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Good morning. Good morning. Yes. So I want to pick up where we were last time. We talked last time about Mendel's elegant experimental design. And not just elegant but very careful, too, in having organisms that bred true.

And a lot of work went into that. We talked about his observations and his really great choice to count. We talked about his ability to look at numbers that were approximate and somehow intuit what was interesting about them. Namely, he had to take rough numbers and say, hmm, I think this is a 3:1 ratio, although that was an abstraction, but a very good one on his part. And it's hard to know when to make those leaps and when you're kidding yourself, but Mendel got a lot of data. I didn't mention that he worked on not just round and wrinkled, but he worked on seven different traits across pea plants.

All seven showed these very consistent properties.

There was a recessive and a dominant phenotype and then a first-generation. The dominant phenotype by definition was evident in full force.

And in the second-generation we saw 3:1 segregation.

He felt pretty good about that. He made other predictions based on this. And he was able to put together a very coherent story.

And, as I also explained last time, it sunk like a stone because it was an utterly abstract story, the idea that there were these particles of inheritance, factors of inheritance. You couldn't put your finger on them, and people hate stuff you cannot put your finger on. They say it's just a model.

Well, as I mentioned last time, the discovery of chromosomes in cells really laid the foundation for the beginning of a rebirth of interest in Mendelism, in Mendel's ideas. And the interesting part of that characterization of chromosomes was the choreography that we talked about last time.

That normally in cells undergoing mitosis, normal mitotic division to make more and more cells, when you stained the cells and looked at them before they went into mitosis you saw these X-like structures. However many there were, they lined up along the midline of the cell. They appeared then to sometimes you could even see them kind of attached to something pulling them back.

And they would pull back to make two cells each of which had half of the X. Somebody asked last time, I drew four chromosomes, was that because cells have four chromosomes?

And the answer was no. It's because I had room to draw four chromosomes in that cell. And so this time I drew six chromosomes to indicate that you can have different numbers of chromosomes. They are usually, but I should

note not always, an even number of chromosomes in higher organisms. But anyway.

So I drew six this time. And what's interesting was this meiosis. The generation of sperm and eggs, for example, in animals, they are the chromosomes lined up with a different choreography. They lined up in pairs. And where you could see differences in the shapes of chromosomes, like maybe the little crossing point was lowered down or the chromosomes were shorter in length, there would appear to find their own partner, the one that had the same basic shape. And they would line up in pairs. And then they would undergo a series of two divisions, a meiotic one division, meiosis one and a second division, meiosis two.

And in meiosis one you would get one copy of each pair.

Then it would undergo a second round of division that looked very much like mitosis where these X structures would be split into two pieces. The notion then that pairs would go to singletons and then upon fertilization singletons would come together to reconstitute a pair really did fit Mendel. And thus was born the Chromosomal Theory of Inheritance. So, whoops, the Chromosomal Theory of Inheritance. Are you overwhelmed by the Chromosomal Theory of Inheritance? Have I given you overwhelming evidence to believe it? No. How come?

It seems natural to you now.

But, I mean, you know, the only evidence is that there's something else that has got pairs in cells, right? What's to say that some other thing that pairs up in cells actually is the carrier of genes?

The Chromosomal Theory of Inheritance is that Mendel's abstract factors, genes live on these chromosomes, are these chromosomes, or something like that. They're carried by these chromosomes. And simply the fact that the choreography of the chromosomes is not the same, oh, sorry, is the same as the choreography of Mendel's genes, that's correlation. In fact, it's ex post facto correlation.

I didn't have any prediction that these chromosomes would do it.

I just saw that the chromosomes did it and I said, OK, you know, that could explain Mendel's observations about genes.

And there's a world of difference between that could explain, that is consistent with the data, and that presents a compelling case that this is true. So there were some people who immediately bought into the idea of the Chromosomal Theory of Inheritance, and there were other people who remained great skeptics about this, that these chromosomes were themselves quite irrelevant to inheritance. And indeed many people who, at this point, the early 20th century, felt that the whole business of genes was still not such an overwhelming idea anyway.

