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7.014 Introductory Biology, Spring 2005
Transcript – Lecture 22

Just wanted to begin today by pointing out a couple of articles from today's Boston Globe. There's an article that's on the financial pages about investors reconsidering gene therapy, and startups funded as technology evolves. A lot of you have heard the words gene therapy. A lot of you, at the end of that bacterial genetics lecture, said you weren't quite sure what complementation was. But, gene therapy is basically complementation put to work.

The idea is if you got a broken gene, and you can put in a good copy, then you'll take the cell back to being normal, which is exactly what we're doing in those phage crosses where we had two phage, one with the mutant copy of the gene, and one with the wild type copy of the gene. And they're saying here that there's a renewed interest. Now, the basic strategy in these things is to take usually a retrovirus, the same kind of idea that we heard about with the HIV-1 virus that will make a DNA copy, and then the copy gets inserted somewhere in the chromosome.

So, the good thing is it puts in a new copy in a chromosome. The bad thing is you got a piece of DNA being stuck somewhere in the chromosome. And there are places where it can go where it doesn't matter, and there are other places where it really does matter. So, it's been a very tricky business with gene therapy. Part of the thrust here is they're thinking that maybe they need to pick targets were the person's going to die anyway so that if there is a risk of getting cancer or something, it's outweighed by the possible thing.

That's sort of the thrust. You can see the article; it's in today's paper. It's very timely for what we are talking about now. And then on Friday I'm going to start talking about recombinant DNA strategies and stuff. But there's another article in today's paper. This is one of those things that I told you about where an article is published in the, in this case, online in the journal Nature.

They have an embargo on a press thing until Thursday or so, and then the article is on, the hot papers that have just come out show up in the newspapers, usually either on Friday or Monday. And this is yet another system that they describe as making a molecular repair kit that corrects mutations in the cells' DNA. So far, this has only been done in cells. But it's working well enough, and the article is saying this approach could become a serious competitor to conventional gene therapy.

In here, you have sort of a layman's account of this kind of complementation by gene therapy. We're talking about gene therapy in that field which attempts to force feed healthy genes into cells hobbled by defective ones has been plagued by failure, and recently was found to cause leukemia in some patients. That's probably because of the insertion events associated with these viruses.

This new system rewrites the small stretch of misspelled genetic code. That's typically the reason the gene has gone bad. So it's a different kind of strategy. This is the first report I've heard of that. Some of the stuff we're talking about is sort of

inescapable because you're going to see it in the paper. Here, they're telling you the sort of thing I was just saying.

The viruses inject their payloads at random within the cell's mass of DNA sometimes disrupting normal genes. Even when genes land in good locations, the molecular machinery that regulates their activity is also often thrown off, leaving the healthy genes operating at a level too low to be helpful or functioning in the wrong parts of the body. It must begin to sound familiar. You stick a random piece of DNA somewhere, you can disrupt the regulation in the gene as well as just landing in the open reading frame.

So there's a problem with gene therapy. Now, they'd like to make you think that this is going to be the promise to everything, but as always it's more complicated. And so, I just picked up the last paragraph of this article. Other scientists said the approach looked promising, but predicted it would end up struggling with this problem of its own, James M. Wilson, a gene therapy researcher at the University of Pennsylvania.

Now, there's somebody who's in a position to criticize, but also has a vested interest himself in the alternative therapy, noted that the first step of the new process causes for zinc fingers. It's a kind of protein that's involved in this, to make a fresh break in DNA to accommodate the insertion of the corrected sequence. It's the same kind of break with radiation that can lead to cancer. And we're going to talk today about, you'll see where double-stranded breaks and whatnot can be a real problem in terms of the integrity of the DNA and genome stability, which is maintaining gene stability so important in avoiding cancer.

You guys are a tough crowd. Comments ranged from, this was the best lecture that I'd given to ones that were absolutely the other end of the spectrum. You're a very hard group. I truly am going to take, I don't have time really to sit back and redo all my lectures, but I've a huge amount of input, and I'm going to go back over all this input I'm getting, and take it very seriously in terms of how I go about things next year.

I can see a number of changes I'm going to make. Whoever sent me the e-mail that talked about the Dock Street Bohemian Pilsner brewed in Utica, NY, this classic golden Pilsner, pungent, perfumy taste and so on, it was a moment of lightness, but if I got too many things like that it's not going to help me in trying to figure out how to do. For the person who asked about how to avoid accidental pollination, when they're going to do that, they actually take the stamens off the flowers so you don't get accidental self fertilization.

