The Meaning of Sex: Genes and Gender
Lecture One—Deciphering the Language of Sex
David C. Page, M.D.

1. Start of Lecture One (00:15)

From the Howard Hughes Medical Institute... the 2001 Holiday Lectures on Science. This year's lectures, "The Meaning of Sex: Genes and Gender"... will be given by Dr. Barbara Meyer, Howard Hughes Medical Institute investigator at the University of California-Berkeley... and Dr. David Page, Howard Hughes Medical Institute investigator at the Massachusetts Institute of Technology. The first lecture is titled "Deciphering the Language of Sex." And now to introduce our program, the president of the Howard Hughes Medical Institute, Dr. Thomas Cech.

2. Introduction by HHMI President Dr. Thomas Cech (01:02)

Welcome to the Howard Hughes Medical Institute and to the 2001 Holiday Lectures on Science, the ninth in our series. Our auditorium here is filled with bright-eyed high school students from throughout the greater Washington, D.C., area. Welcome, students, and also welcome to those of you who are joining us by our live webcast through the Internet. Special welcome to the educators and students in Moscow, Russia, who are joining us by a video link. To you, I can't say "good morning." I have to say "good evening"-- [Speaking Russian]--Each of you started out as a single cell, the product of a fertilization event of a sperm and an egg, and for about the first seven weeks of life, you were all generic embryos. But then, in the seventh week, something started to happen that would result in about half of you becoming boy embryos and half of you becoming girl embryos. That's going to be the topic of our lectures this year. Now, all of you know that this has something to do with the X and Y chromosome--that men have an X and a Y; women have two X chromosomes. But what is it about these chromosomes, or about the genes that are located on these chromosomes, that lead to the development of one sex or the other? That's going to be our topic: the genes, the molecules, and the molecular processes that are involved in sex determination. You'll hear about this over the next two days. Howard Hughes Medical Institute hosts these holiday lectures in part as a way of highlighting the world-famous scientists who work in our laboratories. These investigators, over 300 in number, and their research groups, are located at more than 70 host institutions, including M.I.T. in Cambridge, where David Page comes from, and U.C.-Berkeley, in California, which is the laboratory home of Barbara Meyer and her group. You can learn more about our investigators by logging onto our web site. Now, in addition to our biomedical researchers, we also, as part of our mission, support science education at all kinds of levels, from public outreach through our museums program, through K through 12 education and teacher education. We support undergraduate research experiences for college students. We support graduate fellowships and medical education. And one of the great things about the holiday lectures is it really brings together these two sort of arms of Howard Hughes Medical Institute: the investigators program and the researchers and the science education. So, this is one of the reasons we're particularly excited about this annual event. You're going to hear four lectures. The first is going to be presented by David Page, who's a Hughes investigator at M.I.T. He's also a professor of biology there and a member of the Whitehead Institute. And David is--I've known David for a long time. He's a very skilled researcher but also presents very well, so I think you'll really enjoy his lecture, the first of which is going to be entitled "Deciphering the Language of Sex." David will speak for about 40 minutes, and he'll have questions halfway through, and then again at the end, so as he's talking, you might want to think about what questions you would like to ask. Then we'll have a half-hour break and hear from Barbara Meyer. David, I know you've always wanted to be on MTV. Well, we didn't--we weren't able to arrange that. But next best thing, we have a video about you and your research interests, which we're going to show now. And after the video, the stage is yours.

3. Introductory interview with Dr. David Page (05:18)

1957, year of space and Sputnik dogs...How did I get interested in science? The mid-1950s, when I was born, was the time of Sputnik. So the Soviets sent that satellite around the earth. At 600 miles, the half-ton satellite joined the meteors in outer space... And the adults of my parents' generation decided that kids needed to learn science if the United States was to be strong. I started some research while I was in medical school, and I couldn't bring myself to giving it up. In fact, I am today continuing the research that I began while I was a medical student. I was lucky enough to enter the Human Genome Project absolutely--I wouldn't even call it the ground floor; it was below ground level. I started on this project to make a genetic map of the human genome, and I quickly found myself with some DNA markers for the human X and Y chromosomes, purely by accident, by picking these DNA probes for the X and Y chromosomes. That got me interested in sex chromosomes and in how male and female appear during embryogenesis. Jeremy, hey, how's it going? In our lab, we're looking for several things. We want to understand what sex chromosomes are and how to think about them--that's one thing. A second thing that we want to understand is, "What do genes have to do with infertility in humans?" Right now, our work is focused particularly on male infertility. Is it environment? Is it genes? We don't fully know, but we're clearly finding that a good bit of it is due to genes. My goals for the holiday lectures are two things-- there's some biology that I want to explain. Some biology that I'm very excited about-- what it means to be male, what it means to be female. When I was in high school, I had never met a scientist, and so science for me was very abstract. So the second goal for me-- in my being and my presenting-- to be a scientist and to show what a scientist is. I want to provide a glimpse of what it is to be a scientist, a glimpse of what it is to think like a scientist, and why it's an exciting career option.