And trying to unit these two was going a bit far out.

So now I have to bring you back to some of the things that we left unresolved last time, which is Mendel's Second Law of Inheritance. Because if we're really going to start building a case that chromosomes really do carry genes then we better get some serious consistency with much more complex aspects of the theory or we better look for some contradictions. So you recall, and I mentioned, that Mendel studies seven different traits.

Two of them, roundness and greenness, both dominant phenotypes underlain by these hypothetical genes, big R, big R, big G, big G, and the recessive traits associated with these same genes, wrinkled and yellow, little R, little R, little G, little G. When you make a first-generation cross what do you get? Sorry? You get round and green phenotypically. And genotypically what are they?

Big R, little R, big G, little G, right? That would be the genotype.

These organisms would be heterozygotes.

In fact, they would be double heterozygotes.

They'd be a heterozygote for the gene that controls shape and they'd be heterozygous for the gene that controls seed color.

OK? Now, suppose we do a cross back to RRGG, the parent that has the recessive phenotype for both of these traits.

We're practicing our words here, right? What will this parent, the second parent contribute in its gametes? What will the gametes from that parent be? Little R, little G.

They have to be little R, little G because that's all it's got to offer. So little R, little G.

OK? What will this parent contribute? It could give a big R, big G. Could give a little R, little G. Could give, in principle, a little R, big G or a big R, little G.

In theory any of those are possible. And what's the ratio that Mendel reports? 1:1:1:1, so equal.

That's right. 1:1:1:1. That's the independent assortment of traits. That's what he calls this. Independent assortment of traits.

That is to say the inheritance of round and the inheritance of green are uncorrelated to each other, right?

Knowing which one you got for roundness, which one you got for greenness, they don't convey any information

about each other.

So how could we explain this in terms of Chromosomal Theory of Inheritance? Well, we could explain this in terms of the Chromosomal Theory of Inheritance by saying, for example, that in this heterozygous parent here big R and little r were carried on chromosomes that paired up with each other, homologous chromosomes. And big G, little g were carried on a different pair of homologous chromosomes in my meiosis picture there. OK? So if that was the case then when these chromosomes segregated in the first meiosis step, meiosis one, it might be that big R and big G were on the left side. It might be big R and little g were on the left side. It might be that little r and big G were on one side, etc. Because these are different chromosomes. They could have chosen to line up in different ways.

That's all cool. So Mendel's Law of Independent Assortment is consistent with the Chromosomal Theory, except we pointed out last time, except if big R and big G were on the same chromosome.

Then we'd have some explaining to do. So maybe Mendel was just lucky and big R and big G happened to be on different chromosomes.

But what if he takes a third trait? Well, maybe the reason he got 1:1:1:1 for those traits was it was also on a different chromosome, a fourth trait. And I said he studied how many traits?

Seven traits. If they all gave 1:1:1:1 assortment they'd all have to be on different chromosomes. How many chromosomes do peas have?

How many pairs of chromosomes do peas have? Seven.

Very interesting. He might have just gotten lucky.

In fact, he did. We know that. They are on different chromosomes.

Though, it makes you wonder whether maybe he had an eighth trait that did something funny and decided not to put it in this paper.

I don't know. It's interesting. Like I say, there's choice involved in what you want to report at what point here. So suppose we instead had big R and big G, little r and little g happen to have been on the same chromosome. Then they would have been inherited from the common parent here, say from here into the F1. The F1 would look like this. If they were on different chromosomes it would look like this. If it were from the same chromosome it would look like this. And now let's make a little scorecard of what's going to get passed onto the next generation.

We've got the possibility that it will pass on. This one could pass on. Oh, let's keep score. Big R, big G could get

passed on.

