ERIC LANDER: Let's talk about what Mendel really did in his experiments. So section one, Mendel's experiments. Mendel did a lot of really cool things. The first thing he did was, in order to study heredity, that was his assignment as a monk-- go study heredity-- he had to get some material to work with. He decided to use peas. Why peas?

Well, there are a lot of varieties of peas in the market, many different kinds of peas. And you could breed them together. There were tall peas, short peas, green peas, yellow peas, round peas, wrinkled peas, all kinds of peas that you could find in the market. They grew very well in the garden. And when you're done with the experiment, you could feed them to the monks.

So the first thing he did was he got his material. And did he immediately start crossing his peas together? No. What did he do?

AUDIENCE: [INAUDIBLE].

ERIC LANDER: Sorry?

AUDIENCE: He grew them separately.

ERIC LANDER: He first grew them separately. Because he wanted to see if he was going to study how traits were inherited, he first had to do the control experiment. He first had to show that if he took each variety of peas, they would breed true.

So the first thing is, Mendel did controls. That's an important thing we learned from Mendel. He took round peas. He took wrinkled peas. And he bred them with themselves. And they always came out round. And he took wrinkled peas and he bred them with themselves. And they came out wrinkled. And if they hadn't always come out round or hadn't always come out wrinkled, it would've been a much

harder experiment to interpret later. So that was incredibly important thing to do, was do the controls, round and wrinkled.

Then, when he was satisfied that he had pure breeding or true breeding plants, then and only then did he do an experiment. What experiment did he do? You all know Mendel. The truth is, this is not like a surprise here. So what did he do?

He crossed the round and the wrinkled. I'm trying to draw out the new things here, but some of the old ones you know. And when he crossed round and wrinkled-- We'll call this the F 0 generation. In the F 1 generation, what did he see? Round. You all know this. He saw all round. He didn't see puckered, slightly puckered or anything like that. He didn't see any wrinkles. They were all every bit as round as the rounds in the parental generation.

That was an extremely important point, because of course, a competing theory of inheritance was blending inheritance, where the offspring would be intermediates. And the truth is almost every experiment that you do when you take plants and you cross them, or animals and you cross them, despite your biology textbook, shows blending inheritance. A tall plant and a short plant, you breed them. Almost always is a middle plant.

But not for the peas. The peas were a beautiful system. And Mendel very lucky to have chosen it, because truth is, there was only one gene difference that was controlling these traits. If there'd been 10 genes controlling this, you'd get some blending, blah, blah, blah. But Mendel got a situation with really clean experimental data. The round was every bit as round. And so that said, no blending. Now what did he do?

Next, what Mendel does is he crosses these round peas to themselves. He selfs them. So we're going to self the peas. The peas can be selfed. They have both male and female reproductive parts. And when he selfs them, they self pollinate. And what do they produce? Peas. That's good. They produce peas.

And what does he notice? He notices that now they're not all round. Some of them

are wrinkled. And the wrinkleds are every bit as wrinkled as the wrinkleds were in the parental generation F 0. And the round were every bit as round. So suddenly wrinkled had gone away.

And what had happened? Sorry. Wrinkled had gone away in this generation. And now it had reappeared. The trait reappears. It's quantal. It's discrete. It's not blended out in any way. It's not blended. It's not imperfect. It's the same wrinkled that was there before. That's a big qualitative observation. This whole blending notion can't be right, at least for this experiment. Discreteness rules.

So that was his experiment. Mendel could've written it up and said, wow, the traits don't blend. They're discrete. But Mendel, being an MIT kind of monk, went further. What did he do? Sorry?

AUDIENCE: He repeated it.

ERIC LANDER: He repeated it. And it still showed some rounds and wrinkleds and all that. But he was a very quantitative MIT monk. He counted them, which seems obvious, but ain't so obvious. He counted them. And what did he find? A fixed proportion? What?

AUDIENCE: A ratio.

ERIC LANDER: A ratio.

AUDIENCE: Wasn't there 1:3?

ERIC LANDER: 1:3 or 3:1 or something like that? No. No. Nope. No, he counted. He counted. And what he found was rounds: 5,474. Wrinkleds: 1,850. Ratio, not 3:1 at all. 2.96:1. No, no, no. But you see, you say because your books all tell you 3:1, that it's obvious if you do that, you say, that must be 3:1. It not must be 3:1. It's 2.96:1. And if you do it again, you might get 2.87:1.

And it actually takes quite an imagination to say, it's trying to be 3. Just think about it. You come to this experiment and you say, it's trying to be 3. That's a separate leap and an important leap.

He counted. And he got numbers, 2.96:1. And he got other numbers. He then, as you've done so quickly, made a hypothesis. That hypothesis was that, in fact, this was trying to be 3:1, that it quote "wanted to be 3:1." It was near 3:1. And that really the reason it was trying to be 3:1 was because-- Well, there was a pretty nice explanation here.

