7.012 Introduction to Biology, Fall 2004

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Transcript – Lecture 9

I want to go back a second to the end of last time because in the closing moments there, we, or at least I, got a little bit lost, and where the plusses and minuses were at a certain table.

And, I want to go back and make sure we've got that straight.

We were talking about a situation where we were trying to use genetics, and the phenotypes that might be observed in mutants to try to understand the biochemical pathway

because we're beginning to try to unite the geneticist's point of view who looks only at mutants, and the biochemist's point of view who looks at pathways and proteins. And, I had hypothesized that there was some biochemists who had thought up a possible pathway for the synthesis of arginine that involved some precursor, alpha, beta, gamma, where alpha is turned into beta; beta is turned into gamma; and gamma is used to turn into arginine.

And, hypothetically, there would be some enzymes: enzyme A that converts alpha, enzyme B that converts beta, and enzyme C that converts gamma. And, we were just thinking about, what would the phenotypes look like of different arginine auxotrophs that had blocks at different stages in the pathway. If I had an arginine auxotroph that had a block here because let's say a mutation in a gene affecting this enzyme, or at a block here at a mutation affecting, say,

the gene that encodes enzyme C, how would I be able to tell very simply that they were in different genes? Last time, we found that we could tell they were in different genes by doing a cross between a mutant that had the first mutation, and a mutant that had the second mutation, and looking at the double heterozygote, right? And, if in the double heterozygote you had a wild type or a normal phenotype, then they had to be in different genes, OK? Remember that?

That was called a test of complementation. That was how we were able to sort out which mutations were in the same gene, and which

mutations were in different genes. Now we can go a step further. When we've established that they're in different genes, we can try to begin to think, how do these genes relate to a biochemical pathway? I wanted to begin to introduce, because it'll be relevant for today, this notion: so, suppose I had a mutation that affected enzyme A so that this enzymatic step couldn't be carried out.

Such a mutant, when I just try to grow it on minimal medium won't be able to grow. If I give it the substrate alpha, it doesn't do it any good because it hasn't got the enzyme to convert alpha. So, given alpha, it won't grow. But if I give it beta, what will happen? It can grow because I've bypassed the defect. What about if I give it gamma? Arginine?

Now, if instead the mutation were affecting enzymatic step here, then if I give it on minimal it won't grow, alpha won't suffice. If I give it beta, it won't suffice. If I give it gamma, however, I've bypassed the defect and it will grow. So, that's a very different phenotype. The ability tor grow, here, given beta, in this strain here. The inability to grow, this has an inability to grow on beta,

but it can grow on gamma. What about this last line? If I have a mutation and the last enzymatic step, minimal medium can't grow with alpha, can't grow with beta, can't even grow with gamma. But, it can grow with arginine because I've bypassed that step. So, I get a different phenotype, the inability

to grow even on gamma, but I can grow on arginine. Now, here, if I put together those mutants and make a double mutant, a double homozygote, let's say, that's defective in both A and B, which will it look like? Will it be able to grow on minimal medium? Will it be able to grow on alpha? Will it be able to grow on beta?

Will it be able to grow on gamma and arginine? What about if I have a double mutant in B and C, minus, minus, minus, minus, plus? So this looks the same as that. This looks the same as that. And so, by looking at different mutant combinations, I can see that the phenotype of B

here is what occurs in the double mutant. So, this phenotype is epistatic to this phenotype. Epistatic means stands upon, OK? So, phenotypes, just like phenotypes can be recessive or dominant, you can also speak about them being epistatic. And epistatic means when you have both of two mutations together, epistatic,

then one of them is epistatic to the other, perhaps. It will, in fact, be the one that is present. So, this is not so easy to do in many cases because if I take different kinds of mutations affecting wing development, and I put them together in the same fly, I may just get a very messed up wing, and it's very hard to tell that the double mutant has a phenotype that looks like either of the two single mutants. But sometimes, if they fall very nicely in a pathway where this affects the first step, this affects the second step