Little R, little G could get passed on. Big R, little G could be passed on. And little R, big G could be passed on.

And if they are on different chromosomes we expect a quarter, a quarter, a quarter and a quarter. But if they're on the same chromosome what do we expect? What will come out of this? Either you're going to get this, in which case you get both big R and big G, or you're going to get this one, in which case you get little R and little G, a half, a half, zero, zero. Ooh, that's very different. What is Mendel's Law of Independent Assortment say? It favors this.

But Mendel's Law of Independent Assortment cannot possibly be right if we see this. So Mendel didn't observe this.

But if we really believe this Chromosomal Theory we would expect to see it eventually. So who's going to be right, Mendel or Chromosomal Theory? You vote for both.

How many vote for Mendel? How many vote for Chromosomal Theory? How many vote for both? How can you have both? The data would be contradictory. How many vote for neither?

Hmm. OK. Fine. So we have a very different prediction.

Notice that these are the parental types of chromosomes.

They're the ones that went into the cross in the first place, big R and big G. These are the non-parental types of chromosomes.

They're the ones, they're the combinations, a big R and a big G that didn't match either of the two parents. That's a new combination.

Well, it took a while before folks sorted this out.

And it was eventually sorted out in fruit flies.

And it is, of course, the case that neither Mendel nor this strict prediction from the Chromosomal Theory turns out to be correct. Mendel's Law of Independent Assortment does not hold for all traits, but this very rigid model of two alternatives does not hold either. So let's take a look at some real data. The data comes from Thomas Hunt Morgan, a developmental biologist who eventually became one of the great geneticists of the century at Columbia. He was at Columbia University studying fruit flies. And he studies fruit flies rather than peas. Can you think of any good reasons why it would make sense to study fruit flies rather than peas? Sorry? It has four chromosomes instead of seven. No, four, seven.

Anybody been to Columbia University? I mean where are you going to plant peas, right? [LAUGHTER] I mean it's in Manhattan.

Also, what else is wrong with studying peas?

They take too long. How many generations of peas are you going to get a year in Manhattan? Not so many. Fruit flies, how long do they take? A couple weeks. You get a generation every couple weeks. If you actually want to write some papers.

I mean if you have a day job as a monk, you can do these pea things that take a long time. But, for example, if you were trying to get tenure at Columbia, you might want to actually do something that you could get a couple generations every month or something like that. So the fruit fly was much better.

They also, you know, they don't take fields and things.

You grow them in little vials with some food at the bottom, some yeast medium at the bottom and a little cotton stopper at the top.

And, you know, it's very convenient. You can grow zillions and zillions of fruit flies. So that's why the fruit fly was chosen, easy, short generation time, etc. And there are a lot of natural variations out there. Geneticists love to choose organisms that are just easy to work with so you can do a lot of work.

And fruit flies do have four chromosomes. So N equals four.

That is four pairs of chromosomes. So he set up a cross. The F_0 cross was between a normal fly. And the way we say normal in genetics is wild type. OK? Wild type. That is the type in the wild. It actually doesn't mean that it is the type in the wild.

It means it's whatever type the geneticist has chosen as his or her reference strain, but it's called wild type.

And he set up a cross between a wild type fly, by a fly that had two interesting properties. Its body was black and its wings were in bad shape, and they were called vestigial.

You know, these funny little wingy things that didn't work, hadn't grown out right, etc. So instead of the normal fly body color, which is kind of a tan around its middle, it was black all around its middle and its wings were very short. The hypothesis is that there were genes controlling. And, in fact, by demonstrating Mendelian Inheritance black was a single Mendelian trait which was recessive to the normal body color, vestigial was a single Mendelian trait which was recessive to the normal body shape.

And the genotype of wild type was homozygous normal, which I'll write as plus over plus now. Geneticists actually prefer these plus terms rather than big Rs and little Rs.