His cool explanation was, the round plants and the wrinkled plants, well he made up a model. These guys had two particles of inheritance, big R big R, little r little r. When you cross them together, these guys were big R, little r. And when you self them, if you randomly chose one particle from the sperm and one particle from the egg, ovule, you would have big R, big R, big R, little r, little r, big R, and little r, little r, all as possibilities.

And that these guys, big R, big R, they would be round. Why would they be round? Well because that's what the parental generation here was. The little r little r, they would be wrinkled. Because that's the parental generation there. And these guys that have one of each, what would they be? Round, because we saw that in the F1 generation, one of each makes it round. So we had a model, a hypothesis, a model. Pretty cool.

You can come up with this model by saying, the contribution from the male, the contribution from the female, this is the male gametes, the female gametes. You get this nice little thing sometimes referred to as a Punnett square. Although he didn't use Punnett squares. And Punnett wasn't born yet.

Now what do you do? Mendel went out and got experimental material. He did controls. He did an experiment. He counted. He then made this creative leap to say, I see something cool going on. Integers are what's going on. And made up a model. What does a scientist do at that point? Sorry? Oh come on. In this modern world, if you got a result this cool, what would you be doing? Sorry?

AUDIENCE: Publish it.

ERIC LANDER: Publish it right? You're going to get out there quickly and publish it. Mendel whips off

an email to *Nature* in London, saying-- Or whatever the 1865 emails. Actually it wasn't *Nature*. It gets published in the *Proceedings of the Royal Society of Brun.* But forgive me. I'll use *Nature*, OK.

So he whips off an email to *Nature*, which is what we do today, telling the editor, we have this really cool result. I think it'll be of broad interest to the readers of *Nature.* We're going to try to send you a paper next week, et cetera, et cetera. Are you interested? They write back, oh yeah. We'd love to see your paper Gregor. And Mendel whips together a paper.

What happens when Mendel whips together this paper and it goes off to London, to *Nature*, the offices of *Nature*? What does *Nature* do with it? They just set it and type and say, here it is? What's the scientific process? Peer review.

Before you go print this thing, you've got to send it out to some other scientists as anonymous reviewers and say, we've received this paper, this correspondence from Brother Mendel in Moravia. Would you review it for the journal *Nature* and tell us your candid opinion? And they write it up. And they send it back to *Nature*. And *Nature* makes a decision whether to publish the paper. So you're the reviewers. Should we publish Mendel's paper? Who says yes? Who says no? Why no?

AUDIENCE: He needs more examples.

ERIC LANDER: Needs more examples. So you're right. One lousy trait. Mendel actually had seven traits in the paper. It turns out I didn't tell you them all, green and yellow, and tall and short. And they're all in the paper. He actually has seven separate examples that show the same thing.

Should we publish it? Why not? It's just peas. Oh boy, you're churlish there. I mean, come on. It's peas. People eat a lot of peas. It's a result. It'll get others in the scientific community interested.

AUDIENCE: Who are the peer reviewers?

ERIC LANDER: You. I've assigned you as peer reviewers. I'm asking you, should we publish this

thing? We got seven traits we're going to publish. And it's pretty cool. Nobody's ever reported this 3:1 ratio in this model.

AUDIENCE: That's true. But I wasn't the peer reviewer back then.

ERIC LANDER: You are now.

AUDIENCE: Then yes, I would publish it.

ERIC LANDER: You'd publish it. OK. He'd publish it. Because nobody's reported this. It's pretty cool. The model perfectly fits the data. Yes.

AUDIENCE: It's got to make predictions.

ERIC LANDER: It's going to make predictions. But the model fits the data.

AUDIENCE: The model needs to make predictions [INAUDIBLE] data.

ERIC LANDER: Are you saying that we made up the model after we saw the data? And that it's not a surprise that the model fits the data? Yeah, that's right, isn't it. That's a real problem. If you make up models after they fit the data, they tend to fit the data. Well they do. That's a real problem.

So the reviewers write back to Mendel and say, Mendel-- this isn't actually how it happened, you understand. But anyway, they write back to Mendel. They write back to the journal *Nature*. And they anonymously say, we would like to see some predictions of this model to see if this is really true. And *Nature* writes back to Mendel. And the email says, could you just show us some predictions from this?

So to help Mendel out, what predictions can we make? What surprising predictions could you make for Mendel's experiment? Well, this experiment, round by wrinkled, gives round, gives some rounds and some wrinkles, which we think are big R, big R, big R, little r little r, big R, little r, little r. And that this is big R, big R. How could we prove something's going on in this generation?

AUDIENCE: Self them.

ERIC LANDER: Self them. If we pick out a round and self it, what's going to happen? Sorry?

AUDIENCE: It depends on which round.

ERIC LANDER: So how do I know which round to pick. They all look the same.

AUDIENCE: You just try all of them.

ERIC LANDER: Try all of them. If I try to all of them, what am I going to see?