this affects the third step, this affects the fourth step, then the double mutant will look like one of those, OK? And, that way you can somehow order things in a biochemical pathway. Now, notice, this is all indirect, right? This is what geneticists did in the middle of the 20th century to try to figure out how to connect up mutants to biochemistry. Actually, that's not true. It's what geneticists still do today because you might think that,

well, we don't need to do this anymore, but in fact geneticists constantly are looking at mutants and making connections trying to say, what does this double combination look like? What does that double combination look like, and how does that tell us about the developmental pathway, which cell signals which cell? This turns out to be one of the most powerful ways to figure out what mutations do by saying the combination of two mutations looks like the same as one of them, allowing you to order the mutations in a pathway.

And, there's no general way to grind up a cell and order things in a pathway. Genetics is a very powerful tool for doing that. Now, there are some ways to grind up cells and order things, but you need both of these techniques to believe stuff. Anyway, I wanted to go over that, because it is an important concept, the concept of epistasis, the concept of relating mutations to steps and pathways, but what I mostly want to do today is go on now to talk about genetics

not in organisms like yeast or fruit flies or even peas, but genetics in humans. So, what's different about genetics in humans than genetics in yeast? You can't choose who mates with whom. Well, you can. I mean, in the days of arranged marriages maybe you couldn't,

but you can choose who mates with whom, but only for yourself, right? What you can't do is arrange other crosses in the human population as an experimentalist. Now, your own choice of mating, unfortunately or fortunately perhaps produces too few progeny to be statistically

significant. As a parent of three, I think about what it would take to raise a statistically significant number of offspring to draw any conclusions, and I don't think I could do that. So, you're absolutely right. We can't arrange the matings that we want in the human population.

So, that's the big difference. So, can we do genetics anyway? How do we do genetics even though we can't arrange the matings the way we'd like to? Sorry? Well, family trees. We have to take the matings as we find them in the human population. You can talk to somebody who might have an interesting phenotype, I don't know, attached earlobes, or very early heart disease, or some unusual color of eyes, and begin to collect a family history on that person. It's a little bit of a dodgy thing because you might just be relying on that person's recollection. So, if you were really industrious about this, you'd go check out each of their family members and test for yourself whether they have the phenotype. People who do serious human genetic studies often go and do that. They have to go confirm, either by getting hospital records or interviewing the other members of the family, etc. So, this is not as easy as plating out lots of yeasts on a Petri plate. And then you get pedigrees. And the pedigrees look like this. Here's a pedigree. Tell me what you make of it.

Now, symbols: squares are males, circles are females by convention, a colored in symbol means the phenotype that we're interested in studying at the moment. So, in any given problem, somebody will tell you, well, we're studying some interesting phenotype. You often have an index case or a proband, meaning the person who comes to clinical attention, and then you chase back in the pedigree and try to reconstruct. So, suppose I saw a pedigree like this.

What conclusions could I draw? Sorry? Recessive, sex link trait; why sex link trait?

So, let's see if we can get your model up here. You think that this represents sex-linked inheritance. So, what would the genotype be of this male here? Mutant: I'll use M to denote a mutant carried on the X chromosome, and a Y on the opposite chromosome. What's the genotype of the female here?

So, it's plus over plus where I'll use plus to denote the gene carried on the normal X chromosome. OK, and then what do you think happened over here? So, mutant over plus, you mate to this male who is plus over plus. Why is that male plus over plus? Oh, right, good point.

It's not plus over plus. It's plus over Y. Why is that male plus over Y as opposed to mutant over Y?

He'd have the mutant phenotype. So, he doesn't have the mutant phenotype so he can infer he's plus over Y. OK, and then what happens here? Mutant over Y; this is plus over Y. How did this person get plus over Y? They got the plus from mom, and the daughters, Y from dad, and a plus from mom. That's cool. Now, what about the daughters there?

