MITOCW | 7.013-S05-L07

OK. Let's get started. We're going to complete our discussion about mitosis and meiosis today. And then get into a topic called Mendelian Genetics, understanding genetic principles. And we'll give you as examples the work of the famous Austrian monk Gregor Mendel who sort of set down the rules that we still follow today regarding simple genetic inheritance. So I mentioned to you last time, and I think you all know that your genes are carried on chromosomes. And chromosomes come in different sizes and shapes. You have 46 total chromosomes in all of your cells. Those chromosomes come from your parents. You get one set from one parent and another set from another parent, so you have 22 pairs plus the two sex chromosomes. And the chromosomes are made of DNA, and along those DNA sequences are your genes scattered along the length of the chromosomes. And there are about 30,000 genes in total. Now, I've also told you that the genome, the whole sequence of your DNA has been determined over the last couple of years. We now know that in great detail. We know every single nucleotide of the three times ten to the ninth base pairs of DNA, and we can actually go to a website and look at it. You can do this. It's publicly available, sponsored by the government, but it's a little like hacking into the database of humanity. So if you go to this website that I just showed you, you'll find access to the genomes of many organisms. This is an evolutionary tree which shows the relationship of these organisms from an evolutionary perspective. There are nine mammalian genomes that are present within this database. If you clink on that link to homosapiens, that's us, assuming this is functioning. I had this working. I'm not sure why it's not working. I'm getting a good signal here. Oh well. Had this worked, you would have seen an alignment, a diagram of all the human chromosomes, one through 22, plus X plus Y. You could then click on chromosome whatever you're interested, let's say chromosome one. It would show a diagram of chromosome one from end to end. And you could then click on the sequence of chromosome one. All two point four times ten to the eighth base pairs of chromosome one. It would show you all of the genes on chromosomes one. You would know exactly where they were. And you could then click on a particular gene and look at its sequence. And it would actually give you information about that gene, as much information as is known. So, we know the nucleotide sequence of all the genes. And the question is, is that sequence that's in that database applicable to all of you? Is that the sequence of your DNA? What do you say? Why do you say no? Right. So it's somebody's DNA. Actually, the genome sequence that's present in a publicly available database is a collection of a small number of people's DNA, but it's a representation of the human genome. And you all have subtle differences. In between genes quite a few, and within your genes some. And we call those differences within genes allelic differences, you have different alleles, and that's what makes you all different, which alleles you carry, and importantly which combinations of alleles of genes that you carry. OK. I apologize for that not working. I don't know why it didn't. All right. Well, last time we left off talking about the fact that you inherit your chromosomes through the process of fertilization. Fusion of sperm and egg produces a diploid cell from two haploid cells. This diploid cell has two copies of all the chromosomes, two copies of all the genes, and then through the process of development there is a great deal of mitosis. We talked about mitosis in some detail last time. The process of chromosome duplication followed by chromosome separation, chromatid separation really, which allows daughter cells, during this process of mitosis to faithfully inherit all of the DNA. And this process continues through development, and it also continues in adults. It's not over when the baby is born. There's a lot of mitosis that takes place in many of your organs, and your intestines for example, your blood. Not in all of your organs. In the brain, for example, there is relatively little mitosis. Once the brain forms, cells don't divide anymore. It's true of the cardiac muscle as well in the heart. But many tissues do continue to divide. So this is happening inside of you as we speak. Now, what I want to turn to for today, though, is to talk about this process. How do you go back to the beginning? How do you generate haploid cells from diploid cells? And this occurs through a related process called meiosis. Now, meiosis takes place at different times, depending on whether you're male or female. As I mentioned last time in males meiosis takes place in puberty. So diploid germ cells are set aside in embryogenesis, but they don't undergo this process of meiosis until males reach puberty at which point it happens very abundantly, as I said, about a million or a couple of million meiotic cells produced per hour. In females meiosis actually begins in embryogenesis, quite amazing. The cells are set aside and they start to undergo meiosis. And they don't make it all the way through. You don't make haploid germ cells in embryogenesis. They get stuck partway through. Then in puberty, during ovulation a subset of those cells continue through the subsequent stages of meiosis. Then