Plus over plus. And we'll take a female and we'll cross her to a male who is homozygous for the gene that controls the body color there and this gene that controls wing shape, and we'll look at the offspring. So makes F1.

The F1 have what genotype? They're plus over black, plus over vestigial F1. OK? So then what he does is he takes, say these males, and he crosses them back to these flies here that have the doubly recessive phenotype doing what we call a test cross.

That's now the name. We're beginning to introduce more of these names. A test cross, when you cross back to the homozygote for the recessive phenotype. And what he gets out, the same exact picture I drew before, but we're just getting used to nomenclature and getting used to slightly different nomenclatures here. He could either get, he always got black, vestigial, black, vestigial, black, vestigial from the parent on the right.

And here he could get plus, plus, he could get black, vestigial, he could get black, plus or he could get plus, vestigial. And, as we said over there, the predictions would be that if these were on different chromosomes he would get 25%, 25%, 25%, 25%. If they were on the same chromosome under a very simple interpretation of the Chromosomal Theory of Inheritance, he would get 50%, 50%, zero, zero.

And, in fact, what did he get? 965, 944, 206 and 185. What do you make of it? Which theory is confirmed? Neither?

Well, maybe this is just a statistical fluctuation around the first line.

You don't think so? How come? Way too wild.

But, I mean, these are wild type so maybe. [LAUGHTER] So do you think those numbers are too far off, a quarter, quarter, quarter to be believable? Ooh. Not only are they way off 25%, 25%, 25%, 25%, but something is fishy. The two parental types are much higher than the two non-parental types.

That's saying something to you. Oh, interesting.

What about this other one, 50%, 50%, zero, zero? Could this be a fluctuation around zero? No. This one is really pretty easy to reject because zero, this is not like close to zero.

This should be zero. You shouldn't see any of those, right? Because they didn't go in if they were on the same chromosome.

So what are we going to do? We're acting like Mendel, good. We're seeing something funny in the data here.

You even saw something that is beyond just, it's a little weird, but it's actually a little weird in some interesting direction.

How many of them are of the parental type?

Well, it's 965 plus 944. How many are the non-parental type?

It's 206 plus 185. So let's figure out what's the proportion, the frequency of non-parental types.

Well, it's 206 plus 185 over 206 plus 185 plus 965 plus 944, which is 17%. OK, so it's 17%.

We now know what the answer is. When you take two traits and you cross them in this fashion, two recessive traits and do a test cross, the ratio will neither be 25%, 25%, 25%, 25% or it's not going to be 50%, 50%, zero, zero. In fact, it will always be 17%.

Why not? But Mendel looks at his data, and he said 3:1.

It's trying to say 3:1. Isn't this trying to say 17%?

Yeah. Well, see, that's the thing, is what to make of this number.

What does this 17% mean? Now, of course, you all know that this is genetic recombination, right? You know that these chromosomes are exchanging material. I cannot kid you about that. But put yourself in the days of Thomas Hunt Morgan looking at these data and trying to figure out what is this 17% trying to tell him.

There were people around Columbia and elsewhere who were saying, oh, this 17% number says a lot about physiology. It's a statement about the developmental relationship of genes. And they were trying to read all sorts of things into these numbers.

The first thing is let's test some more pairs of traits.

How about another pair? If you do that, do you get 17%?

No. It turns out maybe you get 8%. You do it with another pair, maybe you get 9%. So it's not a constant. We can reject the idea that 17% is some constant like e or one over π or something like that.

But we look at these numbers, and a lot of folks wanted to interpret these as physiological numbers. Something about the biology of these traits. So -- -- we can give this thing a name, the frequency of non-parental types.

We can call this the Recombination Rate. Because we've got new combinations, right? This recombination rate might mean, and you know already that you're thinking what it really means is -- -- somehow we have black, black, plus, plus. And in the F1 we have vestigial, vestigial, plus, plus. And that somehow these two chromosomes have exchanged genetic material so that the new chromosome you get is like this. And you get a recombinant type.