They're plus over plus, or M over plus? Is one, one, and one the other? Well, in textbooks it's always plus over plus and M over plus, but in real life? We don't know, right? So, this could be plus over plus, or M over plus, we don't know, OK? Now, what about on this side of the pedigree here? What's the genotype here? Plus over Y, OK.

Why not mutant over Y? Because if they got the mutant, it would have to come from the, OK, so here, plus over plus, and then here, everybody is normal because there's no mutant allele segregated. Yes? Yeah, couldn't this just be recessive? I mean, it's a nice story about the sex link

but couldn't it be recessive? So, walk me through it being recessive. M over plus, plus over plus. Wait, wait, wait, hang on. Could this be M over plus, and that person be affected? It's got to be M over M, right so mutants over mutants

but that's possible. Yeah, OK. So, what would this person be? Plus over plus, let's say, come over here. Now, what would this person be? M plus. It has to be M plus because, OK, and what about this person here? M plus, now what about the offspring?

So, one of them is M over M, plus over plus, and two M pluses. Does it always work out like that? [LAUGHTER] No, it doesn't always work out like that at all. So, I'm just going to write plus over plus here just to say, tough, right? In real life, it doesn't always come out like that. What about over here?

It would have to be plus over plus. Why not? It doesn't because it could be M over plus and have no effect on offspring by chance, right? But, you were going to say it's plus over plus because in the textbooks it's always plus over plus in pictures like this, right? And then, it all

turns out to be pluses and mutants, and pluses and mutants, and all that, right?

Well, which picture's right? Sorry? You don't know. So, that's not good. There's supposed to be answers to these things. Could either be true? Which is more likely? The one on the left? Why? More statistically probable, how come? Because it is. It may not quite suffice as a fully complete scientific answer though.

Yes? Yep. Well, but I have somebody who is affected here. So, given that I've gotten affected person in the family --

yeah, so it is actually, you're right, statistically somewhat less likely that you would have two independent M's entering the same pedigree particularly if M is relatively rare. If M is quite common, however, suppose M were something was a 20% frequency in the population, then it actually might be quite reasonable that this could happen. So, what would you really want to do to test this? Sorry?

Well, if you found any females here maybe you'd be able to conclude that it was autosomal recessive because females never show a sex-linked trait. Is that true? No, that's not true. Why not? You're right. So, you just have to be homozygous for it on the X. So, having a single

female won't, I mean, she's not going to take that as evidence. Get an affected female and demonstrate that all of her male offspring show the trait. Cross her with, wait, wait.

This is a human pedigree guys [LAUGHTER]. Whew! There are issues involved here, right? You could introduce her to a normal guy, [LAUGHTER] but whether you can cross her to a normal guy is not actually allowed. So, you see, these are exactly the issues in making sense out of pedigrees like this. So, what you have to do is you have to collect a lot of data, and the kinds of characteristics that you look for in a pedigree, but they are statistical characteristics, and notwithstanding --

So, this could be colorblindness or something, but notwithstanding the pictures in the textbook of colorblindness and all that, you really do have to take a look at a number of properties. What are some properties? One you've already referred to which is there's a predominance in males if it's X-linked. Why is there a predominance

in males? Well, there's a predominance in males because if I have an X over Y

and I've got a mutation paired on this X chromosome, males only have to get it on one. Females have to get it on both, and therefore it's statistically more likely that males will get it. So, for example, the frequency of colorblindness amongst males is what? Yeah, it's 8-10%, something like that. I think it's about 8% or so. And, amongst females, well, if it's 8% to get one, what's the chance you're going to get two?

It's 8% times 8% is a little less than 1% right? It's 0.64%, OK, in females. So, we'll just go 8% squared. So in males, 8% in females, less than one percent.

So, there is a predominance in males of these sex-linked traits. Other things: affected males do not transmit the trait to the kids, in particular do not transmit it to their sons, right, because they are always sending the Y chromosomes to their songs. Carrier females

transmit to half of their sons, and affected females transmit to all of their sons. And, the trait appears to skip generations, although I don't like this terminology.