they get stuck again. And only at fertilization does meiosis get completed, a haploid cell is produced which is then fused with the sperm cell, a diploid cell is generated and development proceeds. So what is meiosis and how does it compare to mitosis? Well, they're related in the sense that both of them follow S phase. If you remember during S phase chromosomes get duplicated. And during chromosome duplication two chromatids are produced. You're not going to start singing, are you? No. Just kidding. When a chromosome gets produced two chromatids are generated and then they stick together at the centromere. Remember that? Now, in mitosis, as we talked about before, this is followed by one round of chromatid separation. That's all it is. The chromosomes with their two chromatids line up along the metaphase plate, and they get pulled apart during anaphase and telophase. And importantly the homologs don't pay any attention to one another. The maternal copy of chromosome one and the paternal copy of chromosome two ignore each other in mitosis. They could be anywhere along that metaphase plate. It doesn't matter. They ignore one another. OK? That's relevant because it's different in meiosis. In meiosis, also following one round of chromosome duplication and the generation of two chromatids per chromosome, this involves one round of chromosome separation. And when I say chromosome here, I'm talking about the chromosome which is at this point composed of two chromatids. In this case the homologs do pay attention to one another and they separate from one another. Followed by one round of chromatid separation. Which is very similar to what happens over here. OK? So the way you go from having 46 chromosomes to 23 chromosomes is you go through one round of duplication but two rounds of separation. The way you maintain 46 chromosomes in mitosis is to go through one

duplication but two rounds of separation. The way you maintain 46 chromosomes in mitosis is to go through one round of duplication and only one round of separation. Make sense? OK. So let's look at that in detail. And I won't draw these pictures on the board for you because, actually, I want to review it in writing one more time. I'm not going to draw the details of meiosis for you on the board because it just takes too long, and the book does a perfectly good job diagramming it for you. And I'll show you those diagrams in a second. The terms that we use in meiosis are the same terms that we use in mitosis. But there are two rounds, as I mentioned, and they're broken down by meiosis one and meiosis two. In meiosis one you have a prophase, and it's called prophase one. You have a prometaphase, prometaphase one. A metaphase where the chromosomes align on the metaphase plate. And anaphase where the chromosomes get pulled apart by the mitotic spindle, actually, in this case the meiotic spindle. And finally a telophase where they get pulled all the way to the poles. And then there's a second round, meiosis two, where the same terms are applied but they're denoted with twos. So there's a second phase of prophase, of prometaphase, metaphase, anaphase and telophase. And this is where the chromatids align on the chromosome plate and get separated. OK? Now, there's a very key event, and I'm going to draw it for you because it's so important, that takes place during prophase of meiosis one. And this is the distinguishing feature between meiosis and mitosis. As I said in mitosis, the homologs, the two copies of chromosome one, the maternal one and the paternal one for example ignore one another. That's not true in mitosis, in meiosis. In meiosis they bind to one another. So imagine again our, I think I called this the paternal copy of chromosome whatever, one previously. It had four genes that we showed previously. It's represented as two chromatids, which are associated at the centromere. And then you have another homolog, the maternal homolog. It likewise has the same four genes. It's been duplicated so it's represented as two chromatids held together at the centromere. In prophase of meiosis one, these homologs pair. And it's the pairing of the homologs that allows the two to separate faithfully during meiosis one. They also interact in an interesting way that we'll come to in a moment. They don't just pair. They actually undergo interactions between each other which allows them to exchange sequences which is critical for generating diversity amongst our chromosomes. So now I'm going to take you through these steps as shown in your book. This is figure 9.14 in your book. We're going to go through meiosis one first. So in prophase of meiosis one, we've undergone chromosome duplication already into the chromatids. Now the chromosomes are going to condense, and you can see that here. And importantly during prophase the two chromosomes, represented by the four chromatids align. In this picture you're seeing two different chromosomes, a larger one and a smaller one. And you can see that the maternal and paternal copies have paired with one another. OK? So we get pairs of homologs. Still later in prophase they interact in this other fashion that I just alluded to where they actually exchange information. They exchange genetic information. And we'll go through this in a little bit more detail in a bit. At metaphase of meiosis one, metaphase one, the homologs line up on the metaphase