You get recombination between these chromosomes. And there's a recombination rate. And the recombination rate is how often this kind of an exchange occurs. And what does the recombination rate depend on? The distance between those two genes.

You know this because you've been told this since kindergarten, right? It's in all the high school textbooks and things like or whatever. They teach genetics earlier and earlier these days and it's on TV and stuff. But that's a nice idea that the recombination rate depends on the distance. And this rate, which might be 17% or it might be 1% or it might be 8% or it might be who knows, depends on the distances, reflection of the distance.

But, golly, what's the evidence for that? Aren't we just making up a theory to explain the data here? We don't have a theory to, we're just trying to fix the Chromosomal Theory. The Chromosomal Theory wouldn't predict these recombinant types. It would have predicted we only get parental types out. So because we do get non-parental types out we say, well, chromosomes are promiscuous and they'll exchange parts. Because we don't always get the same ratio, we have to make up the fact that somehow the ratio is different because of something, distance. We cannot observe distance. No way that Morgan was able to look at the chromosome and see where the genes were. So basically any number you want to give him, he'll just say it's the distance. This is not overwhelming.

Now, what's even the evidence that chromosomes exchange material?

Why do we think stuff like that even happens?

Ah, it turns out you can take fruit fly gametes, and other gametes, and look at them in the microscope. What you do is to look at them closely, the chromosomes during meiosis. You put a cover slip on them, you squish them down, add a little dye and you look.

And it turns out that really truly, when you look in the microscope, you can see stuff like that, of chromosomes lying on top of each other like that. These are called chiasmata, crosses. Chiasma or the plural chiasmata. You can see it in the microscope. So does that convincingly demonstrate that recombination occurs? Are you overwhelmed? Why not?

Yeah. You put a bunch of chromosomes down, you put a glass cover slip and squish them. The fact that two things lie on top of each other, I mean this is what it takes to do science. Is you actually have to be pretty hardnosed about not being willing to take evidence that supports your theory just because it supports your theory.

Skepticism is pretty important here. So you squish down the cover slip and sometimes, not always, sometimes some chromosome lands on top of some other chromosome.

Big deal. So how are we going to actually get any convincing predictions? That's what it took with Mendel. What convincing predictions can we make that this recombination phenomenon has something to do with the disposition of genes along chromosomes?

And, if so, might provide some support for the Chromosomal Theory of Inheritance? Well, when you're in a quandary, you've got some new area, you've got messy data, you need new thinking.

Where do you get new thinking from? You get new thinking from students because old folks are thinking, you know, in whatever way they were thinking. So what you really need are young students to come along into the field and look at the data in some fresh way.

So, in this case, the hero was a UROP student at Columbia. They didn't call it UROP, but it was the same thing. He was a sophomore working in the lab of Thomas Hunt Morgan who came along and solved this problem very nicely. You know, I think in part because sophomores had not been polluted by all sorts of prior thinking.

So the idea of genetic maps arises through the work of one Alfred Sturtevant. Sturtevant was a sophomore at Columbia in 1911. And while an undergraduate working in the lab of Thomas Hunt Morgan, he went home, you know, he was working in the lab, and he took home a pile of data.

And he said I've got to make sense out of all this data.

I don't understand exactly what's going on.

Here's some of the data he took home. Morgan's lab had set up crosses, not just involving two traits but three traits simultaneously.

They actually set up crosses involving three traits, black, what's called cinnabar which is an eye color, and vestigial. And they looked at the F1 when crossing back to the triply homozygous fly here, and they counted the number of recombinant types of different sorts.

You could look at recombinant types between black and vestigial.

We've already got that data. You could look at recombinant types between black and cinnabar. You could look at recombinant types between cinnabar and vestigial. Now, I've drawn this as if these live on a chromosome and I know their order. You've got to remember, we don't know that they live on a chromosome. And Sturtevant certainly didn't know their order. OK? But I have to draw it for you, so I'm drawing it for you because the notation

he would have used was much too messy and there's no point in learning it.