It skips generations. These are the kinds of properties that you have. So, hemophilia, a good example of this, if I have a child with hemophilia, male with hemophilia, would you be surprised if his uncle had hemophilia? Which uncle would it be, maternal or paternal? The maternal uncle would have hemophilia most likely.

It's always possible it could be paternal. This is the problem with human genetics is you've got to get enough families so the pattern becomes overwhelmingly clear, OK, because otherwise, as you can see with small numbers, it's tough to be absolutely certain. So, these are properties of X linked traits. How about baldness? Is baldness, that's a sex-linked trait? How come? You don't see a lot of bald females. Does that prove it's sex linked?

Sorry? Guys are stressed more. [LAUGHTER] Is there evidence that it has anything to do with stress? Actually, it has to do with excess testosterone it turns out, that high levels of testosterone are correlated with male pattern baldness, but does the fact that males become bald indicate that this is a sex linked trait? No. Just because it's predominant in male, we have to check these other properties.

Is it the case that bald fathers tend to have bald sons? Any evidence on this point? Common-sensical evidence from observation? It's pretty clear. It's very clearly not a sex-linked trait. It's a sex-limited trait, because in order to show this you need to be male because the high levels of testosterone are not found in females even if they have the genotype that might predispose them to become bald if they were male.

So, it actually is not a sex-linked trait at all, and it's very clear that male pattern baldness does run in families more vertically. So, you've got to be careful about the difference between sex linked and sex limited, and sex linked you can really pick out from transmission and families. OK, here's another one. New pedigree.

She married twice here.

OK, what do we got? Yep? She married again. She married twice. She didn't have any offspring the second time.

But that happens, and you have to be able to draw it in the pedigree. She's entitled, all right. OK, so she got married again, no offspring from this marriage. That's her legal symbol. You guys think that's funny. It's real, you know? OK, that doesn't mean she's married to two people at the same time. This is not a temporal picture. So, what do we got here? Yep? Sorry, of this person?

Well, I'm drawing them as an empty symbol here, indicating that we do not think they have the trait. They're not carriers. How do you propose to find that out? Look at the children. Well, the children are affected. They could be carriers.

The data are what they are. You've got to interpret it. Does this person have to be a carrier? What kind of trait do you think this is? Dominant? Does this look like autosomal dominant to you? Yep? Oh, not all the kids have the trait

in the first generation, and if this was dominant, they'd all have it? What's a possible genotype for this person? Mutant over plus. And, these kids could be mutant over plus. This could be plus over plus, and this could be plus over plus, mutant over plus, plus over plus, mutant over plus, and plus over plus would be one possibility. On average, what fraction of the kids should get the trait? About half the kids, right?

So, let's see what characteristics we have here. We see the trait in every generation. On average, half the kids get the trait.

Half of the offspring of an affected individual are affected. What else? Males and females? Roughly equal in males and females? Sorry?

One, two, three, four, five to two. So, it's a 5:2 ratio? Oh, in the offspring it's a 2:1 ratio. So, this is like Mendel. You see this number and you say, OK, 2:1. Isn't that trying to tell me something? Not with six offspring. That's the problem is with six offspring, 2:1 might be trying to tell you 1:1.

And it is. If I had a dominantly inherited trait where there's a 50/50 chance of each offspring getting the disease and it was autosomal, not sex linked, there would be very good odds of getting two males and one female because it happens: flip coins and it happens. So, you have to take that into account, and here you see what else we have. Roughly equal numbers of males and females, they transmit equally, and unaffecteds never transmit.

This would be the classic autosomal dominant trait. Right, here this mutant would go mutant over plus, mutant over plus, plus over plus, mutant over plus, plus over plus, plus over plus, and you'd see here that three out of the five here, and one, two, three out of the six there: that's a little more than half but it's small numbers here, right?

This is a classic autosomal dominant as in the textbooks. Yes? Turns out not to make too much of a difference. It turns out that there's lots of genome that's on either. And so, it is true that males are more susceptible to certain genetic diseases.