plate with one homolog to the left, the other homolog to the right, one homolog to the left, the other homolog to the right. This is one of two possible configurations that could take place here. In fact, in another cell undergoing metaphase one, the red one might be on the left, the blue one on the right, but here the blue one might be one the left, the red one might be on the right. And that's important. You'll see why later. So the homologs line up along the metaphase plate. And now during anaphase one the homologs separate from one another. The two chromatids of each homolog separate from one another, and that's completed in telophase. Now, without an intervening round of DNA duplication, this does not involve another round of S phase, we go straight into meiosis two where again the DNA condenses, a mitotic spindle is built. And now, just like in mitosis, the two chromatids line up along the metaphase plate with one chromatid to the top, the other chromatid to the bottom, one chromatid to the top, the other to the bottom. And then they get separated during anaphase and telophase of meiosis two. The end product of that are germ cells which are now haploid. They have only one copy of each of the chromosomes, one of the big ones and one of the small ones. So that's how you go from a cell that has two copies of each to a cell that has one copy of each. One round of DNA duplication, two rounds of chromosome or chromatid separation. Now, importantly you'll see if you can squint a little bit, that the chromosomes that come out of this process of meiosis don't always look, in fact, never look like the chromosomes that come in. They undergo this process of exchange of genetic information. This process of exchange of genetic information is called meiotic recombination. And I'll show it to you in a figure in a second. But it generates first recombinant chromatids, chromatids that look different from the chromatids that were generated initially. That's why they're called recombinant. And these, when resolved during meiosis two, generate recombinant chromosomes. So, again, if we imagine our two homologs of a given chromosome with the four genes that we talked about previously lined up along the length of those chromosomes, during this process of meiotic recombination -- -- new versions of the chromosomes are produced. We can generate a chromosome which has a little bit of Dad's DNA and a little bit of Mom's DNA. A chromosome that was generated specifically in you. It's your unique contribution to the offspring. It's not solely what you got from Mom or Dad. It's your unique version of that chromosome that's a hybrid between what you got from Mom and what you go from Dad. And this process of meiotic recombination allows for the increased diversity in the population. You don't just pass on what you inherited. You actually mix it up a little bit and pass on new combinations of the alleles that you got from your parents. So this is shown in greater detail here. And, again, gone through in much detail in your book. This is figure 9. 6. Here we are in prophase of meiosis one. The homologs have paired and they've undergone a genetic interaction. The DNA of the paternal and the maternal chromatids have literally exchanged information. That's what this crossover is called. It's referred to as a chiasma. And you can literally see it in the electron microscope. When this gets resolved, like a cut and paste reaction. When this gets resolved, you generate new chromatids. This chromatid has mostly red sequence but a little bit of blue sequence. And this chromatid has mostly blue sequence and a little bit of red sequence. If you think about that with respect to genes in our analogy over here, the red chromosome had alleles that we'll refer to as the white versions of gene one, two, three and four. The blue homolog had the black versions of genes one, two, three and four. The products of this reaction include chromatids that look just like the parental ones, a red chromosome with white one, two, three and four, a black chromosome with, a blue chromosome with black one, two, three and four, but also new

chromatids that didn't exist previously, a red one with white one, two, three but a black four, and a blue one with black one two and three and a white four. New versions of the chromosomes. And this is important. It's important for you to understand how genetics works, but it's also important for the species to generate increased diversity which when acted upon by natural selection forces might select out more fit organisms. So that is mitosis, meiosis and meiotic recombination. And we'll be drawing on your knowledge of meiosis and mitotic recombination to understand the principles of genetics. And that will be the next topic that we turn to. Before I do so I want to just mention that this process of meiosis doesn't always work perfectly. No biological system works perfectly. There's always some error rate. And that's true in meiosis in germ cell development, although it's supposed to be the case that during metaphase one the homologs, which are paired together, separate to the two daughters. That doesn't always happen. Occasionally errors take place such that one daughter gets nothing and the other daughter gets both copies. This is a problem because now when these guys go through meiosis two they have two copies of a given chromosome instead