You actually go out and make ones that are just male or just female flowers. You can do that rather easily. OK, so what we got into last time, or what I told you last time, and I promise you that there's another Mendel lecture coming. For those of you who thought this was a little slow, you may find the next one is all too fast. But anyway, that will be how it goes.

Mendel had carried out this fundamental series of experiments. And I did linger over it because I think it's so simple you can actually see the scientific process in action, and it also isn't complicated by any techniques that we can't see. And it was a tremendously important insight that genetic information came in units. But as I told

you, it wasn't accepted because for most of the world at the time, it was a statistical argument.

There weren't any entities that were two of inside a cell, and all that sort of thing. So, it didn't take over scientific thinking. It wasn't until about 1900 when several other geneticists did finally find systems that duplicated Mendel's results, and therefore showed that these were general inferences, something that Mendel himself, as I told you, by choosing weeds and bees as follow-up systems hadn't been able to do.

These other geneticists showed them in other systems. But the other thing that made the difference at the time, was by this point cytologists, who were looking at cells under microscopes, had found entities whose behavior seemed to match those of these particles of information that Mendel had postulated to explain these patterns of inheritance that he was seeing. These particles, because they were called chromosomes, which literally means colored things, the reason they were colored was not because they were inherently colored, but because cytologists were staining the cells with a variety of things.

And that was what allowed them to visualize these. And so, by staring into microscopes, right around this time, around the turn of the century, 1900s or so, cytologists had come up with three key observations. One was that chromosomes came in matched pairs. So, let's say in this cell, there were too long and too short. So that's a chromosome. And it corresponds, we now know, to a double-stranded DNA molecule that's been all condensed up.

And there are two copies of each chromosome in this thing. So: two long, two short, one came from mom, one came from dad. And for bookkeeping purposes, I'm going to color them so that from one parent is unshaded, and the other one is shaded. Most of you know in human cells we have 23 pairs of chromosomes. This is a now fancier method of visualizing chromosomes called painting chromosomes where you take little stretches of DNA that are unique to particular sequences, attach dyes, and then use them to stain the cells, and so they will color only particular chromosomes.

And we have 22 pairs of identical chromosomes, and then the sex chromosomes here, X and Y, this would be a male, or two X's if we were . We'll return to those in the next lecture. Kim Nasmyth, who spent his life working on how these chromosomes segregate gave a talk a year ago. He's in London at a hospital in London. And then he brought in the next slide. There was an artist who spent several months visiting with him, trying to find ways to represent in art some of what she saw going on.

And I thought you might enjoy seeing this, the slide. This is the human complement of chromosomes, represented in stripy socks that various staff members from the hospital brought in for her to do this. So, a little touch of scientist humor which some of you may think is pretty nerdy, but anyway there it was for what it's worth. He showed that in our departmental colloquium.

OK, the second thing, then, that the cytologists noted by staring at this was during ordinary cell division, which gives two identical daughters the numbers of chromosomes per cell is preserved. And this ordinary cell division is given a special name of mitosis. So if we take this cell, the first thing that happens, then, is the

chromosomes are duplicated. We've talked a lot about DNA synthesis at the molecular level.

This is looking at it. Excuse me, and so, there are now two DNA molecules, that each one of these new DNA molecules is given a special name. This is called a chromatid. So there was one DNA molecule here. It's now duplicated, but you'll notice these are still joined together. The point at which they are joined together is known as the centromere. And then, after this, after the DNA's been copied, these things are lined up at the center of the cell and then they are pulled apart to give two daughter cells that are just like what you started with.

This part, so this is 2N, if N is the number of kinds of chromosomes. And then there's two each. This is 2N. At this point, the DNA contents of the cell is 4N. This is 2N. This is 2N. We're back to where we started. This part was invisible to the cytologists, at least in the sense the chromosomes at this point are extended. And so, they weren't able to visualize them by looking through the microscope.

But as it came time for cell division, then the chromosomes condensed up very tightly. This is probably to avoid tangles. And you need to pull them apart into the two daughter cells. And then the part that you could see, this was known as mitosis, this process by which the chromosomes are pulled apart. So, mitosis is a mechanism for nuclear division that results in two daughters with identical genetic information.