So, it'll be some excess, but it won't matter for this. Now, in real life it doesn't always work so beautifully. We'll take an example: colon cancer. There are particular autosomal dominant mutations here that cause a high risk of colon cancer. People who have mutations in a certain gene, MLH-1, have about a 70% risk of getting colon cancer in their life. But notice, it's not 100%.

You might have incomplete penetrance. Incompletely penetrance means not everybody who gets the genotype gets the phenotype. Not all people with the M over plus genotype show the phenotype. Once you do that, it messes up our picture colossally,

because, tell me, how do we know that this person over here is not actually M over plus. Maybe they're cryptic. They havenít shown the phenotype. And maybe, it'll appear in the next generation. That'll screw up everything. It screws up our rule about not transmitting through unaffected, it screws

up the rule about not being shown in every generation, and it will even screw up our 50/50 ratio because if half the offspring get M over plus, but only 70% of that half show the phenotype, then only 35% of the offspring will show the phenotype. Unfortunately, this is real life. When human geneticists really look at traits, many mutations, most except the most severe are incompletely penetrant.

And so you have to really begin to gather a lot of data to demonstrate that you're dealing with an autosomal dominant trait that's incompletely penetrant. And then there are other issues. There's a gene on chromosome number 17 called BRCA-1, mutations in which predisposed to a very high risk of breast cancer but only in women. Males carry the mutation and do not have breast cancer. There are other mutations that do cause breast cancer in males.

Males have breast tissue, and can have breast cancer, but the one on chromosome 17 does not. And so, there you would only see this transmitted through females. It would skip into males without showing a phenotype, etc. So, in real life, life's a bit more complicated. All right, so autosomal dominance. Now, let's take one more pedigree. Sorry? Sex limited, but not sex linked.

So, on chromosome 17, which is a bona fide autosome, but it's sex limited in that phenotype can only show itself in an individual who happens to be female. Yes? Sorry? How come autosomal recessive? So, if that left guy up there is actually a heterozygote, and up there that individual, so if we had a homozygote, homozygote, heterozygote,

homozygote, ooh, you can interpret that pedigree if you want to as an autosomal recessive, provided that M is pretty frequent in the population. That's right. Human geneticists, in fact, to really prove that they've got the right model, collect a lot of pedigrees and run a computer model. The computer model first tries out autosomal recessive, tries out autosomal dominant, tries out dominant with incomplete penetrance, and for every possible model figures out the statistical probability that you would see such data under that model.

And when the data become overwhelming and you say, yeah, with one pedigree, any pedigree I draw on the board, it could actually fit almost any for the models. It doesn't say this in the textbooks, but it's true. I get enough pedigrees, and eventually I say the odds are 105 times more likely that this collection of pedigrees would arise from autosomal dominance, inheritance with incomplete penetrance of about 80%. Then, from autosomal recessive inheritance, then I get to write a paper about it. That's really what human geneticists do

is they have to collect enough, now, any other organism, you'd just set up a cross, but you can't. And, as long as we have nontrivial models, we really have to collect a lot of data. Let's take the next pedigree, great, that you're thinking like a human geneticist. It's very good. Here's the next pedigree. Actually, I'm going to reverse it. There we go.

What's that? Who knows? You can't tell. Good, I've got you up to training to the point where, but in textbooks, this would be autosomal recessive. Or it could be anything. You know that, right? But the textbooks would show you this picture as an autosomal recessive. But of course, what else could it be? It could be an autosomal dominant with incomplete penetrance. It could be sex linked. It could be a lot of things. It could also be, I haven't told you the phenotype.

What if the phenotype here was getting hit by a truck? [LAUGHTER] Would you tend to observe this? Yep, so getting hit by a truck, for example, if someone gets hit by a truck, it's unlikely either their parents were hit by a truck, or going back several generations that their grandparents were hit by a truck. So, how do you tell being hit by a truck from, I mean, that is to say, how do you know that something's genetic at all?