of just one. And if those germ cells, in this case they're eggs, and that's usually the problem in humans where it occurs, if those eggs get fused by a sperm that carries its own copy of that chromosome the zygote, instead of having just two copies, has three. And this is a situation called trisomy, an extra copy of a given chromosome. The opposite can happen as well. This guy, this egg, if it were to be fertilized would have only a single copy of that given chromosome. That would be monosomy, single instead of two. This does happen during human development. In the vast majority of cases when it happens it's incompatible with early development and the fetus aborts. There are a few examples where the fetus can actually make it quite late in gestation and even be born but then doesn't thrive thereafter. But there's one example where the fetus comes to term, is born and the individual can survive, and that's chromosome 21 trisomy or Down syndrome. This happens when during meiosis one nondisjunction takes place such that two copies of chromosome 21 wind up in an egg. Sperm comes along and delivers another copy of chromosome 21. Now that zygote is trisomic for chromosome 21. And you can see the karyotype here. Everything else is diploid but this has three copies of chromosome 21. And this leads to a characteristic defect in development which results in an individual with very characteristic features. And this extra copy of 21 is responsible for this too much gene product from the genes on chromosome 21. And I don't remember how many there are. There are 600 or so genes on chromosome 21. Having too much of some or some of them, some combination of them, too much product from those leads to defects in development, which results in this very clear phenotype. So meiosis usually insures that you get just one copy of each chromosomes, but it doesn't always work. And this can be one consequence. OK. Let's take a breath and change gears. So we're going to move now from mitosis and meiosis to genetics and genetic principles, and specifically Mendelian genetics. So what we want to now begin to understand is besides the mechanics, what are the consequences? What happens when you inherit alleles of given genes? What is the effect of the inheritance of those alleles and what are the principles that guide that? Why is it that when a child is born of two blue-eyed people that child has blue eyes? When a child is born of a brown-eyed person and blue-eyes person that child is likely to have brown eyes, but not always. Maybe they'd have blue eyes. What governs the presentation of a given trait based on the genes that that individual inherits? Or more precisely the alleles of the genes that individual inherits. You might actually be able to see that the murderer can be seen in the reflection of this person's eye right here. You've got to look carefully. We can learn a lot about this by looking at inheritance patterns in humans. And that's increasingly powerful given our knowledge of the human genome today. There's a lot more we can do in human genetics today than we could have done ten years ago. But the field has actually been brought along to this point using genetics in model organisms. And this is a fly, a fruit fly, drosophila melanogaster, a major genetic organism in biology. And you can see again that you can isolate flies with different colored eyes, red eyes, white eyes, dark eyes. And you can understand the principles of genetics by crossing, mating flies together and looking at what happens in the eye color of the offspring of flies that start off with a given eye color. Now, the principles that guide us in our thinking about genetics derive from this individual here whose name is Gregor Mendel. And the principles that he laid down are referred to as Mendelian inheritance. And he, through work that I'll briefly summarize, developed certain laws of inheritance which turned out to be true. And we use them even now as we think about how genes and alleles get passed on through the generations. Mendel lived in the 1800s. He did his work around 1850s, 1860s. His organism was the pea plant and the peas that give rise to the pea plant. And he spent a lot of time observing peas and pea plants, breading or crossing pea plants together, looking at the products of those crosses and coming up with these theories. He published a paper on that work in, I think, 1865, and it was roundly ignored. Nobody paid any attention. I should have mentioned that he was an Austrian monk. He lived up in the hills in Austria and did his work largely in seclusion. But he did, in fact, publish a paper in 1865 reporting his principles of inheritance. And he was largely ignored until about 50 years later when other workers started to do similar things and basically rediscovered these principles that he had laid down so many years before. And we now give him credit for coming up with these principles in the first place. So Mendel focused on traits, traits that he could observe in the pea plant or in the peas themselves. And this is an example of the traits that he might look at. You may know that peas can come in different shapes and textures. There are peas that are smooth. There are peas that are wrinkled. And Mendel wondered what controlled whether a pea was smooth or wrinkled. If you crossed a pea plant that would have produced smooth peas with a pea plant that would