So he begins to look at the data from these different crosses.

What he finds is when he looks only at black and vestigial, so he ignores what happened with cinnabar, what's the recombination rate, the frequency with which he observes new types, non-parental types? Well, they had already done the experiment in the lab. And what's the answer?

17%. Now, he then looks at black to cinnabar. So he just, you know, covers up the genotype of vestigial. There are four possibilities, black, cinnabar, black, plus, plus, cinnabar, black, cinnabar.

He looks at the parental types, black, cinnabar or plus, plus. He looks at the non-parental types, the recombinant types, plus, cinnabar or black, plus. He counts up the number of non-parental types to the total number of flies and he gets a recombination rate of 9%. OK? So I'm just going to draw you this. He took out a piece of paper and he drew himself black, cinnabar, vestigial. He said I believe this has something to do with distance. This was 17%. The probability of a crossover occurring, of a recombination occurring between black and vestigial 17%. And the probability of a crossover occurring, the frequency of a crossover occurring between black and cinnabar was 9%. Got any prediction? Cinnabar, vestigial should be about 8%, give or take.

But what if his picture is wrong. What's another picture that might be were cinnabar is? Oh, yeah. There's an alternative picture, isn't there? The alternative picture is black, vestigial, cinnabar over here at 9%, 17%. In which case, what's the prediction for cinnabar, vestigial? 26%, give or take, right? We've got to be a little rough about these things.

Well, that's not a single prediction, but it's down to two alternatives.

He's either expecting about 8% or he's expecting about 26%.

So two alternative predictions.

Cinnabar, vestigial combination rate 8%. Mm, that's good.

That's very good. The first time anybody's made a prediction, and a quantitative prediction that's just gotten verified by data.

Sturtevant also does one other interesting thing.

He looks at a fourth thing, which is a little bit interesting.

When I look at the types of gametes that can come out of her, right? If this idea of genetic recombination is correct, that sometimes in this F1 parent a crossover has occurred here, sometimes a crossover has occurred here, and the crossover here would give rise to black, plus, plus or plus, cinnabar, vestigial. Here it would give rise to black, cinnabar, plus or plus, plus, vestigial if it went the other way.

Is it possible that occasionally, under this model, you might get two crossovers? Might it be the case, if we believe in this stuff, that a crossover might occur between black and cinnabar and a crossover might occur between vestigial and cinnabar? Could be. How often do you think that would happen? Sorry? Rarely.

How rarely? What's the chance of a crossover here?

About 9%, right? A crossover here?

About 8%. Let's say 9%, 8% or about 10% just for roundness.

There's about a 10% chance of a crossover in the first interval.

It's about a 10% chance of a crossover in the second interval.

It's about 1% of the time. Much lower than the others.

But about 1% of the time you might see what kind of chromosomes emerging? Black plus, vestigial.

So black plus, vestigial or plus, cinnabar, vestigial. These chromosomes, oops, plus. Thank you. These would be doubly recombinant chromosomes. They would need two recombination events to explain them. And you even have a prediction that you might see them at about 1%. And, sure enough, Sturtevant sees them. It's actually somewhat less than 1%.

It turns out that double is a little less likely than the independent. There's a little bit of what's called interference, but don't worry about it. That's a second order effect.

At a frequency of about 1% he sees double recombinants.

That tells him who is in the middle. If cinnabar is the one that has this property, because if he asked how often does cinnabar get inherited together with plus, plus that's very rare.

But vestigial gets inherited with plus, plus 9% of the time, black gets inherited with plus, plus, sorry, 8% or 9% of the time, but cinnabar is pretty rare. So all this together says that this model here of a linear chromosome is now making some pretty good quantitative predictions about what's going on. But of course this is just three different genes, black, cinnabar and vestigial.