When it's relatively rare and it pops up in a pedigree, how do you know it's genetic? Because of the DNA. But, I mean, it takes a lot of work to find the gene and all that as we'll come to the course. You might want a little bit of assurance before you go write the grant to the NIH and say I'm going to find the gene for this because you write it and say I'm going to find the gene for getting hit by a truck, and they're going to write back and say show me that it's worth spending money to find that gene. Show me that it's true. So, what kind of things would we look for? If we wanted to show something was autosomal recessive in a population, what would we do?

More data. So, we collect a lot of families, and what would we see? As we collected more and more families, we begin to see what things? Sometimes we might see families like this, or we might see families like this. [LAUGHTER]

If both parents were mutants, all the children would be mutant, right? We'd color them in mutant. Is that true? Well, first off, it depends. Some of the things we want to study are extremely severe medical genetical phenotypes, and they're not going to live to have children. So, that's an issue that you have to deal with.

But, it is true that if it was autosomal recessive, a mating between two homozygotes for that gene would transmit. [LAUGHTER] What if they were all in the same car? Which is a very important part, because we joke about the car, but diet, things like that, are familial correlated environmental factors. There are environmental factors that correlate within a family.

And so, it's not trivial to make this point. So, all right, we'll be able to demonstrate what's the real proof of Mendelian inheritance here? Because they could all be in the same car, or they all eat the same kind of food or something like that, which predisposes them a certain way. So, we're going to want some better proofs of these things. How about Mendelian ratios? Mendelian ratios anyone?

No, because it could be incomplete autosomal dominance. I don't want to mess you up. On the exams, you guys can think cleanly about simple things. But, this could be dominant with incomplete penetrance, though the TA's are going to hate me because I'm telling you that, anyway, what about Mendelian ratios? How about something that's a pretty good prediction? What fraction of the offspring will be affected?

We get a lot of families, line them all up. What fraction of the offspring? A quarter. Now, that's a hard and fast prediction. One quarter of the offspring are affected. When I have a mating between two homozygotes, so what am I going to do? I'm going to go out. I'm going to collect a lot of families.

Maybe I'll collect 100 families because it'll be a particular disease, diastrophic dysplasia or something like that, xeroderma pygmentosa, ataxia teleangiectasia, and I will go to the disease foundation, and I will get all the pedigrees for all the families, and I'll see how many times it was one affected, two affected, three affected, etc. And on

average, the proportion affecteds will be a quarter, except it's not true. If I actually do that, I find that the ratio of affecteds is typically more like a third.

It isn't a quarter. Now, this should disturb you greatly because you know full well that M over plus by M over plus should give you a quarter affecteds. But when you actually look at human families, it's not. Why? In other words, when we count up all the matings

between heterozygotes, we'll collect all the matings that produce one affected child. We'll collect all the matings that produce two affected children. We'll collect all the matings that produce three affected children. But, we will fail to collect those matings between homozygotes that produce zero affected children. And so, we will systematically overestimate the proportion. Of course, what we really have to do is go out and get all of those couples who were both carriers, but because they had a small number of children didn't happen to have an affected child.

That's not very easy to do especially when you don't know the gene in advance. So, when human geneticists try to go out and measure the one-quarter Mendelian ratio, you can't. But what you can do is the following, conditional on the first trial being affected, now what will be the proportion of subsequent children who are affected?

A quarter. If I make it conditional, conditioning on having a first child who's affected, number one child who's affected, then I know I've got a mating between heterozygotes. Subsequent offspring now do not have that bias. And so, as a matter of fact, you think this pretty cool thought, right? You've got a condition on one. It turns out there's a very famous paper about cystic fibrosis where somebody forgot this point and made a huge big deal in the literature about the fact that a third of the kids on average

had cystic fibrosis in these families, and proposed all sorts of models about how cystic fibrosis might be advantageous and would lead to fertility increases and all that. In fact, it was just a failure to correct for this little statistical bias. OK, this is what human geneticists do is they've got to deal with the population. Now, there's one other trick that you can use to know that something is autosomal recessive.