have produced wrinkled peas, do you get smooth or wrinkled peas? The principles that guided the thinking previously were that this was some sort of a mixture. If you had one type and another type, the offspring would have some intermediate type. There was sort of a mixing of genetic information, not really referred to as genetic information at the time, but heritable information. And Mendel wondered whether that was true. And then he actually determined that for most things that was not true. One type determined the appearance of the trait in the offspring. In order for you to understand what Mendel did, you have to understand a little bit about pea plants and peas. One thing you need to know is that peas are the embryo. They are the product of fertilization. And when you plant a pea it will develop into a pea plant. And you can score traits either in the pea itself, in the embryo, smooth,

plant a pea it will develop into a pea plant. And you can score traits either in the pea itself, in the embryo, smooth, wrinkled, dark green, light green, or in the pea plant that results from that pea. Does it have red flowers or white flowers or pink flowers? And importantly you also can fertilize one pea plant from another. You can take the germ cells, the male germ cells or male gametes from one pea plant, and purposely fertilize a female gamete of another pea plant. You can carry out these very precise crosses. Or you can do it within the same pea plant. You can take the male germ cells or gametes and fertilize the female gametes from that same plant, so-called self-pollination. OK? And through this methodology, Mendel was able to very precisely control what the pea plants looked like and how he could manipulate them. Through this process of self-pollination, Mendel was able to generate what he called Ã¬pure breading strainsÃ®. That is they always produced the same trait. If you cross them together, if you fertilize, self-fertilize them, you always got the same result, always smooth peas or always wrinkled peas or always red flowers or always white flowers. They were pure. There wasn't any heterogeneity. And we're going to refer to these in our discussion as parental strains. And kind of an example of a question that Mendel would want to know is if you took two parental strains and he crossed pollinated from one that always produced smooth peas, and here we're talking about this X represents crossing fertilization, with a plant that always produced wrinkled peas, what did the offspring look like? What did the pea look like in the product of that cross? These parental strains are referred to as P. The product of a cross between two parental strains is called the F1 or first filial generation. And the question Mendel wanted to know was what is the P type in the F1? The answer turns out, for this particular example, to be smooth peas. And the question is why? Based on this kind of observation, Mendel generated a hypothesis. He suggested that traits in the peas, as well as in the subsequent plants, arise from the inheritance of two units. These units we would think of now as two alleles of a given gene. He wasn't thinking of genes or alleles. He was just thinking of what number of things was contributing to this particular trait. And that these two units were delivered to the embryo from each parent. And importantly the parent then has two units so that each parent delivers one of its two alleles to the offspring via the production of germ cells. So everybody has two. They pass on one of those two to their germ cells. And then the embryo is the product of two germ cells coming together generating, once again, something with two units. OK? So let's think about this with respect to pea plants, and specifically the shape of the peas. So the trait that we're interested in is smooth or wrinkled peas. The gene, in our language, is the S gene. It is going to determine whether or not the pea is smooth or wrinkled. And this gene comes in two varieties, two alleles. One is called big S and the other is called little S. In the cross that was done, the plant that always generated smooth peas, which was a pure breeding strain, had the same allele in both copies. It was diploid for the big S allele. Both of its chromosomes that carry the S gene had the big S version of that gene. And the wrinkled plant, the plant that produced wrinkled peas carried two copies of the other allele, little S. These plants produced smooth peas. These plants produced wrinkled peas. When these plants produced germ cells, what allele of this gene gets put into those germ cells? Big S. It's the only one there. So when these plants undergo meiosis they're going to produce germ cells that carry in them the big S gene. When these plants undergo meiosis what allele of the S gene did they put in their germ cells? Little S. These haploid germ cells have the little S gene. Now, when I cross, I take one of these germ cells, mix it with one of those germ cells in the cross, what gene, what genes, what alleles does that offspring inherit? It gets a big S from here and it gets a little S from here. OK? And what do I observe when I make an organism, a pea, that looks like that? What does the trait look like? It's smooth. OK. Now, I've drawn details without given you some of the relevant nomenclature. The parental strain over here had big S, big S. We call that the genotype. A genotype