4. What was the first thing your parents asked about you? (07:45)

Good morning. I want to begin with a few questions--some pretty easy ones, I think--so feel free to shout out some answers. I really want you to shout out a couple answers. In what year were you born? I hear a lot of '86s and some '85s, something like that. '83, '84... '84. OK, '84 is trying to win right now. In any case, somewhere there-- '83, '84, '85-- it definitely makes me feel a little old. OK. At the moment of your birth, once it was established that you were healthy enough to cry, what was the next question on your parents' mind, on everybody else's mind? Boy or girl? You got it. So how did your parents and your doctors, or whoever else was in the delivery room-- how did they figure out whether you were a boy or a girl? All right, have any guesses? Well, there's a lot of laughing here. So, they took a look, and they saw whether your external genitalia were those of a male or a female, and so, having determined that you were a girl or a boy on this basis, your parents could finally decide what name to give you, and they could announce your existence to the world. Well...maybe, maybe the card announcing your birth didn't look exactly like these. Hopefully we won't be arrested for showing those photographs.

5. Characteristics of male and female (09:31)

But that leads us to a very big question, which is, "How is a human embryo's sex determined?" What determines whether a baby is born a girl or a boy? So, first we have to think about a partial list of the anatomic differences to be accounted for, so we're going to start where we began, with the external genitalia. We got the penis and the scrotum in the male, clitoris and labia in the female; and looking within the body, the gonads: testes in males, ovaries in females; the internal accessory structures: epididymis, vas deferens, I could mention the seminal vesicles in the male, and in the female, the fallopian tubes and the uterus; and finally, the gametes: the sperm and the egg.

6. Electron micrograph of egg and sperm (10:20)

Now, throughout the animal kingdom, the sex that produces the little gametes, or the sperm--that sex is called the male. If you make the little gametes, you're the male. If you make the big gametes, or the eggs, you're the female. And so in a broad biological sense, this is the most fundamental definition of male or

female: big gamete or little gamete. Now, of course, the big gamete is full of nutrients, and the little gamete is--you know, to be honest, the little gamete is nothing more than a tiny packet of DNA in the head, with a propulsion system. Maybe we're connecting back to Sputnik there in some way. Now, how many chromosomes--how many chromosomes do these gametes have? Twenty-three? That was pretty quick. That's a good sign. OK. And so we take--At the moment of fertilization, we add 23 and 23 together and reestablish the diploid number of 46. This is great, we got a chorus here.

7. Embryonic development and the role of gonads (11:27)

OK, so, now while it's obvious that the members of our species come in these two fundamental forms, that is not at all obvious in early embryos, as Tom Cech just mentioned. So, we are born 40 weeks after fertilization, and during the first six weeks after fertilization, the reproductive structures begin to take shape, but there is no sexual differentiation apparent by any measure.

So, at six weeks, human embryos that are destined to become males are anatomically indistinguishable from embryos that are destined to become females. It's only about seven weeks after fertilization--it's only about seven weeks after fertilization that the structure called the gonad, or actually the bipotential gonad, begins to take on the distinctive characteristics of either the testis in the male or the ovary in the female. So the gonad is the first part of the body to take a sexual move. And then, hormonal secretions of the gonads--either the testes or the ovaries--they secrete hormones that determine the sexual fate of all the other reproductive structures, including, as shown here, the internal accessory structures, the external genitalia, and so on. And these sex hormones are responsible for masculinizing or feminizing a lot in the body, including the brain. But what we're going to focus on today is how the bipotential gonad decides to become a testis or ovary, because that's the pivotal and first decision in becoming a male or female.