That trick is this. To site this trick, I have to go back to a person called Archibald Garrett. Archibald Garrett was a physician in London around 1900. Garrett studied children with the trait alkoptonuria.

Alkoptonuria was what, alkopton means black. Uria means urine. They had black urine. This was evident because their urine turned black on treatment with alkaline. How would you treat urine with alkaline? How would people know this? Sorry? Outhouses with lime, yeah, and who's going to look at the children's urine, or something like that?

But you're on the right track. How about diapers? You wash diapers, cloth diapers, in alkali. They turn black. This was evident from black diapers. The kids' urine would turn black. So, he observed this, and you know what Garrett noticed is when he studied, children with alkoptonuria, he found that a very large fraction of affected

offspring were in fact produced from matings of first cousins. Consanguineous matings: now you laugh, but in fact consanguinity has been something that has been favored in many societies,

and in Britain, particularly amongst the upper class in Britain in 1900, marriage of first cousins was quite common, but not as common as he observed. He found that eight out of 17 alkoptonuria patients were the products of first cousin marriages. That's way off the charts because it's nearly a half, when in fact the typical rate in Britain might have been about 5%.

So, on the basis of that in the early 1900's, Garrett was able to show only a few years after the rediscovery of Mendel's work that this property of recessive traits, enrichment in the offspring of consanguineous marriages, was a clear demonstration of Mendelian inheritance. Not only did he do that, but Garrett knew because of the work of some biochemists, and this is way cool, that the problem with the urine was that these patients put out in their urine a lot of what's called

homogentisic acid, HGA, which basically is a phenolic ring. What Garrett did was he... and that stuff turns black on exposure to air.

What might produce, from the things you've learned already, some kind of ring like that? What building blocks do you know have rings like that of things you've studied already? Phenylalanine, tyrosine both have rings. Suppose somebody had problems breaking down homogentisic acid. Suppose there was some pathway where proteins were broken down into

amino acids including phenylalanine and tyrosine. And, they were broken down into homogentisic acid. And they were broken down into I don't know what. And, suppose like we had up there, patients had a mutation in that enzyme. What would happen if I fed patients a lot of protein? In their urine, you would recover lots of homogentisic acid.

Suppose I fed them a lot of tyrosine. I'd get a lot of homogentisic acid because the body couldn't break it down. Suppose I fed them a lot of phenylalanine. They would excrete a lot of homogentisic acid. Suppose I fed them homogentisic acid. I would get quantitative amounts of homogentisic acid. Garrett did this. These are the days before institutional review boards, you know, informed consent. It turns out it's harmless feeding them proteins and things like that.

But in fact, Garrett, in 1911, worked out that this trait had to be recessive because of its population genetics, and inferred a biochemical pathway by feeding different things along the way and was able to connect a mutation in a gene to a problem with a specific biochemical pathway.

Sorry, 1908: this was his Croonian Lecture in 1908. Eight years after the rediscovery of Mendel, he's able to connect genetic defect, showing it's genetic by transmission, to biochemical defect showing that he has a pathway that he can feed things into. And, it all blocks up at the inability to metabolize homogentisic acid. He has connected gene to enzyme by 1908.

What do you think the reaction to this was? Polite bewilderment, and it sunk like a stone. Nobody was prepared to hear this. This is very much like Mendel in my opinion. Now, he was a distinguished professor. It was the Croonian Lecture. He got lots of accolades and all that, and people said, what a lovely lecture that was, and proceeded to completely forget this connection between genes and enzymes, genes and proteins.

It was not until 40 years later or so that Beadle and Tatum, working with a fungus, actually neurospora not yeast, demonstrated that all these mutants interfered with the ability to digest or to make particular amino acids, and wrote this up as the one gene, one enzyme hypothesis of how genes encode enzymes, and won the Nobel Prize for this work, but in fact in their Nobel address,