What would you like? More of them at least. Me, personally, I go for all. I'm with you. But he's an undergraduate and he's got what he can. So more.

Well, it turns out that of course Morgan's lab was busily making crosses and all this kind of stuff and there was more data available.

So when he saw this happening he said, all right, let's look at some more things. And he began, because there was so much data from the lab, going around and taking all this stuff, lobe and curved wing and other kinds of funny traits, and he began looking at frequencies. And he found this was about 9%.

And this was about 8%. And he found this was about 5%.

And he found that this was about 5%. And if these two were 5% his prediction was 10%. And his prediction here would be 13%, etc. And it all pretty closely checked out. This was highly constrained, the idea that the recombination rates would fit a simple linear model. It's not perfect, of course, because imagine what happens. Suppose I have 10%, 10%, 10%, 10%, 10% and I have ten loci, you know, I have ten such intervals. What will the recombination rate be?

100%. And then if have five more? 150%. What does that mean?

So clearly something is wrong about just using percents.

You have to kind of, I mean for the aficionados, really the percent reflects the number of crossovers.

But obviously you have to do a little bit of correction because you cannot have, you know, if I keep piling on the intervals double crossovers will happen which won't produce recombinant types.

But don't worry about it. We can just add percentages for today.

And when you do all this it works. Sturtevant did this all in one evening. In his autobiography that he wrote about 50 years later he says I went home one evening, blew off all of my homework, and stayed up all night and was able to make sense out of all this data.

So I think this is an example of a productive all-nighter.

[LAUGHTER] And also this is an example of when it's the right choice to blow off your homework. If anyone wishes to do things like this and be as productive, you're certainly entitled to blow off the homework here, too. But do bring in good data like this when you're done. Anyway, this notion is a genetic map. A genetic map was a totally abstract concept, much like Mendel's abstract concept that there were even genes.

Now we're going further and we're saying whatever genes are, we still don't know that they're DNA, etc. Whatever they are they live on a line, and they behave as if they live on a line, and they undergo recombinations, etc.

And when I see a recombination rate, a recombination frequency, a recombination rate that's zero, it must mean the genes are very close together. If I see a recombination rate very, very close, never recombine, recombination rates, oh, I don't know, maybe 10% or something, well, there's some distance between them. And if they're further and further and further away, or on totally different chromosomes, what would be the recombination rate here for two different chromosomes?

A half. Half of these are non-parental types.

So when I get up to a recombination rate of 50% then it means that they live on, that they are so-called unlinked to each other.

Either they are on different chromosomes entirely or I suppose it's possible, and in fact it is possible that they're so far away on the same chromosome that the probability of crossovers occurring is so high that they are de-correlated from each other and I cannot observe any recombination rate less than 50%. It turns out many chromosomes are sufficiently big that lots of crossovers can occur and you cannot actually detect linkage at the two ends of the chromosome. But if you string together some genes in between you can see that this is linked to this is linked to this is linked to this is linked to this.

OK? All right. Good. So Sturtevant is another one of my heroes because he comes up with this utterly abstract model here of chromosomes, of genetic maps. All right. I meant to get that board. Does someone have a call? OK. So last of all let me take Section 4 here. This begins to provide fairly convincing evidence for the Chromosomal Theory because it made a whole lot of pretty whacky predictions.

And they pretty much hold up. Here's another thing that provided a lot of good evidence for it, and that was sex linkage.

Also in Morgan's lab, which was a very productive place, I must say, folks were wondering about the fact that chromosomes, although they almost always occurred in pairs that lined up with each other perfectly, in many species there was one odd couple.

A pair of chromosomes that always paired up with each other but they didn't look the same. This one looks like an X.

This one kind of had the shape of a Y. And hence they got the names the X and the Y chromosomes. Now here

was something very interesting. In fruit flies it was always the males that had an XY pair.