When you contrast this to meiosis, which I'll show you in just a minute, this has been studied for years in a kind of observation way. I showed you at some point. This is an animal cell where the chromosomes line up, and then they pull apart. I think I showed you, and you can see the cells divide once they've done that. I'm going to show you this next thing, which everything happens more slow motion.

This is a picture of the blood lily, so it's a plant. Again, the choice of model system is often, if it has a feature that is good for a particular thing. This happens, very easy to visualize in these lily cells. Now here, the cells have duplicated their chromosomes, and the daughter chromosomes are held together. They're glued together, so you can tell in this thing that they've been glued. Now, in order to separate the first thing they have to do is line up at the equator of the cell.

And then it pulls apart and you can see that each daughter cell gets one of the duplicated chromosomes. OK, so that's mitosis. It generates two copies of what you started with. The other observation that the cytologists made was that cell divisions that produce sex cells work by a different system. So, the third thing, And, I'm going to give you the scientific word now for sex cells.

So, they're usually called gametes. General term, so that would be sperm and egg, or pollen would be a kind of gamete. In this process, the number of chromosomes is halved. And this special type of cell division is known as meiosis. It's very important, because if we didn't have meiosis we wouldn't have any progeny. We need to be able to cut the number of chromosomes we have per cell in half, so as Mendel inferred, then when each parent made a contribution you'd be back up to the right number of cells.

Now, so this process begins again by duplication of the DNA. So this would be 2N. Now we go to, as before, with one interesting difference here. So we are at 4N in the cell. But you notice that I've drawn these duplicated chromosomes with chromatids

overlapping. This point of, I didn't do this too well. The point of connection: where the two chromosomes overlap is known as the chiasma.

It's a point of actual physical interaction between the chromosomes. And what it allows the cell to do is to have the two homologous chromosomes, in this case the two long ones, find each other, and actually physically interact. That's a critical event for the next step that I'm going to show you. It's also a point, which you'll see in the next lecture, there is additional genetic diversity introduced into the system. So, at this point, what's happened is that the DNA has doubled, at this point, looks sort of like mitosis except for the fact that the duplicated chromatids have overlapped.

There's a least one of these for every pair of duplicated chromosomes. So what happens in the next phase, which is known as meiosis I is that the pairs of duplicated chromosomes are separated. So, we get two cells. We might get, say, the unshaded of this one and the shaded of the little guys. And the other one then is shaded with a long one and unshaded with this one. This is 2N, and this is 2N. But if you'll take a look at what's happening over here, you will see that we don't have the same thing going on.

In that case, we were producing identical copies of the starting cell. In this case, we've got something different now because we've separated both copies of, let's say, the chromosome from dad from both copies of the chromosome that originated with mom, and the other way over here. These, then, undergo a second round that's known as meiosis II, which resembles now mitosis in the sense that the duplicated chromatids are now pulled apart into daughter cells so that this one will generate one long, unshaded one, one short, and there will be two of those.

In the cell, it will generate a shaded long and unshaded like that. So now, there are four of these. And you'll notice that there is now an N. So, we halved the number of chromosomes during meiosis via a process by two rounds of division. The other thing you can think of is you can begin to see, at least, when the evolution of sex was such a powerful force in driving evolution by introducing so much variation, because each of us has a copy of each of our 22 chromosomes where we have homologous pairs, one from mom, one from dad.

That every time we make a sex cell, a sperm or an egg, what happens is for chromosome 1, you can either get a copy from mom or the copy from dad. And then the next one: copy from mom, copy from dad, and so on. You can see the variation is possible just from that part of the process alone. And there's going to be more variation that comes about from events that happen where this chiasma is as I'll show you.

So, meiosis then, as I said, is a mechanism for nuclear division that produces four daughter cells with half the genetic info of the original. So, how did I write that? And in this case, the daughters are not identical. Does somebody have a question? Yeah? Oh, this part of the process, the cytologists broke this down when they were observing. So, it was a part they couldn't see.

When they started to be able to see it, they first saw this one division, and then the second division. They called the first round of division of meiosis I, and the second meiosis 2. So it was just a name given to the process. Yeah? Oh, sorry, excuse me, I see the problem. OK, it goes this way. This period of time is called meiosis I. That part of the process is called meiosis I, meiosis II, sorry.