refers to which alleles you have; your genotype. The genotype of the other parental strain is S, S. And the genotype of the offspring is big S, little S. That's the genotype. If you have two of the same alleles it is called being homozygous. This also has two of the same alleles so it is also homozygous for the other allele but still homozygous. If you have one allele of one type and the other allele you are called heterozygous. OK. So that's some relevant terminology. Now, in contrast to the genotype, we also refer to the phenotype. And the phenotype refers to the manifestation of the trait. What you look like. Regardless of what the gene combination or allele combination you have, what do you actually look like? So what is the phenotype of these peas? Smooth. And what is the phenotype of these peas? They're wrinkled. And what is the phenotype of these peas? They're smooth. Based on the patterns that he observed when he crossed two pure breading strains and generated offspring that resembled one of the two pure breading strains, Mendel suggested that in this particular cross the big S unit, we would call it allele, is dominant over little S. If you have a big S allele, regardless of what you have as the other allele, you're going to have the big S trait which is smooth. Big S is dominant over little S. And a related term, little S is recessive to big S. The only way you observe the phenotype associated with the little S allele is if you're homozygous for the little S. If you're heterozygous, as in the case in the middle, you manifest the phenotype associated with the other allele. Dominance and recessive. OK. Now, based on these ideas of inheritance of a single unit or allele from the parents who carry two and the concept of dominance and recessiveness, you can come up with methods for determining the frequency of observing genotypes and phenotypes in crosses such as this. So I want to consider now not a parental cross giving rise to an F1, but rather a cross between F1. We call this a hybrid cross. And because we're focusing on one gene we actually call it a monohybrid cross. The genotypes of the plants that we're going to start with in the F1 generation are as we described previously. They're heterozygous big S, little S. And that's true for one plant and the other. They're both F1s. They're both heterozygous for big S, little S. If we now cross these together, we can think about what germ cells these plants produce. So what are the four products of meiosis look like from this? What do you get in the meiotic products starting with these genotypes? Two of them get big S, two of them get little S. And likewise over here. Two of the germ cells get big S, two of the germ cells get little S. Therefore, half of the germ cells are big S, half are little S. If I think about the frequency of big S germ cells it's one-half. If I think of the frequency of little S germ cells it's one-half. And likewise over here, half of the germ cells are big S, half of the germ cells are little S. Based on this idea I can generate a grid -- -- which will allow me to calculate the frequency of offspring that have four different combinations. If this germ cell combines with this germ cell I'll be big S, big S. If this germ cell combines with this germ cell the genotype will be big S, little S. If this germ cell combines with this

this germ cell combines with this germ cell the genotype will be big S, little S. If this germ cell combines with this germ cell the genotype will be little S, little S. And if this germ cell combines with this germ cell the genotype will be big S, little S. This box, which is a useful device for calculating the frequency of the genotypes that you observe in different crosses, is referred to as a Punnett Square. So let's think about what the numbers would be in such a monohybrid cross. There are three possible genotypes. If you look at the Punnett Square there are three possible genotypes. You can be homozygous big S, big S. You can be homozygous little S, little S. Or you can be heterozygous big S, little S. Those are the three possible genotypes from a cross such as this. The ratio of those genotypes, if you look in the Punnett Square is there is one of these for every one of these and two of these. The ratio of the three genotypes is 1:2:1 as determined by this kind of calculation. The reason that you get that ratio is that a quarter of these, sorry. Half of these germ cells are big S, half of these germ cells are big S, so a quarter plus, times a quarter, sorry, sorry, sorry, I said that wrong. Half of these germ cells are big S. Half of those germ cells are big S. So a half times a half is a quarter. Half of these germ cells are little S. Half of these germ cells are little S. The probability of getting one of each is a half times a half or a quarter. For big S, little S you can do it two different ways, so it's a quarter plus a quarter or a half. The ratio of these fractions is 1:2:1 which determines the products that you see. Now, before I let you go, I want you think about the phenotypes. The phenotypes that you observe in these peas is smooth, in these peas is smooth and in these peas wrinkled. So the ratio of phenotypes is 2:1. You'll need to think about why those, sorry, sorry, two plus one is three, 3:1. You'll need to think about why those principles give rise to these calculations and these frequencies.