In females it was always an XX pair. What does that tell us about these chromosomes and what they do? Sorry? Determines gender. Wait a minute. Why do you believe it determines gender?

It just correlated with gender. Females have these two funny chromosomes. Males have, I'm sorry. Females have these two Xs. Males have an X and Y.

Does it have to mean that they determine gender?

Maybe gender determines them. Maybe what happens is that in female cells you get both chromosomes, but in male cells some enzyme comes along and chews off the end of the chromosome.

No, no, really. Maybe this is some physiological state of the chromosomes. Why are you so ready to leap to the conclusion that the chromosomes determine sex, rather the gender, than the gender determines the chromosomes? It's because you know the answer, you've been told all this, etc. But I, again, invite you to take apart what support you have for that and ask how would you know, right? All of these things you get told, but how would you know?

And there was great argument about was this really the case?

So how could you convince people that this was true?

It's not obvious to know which way it would go.

The most convincing evidence, not the only evidence, but the most convincing evidence came from a single fly that had been isolated in Morgan's lab. And F0 fly that had the very interesting property that instead of the normal red drosophila eyes this fly had white eyes.

Whereas, this was the normal fly with red eyes. And we'll use a female here. When you cross together the white eyed fly and the red eyed fly, what you find is that in the F1 generation all the flies, males and females, are normal red eyes.

When I take, however, a normal female and I cross her back, sorry. A normal female emerging from this F1 generation, and now I cross her to a normal male, here's what happens.

All of her daughters are normal, but her sons, half are normal and half are white-eyed again.

That's weird. For the first time we have a genetic trait, eye color, that is showing correlation in its inheritance with sex. So that says for the first time we're beginning to see something that looks like linkage, like genetic correlation,

genetic nearness, like genetic mapping that would relate eye color to sex.

What's the model? Well, of course the model here is that this fly, we know the answer, is X over Y, it's a male. And the X chromosome here has a mutation that makes it white-eyed. What's this normal fly over here?

X over X. And its X chromosomes are normal.

When we go to the next generation, what kind of offspring are there?

The daughters of this cross, what's their genotype? What did they get from dad? They always get a normal X chromosome from dad. I'm sorry, from mom I mean.

What did they get from dad, these daughters? They always got the X with the white eye. Why didn't they get the Y?

Because they're daughters, right? If they got the Y they'd be sons. But they're daughters. So the daughters always are getting this chromosome. Now, when you mate these back to a normal male, X over Y, the daughters are of what type?

What did they get from their dad? Always an X plus.

And what did they get from their mom? Either an X with a mutation or an X plus. Either way they're normal, because we're assuming that this white-eyed mutation is recessive. What did the sons get?

What did they get from their dad? Y. Why don't they get the X?

Because they're sons. What did they get from their mom?

Half of them get the X plus, half of them get the X mutant, and that explains cleanly what's going on. Now, the Y chromosome, being a short stubby little chromosome, doesn't have a copy of this gene for eye color at all.

So you might as well regard it as being, you know, recessive, as carrying the allele for the recessive trait.

It doesn't have any functional copy. So for a male he only gets a copy from mom. And what he got from mom completely determines his phenotype. Thus, the transmission of eye color, a trait controlled by a gene on the X chromosome correlated so beautifully with the transmission of the trait sex.

That provided a convincing argument that it was the chromosomes controlling sex rather than the sex controlling chromosomes.

All right. So you know all this stuff. You've all heard of Mendel.

You've all heard of recombination. You've heard of, I suppose, genetic maps. You know about X and Y chromosomes and things like that.

What I want you to take away from all of this is that in order to really know things you have to struggle against models.

You have to understand whether the model is just being made up to explain the data or whether the model has been proved by testing it in any serious kinds of ways. All this stuff took 30 or 40 years of serious battle before the last people caved in and said this is all proven. Of course, going forward we'll assume it's all proven and you know what to do with it. And onward to next time.