Yeah, I mean what I wrote down as arbitrary. You could've had 2 from mom, and 2 from dad. And in fact, I guess if we have 22 pairs we could eventually have a sperm or egg that had all of the copies from mom, and all of the copies from dad. You could calculate the statistical chances of that happening, but what you'll discover as we'll find next time, is that even if you did that the chromosomes would no longer be identical to what you got from mom or dad, because there's a little bit of genetic recombination going on during that process.

I'll also show in a minute that you can get errors in this process, and that these are important. So, what happens then is that fertilization, what the cytologists can see happened was that the number of chromosomes have been halved. So, you had N plus N giving you 2N where this might be, for example, the egg, and this might be the sperm, since gametes have half the number of genetic content when they fuse, then you go back to the original number.

And this gave rise to what was known as the chromosomal theory of inheritance. Even though cytologists didn't know what these colored things were, they seemed to have the properties that you would expect the carriers of the genetic information to have. Be duplicated before a cell was going to divide and then they seemed to be very precisely segregated so that each daughter cell got one copy.

And it made sense, then, in terms of the formation of sex cells you'd have, and then it would all come back up. So, the cytologists proposed this chromosomal theory of inheritance. Chromosomes were the carriers that carried the genetic information. And you can see now that Mendel's work was rediscovered, which is more or less what happens around 1900, how beautifully it mapped on top of this because the genetic information came in particles.

You'd think, oh, well those particles are sitting on those chromosomes. They get duplicated. They get separated. They get divided in half. Their number gets divided in half when you make sex cells. So, I want to at least point out, let me go onto this next thing here. Here was one other picture I'd shown you. This was a cancer cell dividing again.

We see the same process at work. And that just reminds you, when I was talking about that kind of process, trying to remind you that one cell gives rise to two cells, and one DNA molecule gives rise to two DNA molecules. But these phenomena are related even though one talks about them in different parts of the courses, and if you've got more than one DNA molecule per cell, then each one's a chromosome. And then you have to take care of segregating those as well.

But a point that I'd made is that up until this part to the right could be a yeast or an E. coli, but if it's going to be someone, something more complicated that's got different kinds of cells like us, then we have these ultimately, an adult human with 10^14 cell. So, this process has happened over, and over, and over again. And it has to be really very accurate. And, there was remarkable advances have been made in understanding this process over the last few years.

And a lot of this was due to the work of Lee Hartwell, who carried out experiments, I guess, that offered some key insights into the basis of the whole cell cycle, of which this is just part. So they said, here we can't really see all of this stuff in the

microscope. What cytologists were able to observe was that after the chromosomes had duplicated, then they condensed up.

They became visible, and they could see that part of the system. So, a great body of knowledge has been learned over the past few years. Lee Hartwell, who was a postdoc at MIT with Boris Magasanik a number of years ago, was one of the key people who led to this round of insights. And what we now know, the cell cycle can be basically divided into four parts. So a newly born cell, if you will, undergoes what's known as phase of the cell cycle that's known as the G1 phase.

And you could think of this as, amongst other things, sort of preparation for duplicating the cell's DNA. And then, there's a phase known as the S-phase, which is when DNA synthesis takes place. That now gives the cell an information content of 4N. There was then another phase known as G2, which you could think of as preparation for pulling the chromosomes apart, and for the cell dividing.

And that's known as mitosis. And so, this is quite remarkable. It's quite fundamental. It's a very elegant and very complex system of controls. And what Lee learned is that there is an elaborate system of what we now know as checkpoints in the cell cycle. And the idea is pretty much the same sort of thing that you might do if you were an engineer and you were setting up a quality control process that involved a series of stages.

And what a checkpoint does is it basically demands successful completion of a prior phase before the system is permitted to move to the next stage. And you can sort of see the problem here, that if you are trying to, say you're copying your chromosome, your DNA, and you only got part way through. And then you proceeded to the part where you pulled the chromosomes apart. There would be all kinds of chaos inside of the cells because you would be breaking chromosomes.

You wouldn't be getting identical information. And there are three major checkpoints. There is a checkpoint at the G1/S boundary. There is actually more than one. But there's an intra-S phase checkpoint, and then there's another one at the G2/M boundary as well. And the way that Lee found this out, I wanted to just take you back because remember when I was talking, well, first we talked about how would you get a mutant affecting an essential cell, a gene whose function is essential for the cell.