AUDIENCE: You'll see some that only produce rounds.

ERIC LANDER: Produce rounds. About what fraction of them will only produce rounds? 1/3. And what fraction will produce rounds and wrinkleds?

AUDIENCE: 2/3.

ERIC LANDER: 2/3. We have a prediction. Thank you. The prediction is, test the rounds. And although we don't know which are which, 1/3 of them will give rise to only rounds, whereas 2/3 of them will give rise to our 3:1 ratio. That is a non-obvious prediction. If this model weren't right, it's very surprising if you would have nailed that prediction. Nice. What other predictions can you make? What other crosses could you set up to test it?

AUDIENCE: Wrinkleds by wrinkleds.

ERIC LANDER: The wrinkleds by themselves will only give wrinkles. And that's true. Bingo. So we're doing well. What else?

AUDIENCE: Wrinkleds with rounds.

ERIC LANDER: Wrinkleds with rounds. So I could take these three rounds here and I can cross them to wrinkleds. What'll happen here? If this was rounds, rounds over wrinkled, wrinkled, it's going to give rise to what?

AUDIENCE: Rounds.

ERIC LANDER: All rounds. But if this is round wrinkled, what would it give rise to?

AUDIENCE: Half and half.

ERIC LANDER: 50:50. Half and half. Now we're cooking. There are all these predictions that start dropping out, because your model tells you things you haven't yet seen. Mendel writes back and says, I did all the experiments. I did what the referees requested.

The referees get the paper back. They say, yes indeed, Mendel's done the experiments. We recommend publication. *Nature* publishes it. They put out a press release and all that. Mendel's on the evening news, that kind of thing. It didn't really happen that way exactly. But anyway, you get the point.

That's the process of doing science. It's a cool process. And it's a back and forth. And it's a process of convincing people, and you convince them by predictions. And you can think of the kinds of cool predictions you could make. And that's what's fun about working in a lab, is making those kind of predictions.

Now all right. I need to give you a few definitions. A gene. When I refer to a gene for the moment, I mean a discrete factor of inheritance, discrete particle, factor of inheritance, something like that. Because geneticists early on had no idea what genes were. You know perfectly well a gene is a DNA sequence, blah blah blah blah. But it's useful to be able to think about a gene in the abstract. It's the thing that controls a particular inheritance of a particular trait.

Variant forms of a gene, alternative forms of a gene, are called alleles. When I write big R, little r, they are alleles of the gene for roundness. Allele, from the Greek meaning other or alternative. When I write genotype, I mean the combination of alleles that an individual has. Like when I write big R, big R, that's a genotype. Or big R, little r, or little r, little r, that's a genotype.

When I say the word phenotype, what do I mean? A trait, an appearance. What are the traits under discussion here? Round and wrinkled. Geneticists are like mathematicians. They're very precise about their words.

Now comes the ones that people always have trouble with, dominant and recessive.

Phenotype 1 is dominant to phenotype 2 if the-- Oops, sorry. I meant to add two words here. Heterozygote, homozygote, words you know as well. Heterozygote, having different alleles. Homozygote, having the same alleles. Different, same alleles. So a phenotype, phenotype 1 is dominant to phenotype 2 if the F1 heterozygote, the cross between them, has phenotype 1.

Why did I write this in this wacky mathematical way? That says round is dominant to wrinkled if when I cross round to wrinkled, the offspring are round. So which is dominant, round or wrinkled? Which is dominant, big R, or little r?

No. Big R is an allele. We said phenotypes are dominant, not alleles. We don't say big R is dominant to little r. We say round is dominant to wrinkled.

Now this will bother you greatly. And it will bother about 95% of my biology colleagues. But geneticists who are careful use the word dominant and recessive to refer to phenotypes, not alleles. Why do I care? I care because big R, as a molecular allele, as a variant of a gene, might end up controlling three or five different traits. Some of the traits that big R controls could be dominant. Some of them could be recessive.

Sickle cell anemia, there's a sickle cell mutation. Is that recessive or dominant? Sickle cell anemia is a recessive trait, a recessive phenotype. But sickle cell trait, the tendency for blood cells to sickle at low oxygen tension, is a dominant phenotype. The allele that causes sickle cell anemia causes a recessive trait, anemia, and a dominant trait that can be measured in heterzygotes.

You'll forget this. Everyone will forget this. But I've at least told you once that alleles could control multiple phenotypes and do control multiple phenotypes. And that's why geneticists obsess about using the words recessive and dominant to refer to the phenotype, not the genotype. I've made my plea.

Like all of my colleagues in the biology department, you will continue to misuse the word. But there's a better chance you'll get it right because I've made my little stand here. Recessive is the opposite of this. Good. This is mostly to say, geneticists try to

think carefully about their words. Those are the definitions. You should be able to use the words gene, allele, genotype, heterzygote, homozygote, phenotype, dominant, recessive in a good way.