And again, you know, as I say, I'm trying

to tell you a few things that are besides here are the facts that you need to know on exam.

There's a bigger picture here and this is how research goes, and particularly in an experimental science such as biology. The important early work on this came from a guy who was known as Frederick Griffith. He was in London. He was a physician. He was working in the 1920s. And he was studying pneumonia. That's an infection of the lungs -- -- by bacteria.

There's more than one kind of bacterium that will cause pneumonia, but one of the really important ones clinically was streptococcus -- -- pneumonia. So it was a bacterium. It was given that name. We all have bacteria on us. I think I told you we have about ten to the twelfth on our skin, for example. And if streptococcus is on your skin it's not a problem, but if it gets into your lungs it's a problem.

And so to live with all these bacteria with us our bodies have defenses. So we have this immune system, we'll talk about more, and a bunch of defender cells. Things that you know as white blood cells are defenders. Let's just see here. I'm going to show you this little movie. This is one of your white blood cells, a special kind of white blood cell.

That little thing it's chasing is a bacterium. These round things are red blood cells. I mean doesn't it look like a dog going after a mouse, or a cat going after something? It's chasing it. It can tell it's there. This is remarkable. And it's a little pixilated, but this is real. It's going to catch it right about there. And it eats it. I mean we have these cells inside us. That's why you don't die even though we live in a world that's surrounded by bacteria.

OK, so we'll go on. So getting pneumonia in those days was a really bad thing. You get infected, you get this in your lungs, and then you have four to six days of high fever, and then the patient would reach what's termed as a "crisis". And one of two things would happen. They'd either live or they'd die. And that was it. I mean this was no fun if somebody you knew had it because you didn't know the outcome.

And the outcome wasn't necessarily very good. Now you call up the doctor and they pump you full of antibiotics, but antibiotics hadn't been discovered yet. So this was pretty serious business, and people were trying to understand what was happening. But what was going on during these four to six days that then led to one of these two outcomes? Well, it turns out that streptococcus is a bacteria like this.

So that's the bacterium. And it has around it something known as a capsule. And that capsule is polysaccharide. Remember back to the second lecture when I was confusing you all by showing you how sugars could hook together in all a manner of different ways? Well, that's what polysaccharides are. You just hook a bunch of sugars together. And for this course you don't have to remember the linkages in particular.

You just have to understand that there are different kinds of linkages, and every time you hook at it in a different way you get a different kind of polysaccharide out of it. But anyway, the bacterium make this capsule of polysaccharide. And it's full of hydroxyl groups from all those sugars so it attracts a lot of water around it. And what it does is it causes a problem for those defender cells that we just saw.

Those would be, for example, a macrophagic kind of white blood cell. And it cannot eat something that's got the capsule. Now, here's a picture of one of these capsules on one of these kinds of bacteria. You can sort of see it out here. It's polysaccharide. That's the main part of the bacterium. And here's another pixilated thing of one of these white blood cells eating a bacterium that doesn't have a capsule.

But watch what happens if the bacterium has a capsule. It cannot get a hold of it. It just cannot quite grab hold of it. So what happened during those days, though, was this capsule which is a foreign entity to your body gets recognized in your immune system. And your immune system made antibodies that could recognize that. We'll talk about what these are, but all you need to know for the moment is that they're proteins and they can be tuned to recognize some chemical entity with a very, very high degree of specificity.

So what the body was doing during this thing was trying to make antibodies that would help it recognize this capsule. And then it decorates the capsule with these things. And once it puts antibodies stuck all over the surface now it can get a hold of it. And, again, a fact you don't have to know. This whole process is called opsonization. The reason they use the word opsin because opsin is the Greek word for seasoning.

And it was as if these white blood cells liked to have their bacteria seasoned correctly before they can eat them. And what's really going on is that they're decorating them with antibodies. So what was going on after a person got sick, it was a race between their immune system trying to make antibodies which would let their immune system suppress the infection and the bacterium which is replicating unchecked for the first few days.

And that's why it was such a scary business, because you didn't know what the outcome was and things could tip it one way or the other. Well, this did suggest a kind of therapy. The kind of therapy would be to isolate a capsule to inject a horse. Get the antibodies from the horse. Why a horse? A horse is huge, right? It makes a lot of antibodies. A lot better than injecting a mouse if you want to get antibodies.

So get antibodies and then inject the patient. It's a good idea in principle. So you're sort of short-circuiting this whole process. The problem was there were more than 20 kinds of capsules. And so what people had to do was they had to isolate the bacterium -- -- from the patient, determine the type of capsule. Let's say it's sort of from capsule 1 up to capsule type 20, which one it was, and then inject the correct antibody.

So this was nerve-racking because it took a while for the bacteria to grow so it was a pretty tight time window. And if you saw the patient right away that's good, but if they were partway down the infection not so good. So the one other thing to do this, they didn't bother all the way to isolate the capsule. What they would usually do is use heat-killed bacteria and then you'd have the capsule and everything.