We said you'd have to be conditional in some kind of way, because the organism would be dead, and couldn't use genetics to study it. So, when I introduced you to those phage, and we wanted to study critical functions needed for phage growth, we needed a conditional mutant. Remember, we did look for temperature sensitive mutants. So that's what Lee Hartwell started to do with yeast in 1970 approximately.

He just looked for mutations that were temperature sensitive lethals in yeast. Now, yeast can be diploid, but they also can be haploid, which is just one copy of genetic information. So just like a bacterium, haploid yeast, if you get a mutation affecting a gene, then you see its phenotype right away because there isn't a complication of the second chromosome. And Lee got the Nobel Prize for his work, just, I forget, three years ago or a short time ago anyway.

And so, this was the process he was studying. I showed you this movie. In this case, this is budding yeast, and you can see why it's called budding yeast is that rather

than the still growing and segregating down the middle, the daughter cells grow as little buds coming off the side. The DNA is still going to be duplicated as we got, and then segregated into the daughter. So that part of the process is there, but there's yeast growing sped up a bit so you can see it.

So, what Lee found was that when he looked at his TS mutants, he found that they tended to arrest at characteristic stages, and he was able, then, to figure out that there must be some sort of checkpoint system that is something went wrong during one of the stages, then the cells with all pile up at a particular characteristic stage in the cell cycle. And this was controlled by these checkpoints.

These checkpoints are of enormous importance because if something goes wrong with them, as happens often in cancer cells, then you get a huge increase in instability of the genome very similar to the way, losing, for example, mismatch repair causes instability of the genome and therefore things that can cause a cell to forget to divide when it stopped dividing when it hits its neighbors, which part of the cell it belongs to and so on.

Those kinds of changes will come with much greater frequency. Another thing that was completely remarkable was because it was yeast it was relatively easy to find genes that were broken. Going back to complementation, leaving aside the technicalities, if we had a mutant that's a TS lethal and it's dead, if we put in a good copy we'll know it because the cell won't die at a high temperature anymore.

So, you can sort of see from the first principle it was relatively straightforward to find the genes in yeast that are necessary for cell cycle control. The remarkable thing is that they've been conserved all the way up to humans that the proteins that are involved in the cell cycle control are virtually identical in humans. So, the system, again, is probably locked into place because it works so well.

And once it was working, then evolution didn't have a lot of space. I won't say it's completely identical in human cells, for example, have a few more wrinkles that they throw in. And fundamentally, you can see evolutionarily that the system evolved once. One thing I just want to comment on, and here's just an example of the sort of thing that can happen if you get a problem with pulling chromosomes apart when they're not ready, or something happens that make a break in a chromosome.

You will get a double strand break, and cells don't like that, and they try and fix it up. I think in this case, you can see that chromosome 9 has picked up a piece of a couple of other chromosomes. This piece here came from chromosome 8 over here, and this piece here came from chromosome 22. And so, this cell now has things kind of messed up. And this particular chromosome's got parts of two other chromosomes.

And so, you can start to think about the consequences of that. You'll see when you start segregating chromosomes, there are issues. And also, the junctions themselves can sometimes do things like creating fusion proteins that have aberrant properties, for example, a signaling molecule that's now locked permanently into the on position or something like that.

Those sorts of things can happen by these as well. So, here's a very abbreviated form, the principal that happens, or what happens so that the chromosomes become visible in the microscope. There is about a couple of meters of DNA in every human

cell. So, you can see almost from first principles, it almost has to be packaged in some way to fit in that little, tiny area.

And down at the basic level, the DNA is looped around a little cluster of proteins called histones. And then, as the cells approach the mitotic stage, they package these and higher, and higher, and higher levels of packaging so that the chromosomes get more and more compact, and therefore less like spaghetti, and less likely to get tangled when they are pulled apart. Now, this teaching as part of the course.

It's in the book. It's a little like glycolysis, though, and there's so much detail. It's hard to notice at all. And what I've tried to do here is just sort of take a step back, focus you on the really big parts of the process. But you can see this is a sort of typical textbook thing showing you the various sub stages of this process that cytologists have given names to each part of this.

For example, you can see the chromosomes lining up at the equatorial phase just before they're going to be pulled apart. One little detail which I glossed over at this point as you can see that the chromosomes are, of course, surrounded by the nuclear membrane. And, at least in many cells, what happens is just before the chromosomes are going to be pulled apart, this nuclear membrane in a matter of 20 or 30 seconds goes from being a membrane into sort of breaking into a whole little series of membrane sacs.

And then, after the chromosomes have pulled apart, now you reassemble the nuclear membrane around each set of chromosomes. And I think there's still an awful lot to be learned about how that particular trick is done. And that's a textbook diagram. These are the kinds of things the cytologists were looking at as they were describing it. And one thing you can certainly see, I think, is that there are a lot of, if you want to think of them as cables, this whole process is done by molecular machinery.

And in fact, one of the key things for ensuring that the chromosomes are all lined up is each are attached to each pole of the cell. So, an individual chromosome feels tension on both sides, and there's pretty good evidence at this point that says that what has to happen before mitosis is allowed to proceed is that each duplicated chromosome must feel the tension on both sides. And if one of them is only attached on one side, it's not allowed to go ahead.

Here are a couple more pictures. The chromosomes are in blue, and all this cabling is in green. You can see a molecular machine's basically at work. And I wanted to show you this picture because this is important. There's two parts to this. Julia, could you hit? So, this is a normal mitosis. These are in lung cells from a newt, which are very flat. So it's easy to visualize them. I believe this is by Nomarski, a kind of optics called Nomarksi optics.

What they're doing, the duplicated chromosomes are getting lined up at the equatorial position in the cell, and you get a spindle attached to one side, and then a spindle attached to the other. And once that's happened, then you can see the chromosomes. Watch this one over here, for example. It just got attached, and it's being pulled into the middle. And once the cells feel that all the tension, there's tension on all of them, and then it enables the next stage of the process.

And you will see each of the daughter chromatids segregate before. And, I just want to impress upon you it's complicated enough just replicating the DNA at the fidelity we talked about. An awful lot of other stuff has to go on. And it would be a reasonable question: is there ever a mistake? And there is. This one actually shows another cell where there's going to be a mistake.

You can't see it yet, but you can see the chromosomes are all condensed up. And they are beginning to get these spindles attached. And as they get attached to the site then they get localized in the central part right down the equatorial plane of the cell. But, I think you'll start to see the problem emerging at the moment. I think it's going to be this guy right here.

I think a little arrow will probably appear before too long. But what's happened is this one didn't get properly connected on both sides. But, the cell's going to go ahead anyway. Watch. The one up here is going to get pulled in. There it goes. It's getting pulled in. And then, once it's in there, then the cell is going to go ahead and divide anyway. So you can see what the problem is.

This one's got two over here, and this one over here is missing it. This process is known as non-disjunction. This is the sort of thing that happens in cancer cells that have broken, where the checkpoint gene is broken. And then, if you have that, then the cells go on. The same problem happens in meiosis, and it's up here. It's the same principle that if you end up with, if you don't segregate the cells, the chromosomes correctly, then you can end up with a sex cell that has two copies of one of them.

And the other one has none. And if you have two copies, or 2N plus 1N, then you end up with a trisomy. And if you have zero plus N, you end up with what's known as a monosomy. So, these would be from defects in meiosis. I'll just close by saying the one that you probably have heard of is Down's Syndrome which is trisomy 21. That comes about from this sort of process.

It's a very debilitating genetic deficiency. Most of you are probably familiar with it. This process happens. Things go wrong at meiosis, about one in every fifth detectable human pregnancy doesn't go to completion for the most part because of an underlying problem like this, that the body is set up to need the pairs of each chromosome. If you have one too many or one too few it's usually lethal.

So, if one in every five human pregnancies has that happened, you end up with a miscarriage. My wife and I have been through it. It's a devastating experience. I think you can just look around and figure the odds. A significant number of the people in this room are going to have to cope with this. And I'm just bringing this up for your attention right now is it something that in our society we tend not to talk about very much unless maybe you're a Hollywood movie star and it makes it into the tabloids or something.

But it's a very common human experience, and very difficult to cope with. But there it is, for most of those pregnancies that terminate very early, usually the underlying cause is a problem that traces back to the kind of stuff we see here where something went wrong during the segregation process of making the sex cells. And as I say, if it happens in just our ordinary cells, that's one of the thinks that leads the progression to cancer.

OK, so I'll see you on Wednesday.