The bacterium is dead, it cannot do anything, and they'd inject the horse with that. And that would get you the antibodies with the capsule. So what Griffith was doing was he was fiddling around with this system. And there was one other discovery that he made. Perhaps it wouldn't surprise you that since the bacteria surrounded by a molecule absorbs water that the capsules would look sort of glistening.

They absorbed a lot of water. You can see how they look here. So what they discovered was if they have a capsule you get what are called smooth colonies. And the word colony in this thing just refers to it started out as one bacterium and it kept dividing and dividing and dividing. And maybe there are ten to the eighth or ten to the ninth bacteria in that little colony. But you can see it.

They've all got capsules on the outside so it attracts a lot of water and it looks wet. And those are what you saw. But what they found is if you waited or grew the cultures up that you would see some things that looked dry or they called them rough. And these turned out to be bacteria that lacked a capsule. And so if you might start with a smooth strain S here and then isolate from it a rough strain it might designate it in that kind of way.

So this is the sort of thing that Griffith was fooling around with. So he started with doing this kind of experiment. He took a smooth strain making a capsule type two, OK? So he was injecting a mouse with this. And what happened was the mouse was dead. This was a virulent form of the bacterium. So if he took the rough mutant, injected the mouse, the mouse is alive and you saw why. If it doesn't have a capsule, the mouse has defender cells and white blood cells could eat it.

Then he had heat-killed S3. So this was a strain of streptococcus that had a different capsule, a type 3 capsule, but it was heat-killed. Why was he working with heat-killed stuff? Because that's what you injected the horses with to get it. So what do you think would happen here? Since the bacteria are dead, probably not a big surprise the mouse is alive.

Now, I don't know whether he did this on purpose or he did it as a control, but what he did was he injected at the same time then R2 plus heat-killed S3. So he's got two things that don't do anything, he injects a mouse, and uh-oh, the mouse dies. That is a weird result. That is actually also, though, the first really key step to understanding that DNA is a genetic material. It doesn't look like it at this point probably, but it was.

This is how we learned this really enormous fact from these experiments. He wasn't trying to figure it out. He was trying to work out something else, as you can see, but it was a bizarre finding. So what would you think? I've put in something that used to have a R2 capsule. So did it get rejuvenated somehow by this heat-killed thing or, as you'd suggested, did some characteristic get transferred from here or whatever? So he isolated the bacteria out of this, and what he found now was he had a live bacterium that was making S3.

So something had been transferred from this set of dead bacteria into bacteria that were alive, and the characteristic had been passed from the dead bacterium to the new bacterium, the other bacterium. So this is about what Griffith did, but this problem was picked up by a scientist at Rockefeller, Oswald Avery who worked as part of a team. And he took this finding and started to work on it and tried to figure out, because he saw in this result a way of finding out what was the genetic material because somehow what was in that heat-killed S3 was the stuff that would transfer genetic information into another bacterium.

So he made one really big discovery. And that was you didn't need the mouse at all. All that was happening was the mouse, by dying, was in essence selecting for smooth bacteria. So he could simplify things by just taking a rough bacteria, taking

the heat-killed extract, putting it in, and now he'd just look for smooth colonies. Didn't need any mice at all. So he was able to see the characteristic of the capsule being transferred from some kind of heat-killed mess of things into a rough bacterium and changing it into a live bacterium.

So he started fractionating, and he did exactly the kind of approach that you suggested. And he purified and he purified and he purified using as his assay this ability to pass on this smooth characteristic. And what he ended up with was virtually pure DNA but, as I said, you know, always never quite pure. And somebody can always argue, well, you've got a little bit of something else in there.

So he did a really key experiment and he treated with DNase, your experiment. And it lost the transforming activity. So this process of doing this was called transformation. Initially it described that phenomenon. Now that we know what matters in the thing was taking DNA and putting it in. So if you do a UROP somewhere here, you clone a piece of DNA into a plasma and you stick it into E. coli so you can grow it up, that process of taking the naked DNA and putting it inside the bacteria, you'll call it transformation.

Now, in fact, this result wasn't accepted right away. This was published in 1944. And the general realization that DNA was the genetic material really didn't come until the `50s. Yet this result proved it, if you will, but part of the problem was the world wasn't yet ready to accept that DNA was a genetic material. And maybe you can see the problem. It looked like a monotonous molecule.

It only had four things that were different in it. And if you isolated they were all often kind of there and about the same amount. People thought it was just an analyst GATC. It didn't sound like anything had encoded information. Proteins looked really attractive. Twenty different amino acids that all had different characteristics, so that was a great place for storing information. So the world wasn't quite ready to accept it, even though the experimental evidence was there.

And so the result came later. Now, the last thing I just want to show you, because there's a kind of direct link from that Avery experiment to you guys because a year or two ago it was the 50th anniversary of the discovery of DNA. And Avery worked with a team of two other people called MacLeod and McCarty. This was at the 50th anniversary, the meeting down at Cold Spring Harbor celebrating it.

McCarty was the only member of the team alive. There he was. I asked him to autograph my program. There was his signature. He just died a little while ago, and so there's no living connection to that anymore, but I have a picture to show you guys that takes you back from that experiment to his signature right there. OK? So I'll tell you some more stuff next lecture.