8. Sex determination can’t be explained by the historical idea that heredity is a blending process (13:14)

Well, let's think about some history. It's been obvious that the members of our species come in two fundamental forms. That's been obvious for a long time, so people have been thinking about this for a long, long time, but it was not obvious that sex was determined by genes--at least not until the 20th century, because Mendel's gene concept--Remember, Mendel was working in that pea garden in the 1860s, but nobody paid much attention to those ideas until the opening years of the 20th century--and so...but before Mendel's ideas were widely appreciated, people were thinking about heredity, but the prevailing idea was blended. Those who were thinking about heredity were focused upon an idea of blending. The idea was that you took some of mom's characteristics, and you took some of dad's characteristics, and you threw them in the hereditary blender, and out came the child's characteristics. Well, let's think about blending and sex. Blending didn't seem to provide much of an explanation for this binary decision that sex determination represents, right? With regard to sex, you either look like your mother or your father. You don't look like a blended version of the two. And so, if heredity was blending, then sex must not be a matter of heredity. And so the focus was on environment,

9. Historical ideas on environmental factors affecting sex determination (14:36)

and in the 1890s--10 years before Mendel's ideas would be rediscovered--in the 1890s, the prevailing model of how human sex was determined was that the mother's diet during pregnancy was the critical issue. Now, I've never been able to figure out how this theory accounted for boy-girl twins. And then, there were other theories that focused on things like the phase of the moon or the state of the economy or war or peace, things like that, and if you're looking for new theories of sex determination, you can find them practically any week in the scientific journals at your local supermarket. Now, much earlier, Aristotle had his own theory of sex determination. He claimed that the sex of a human embryo was determined by the father's temperature and level of excitement during intercourse. So, according to

Aristotle, the higher the heat, the greater the chance that one would have a... a boy, you say? I didn't complete the sentence--you did. Ideas--Yes, he did say it was likely to be a boy.

10. Early-20th-century scientists find sex chromosomes in insects (15:54)

So, ideas about how sex is determined began to change in the first years of the 20th century. So, using the light microscope and poring at these blob-like structures in the nucleus called chromosomes. And I should say that in the early years of the 20th century, you could see these colorful bodies, chromosomes, colorful blobs, in the nucleus, but they weren't in any way linked to heredity as yet, but some cell biologists became convinced that there was a systematic difference between the set of blobs that you saw in the nuclei of male and female beetles and also between the male and the female of certain species of flies, including the fruit fly, drosophila melanogaster. So, what these cell biologists, these blob-watchers, noted in the opening years of the 20th century was that in fruit flies, both males and females had three matched pairs of blobs. They shared three matched pairs of blobs, which we'd now recognize to be three pairs of autosomes, but in addition, the males had an unmatched pair, and not knowing what else to call them, this unmatched pair got called the X and the Y, and then it was recognized the females had a fourth matched pair called the XXs.

11. What might the sex-determining signal be? (17:24)

So, now I got a really tough question for you. Given just this data--the data shown on this slide--females are XX, males are XY, do you want to propose--I'd like you to propose some models of how sex might be determined. And I'm actually looking for two competing models. Anybody want to suggest a model? How might sex be determined in flies? Any suggestions? Yes. By forming an amniocentesis. Well, no, what I'm asking is, given that females have 2 X chromosomes and males have an X and a Y, what might the sex-determining signal in the fly be? Yes? The number of X chromosomes. OK, so sex could be determined by the number of X chromosomes--females having two, males having one, OK? You--uh, another possibility, yes? The presence of a Y. OK, it could be the presence or absence of the Y chromosome. So, we have two competing hypotheses now. Sex could be determined by the presence or absence of the Y, or it could be determined by the number of X chromosomes.

12. Sex of fruit flies linked to number of X chromosomes in 1916 (18:35)

So, settling these questions, choosing between these 2, was an important matter, and the answer came in 1916, and it heralded the birth of genetics as a new field in biology. And in the spring of 1916, scientists published the first issue of a new magazine-- it was new in 1916--and this is that first issue.
The journal is called "Genetics," and in an article that begins--and you can look at it afterwards--in an article that begins on page one of volume one of "Genetics," you will read that females--that fruit flies with two Xs plus a Y develop as females, while those with one X and no Y chromosome develop as males. So, what are you going to conclude? It looks like sex is actually determined in flies by the number of X chromosomes. And this was the first time that any organismal trait, or phenotype, in any species was connected to a specific chromosome, and that's why it was page one of volume one of Genetics. And in lecture two, Barbara Meyer is going to discuss that in the nematode, C. Elegans, a very similar counting of the X chromosomes occurs and plays a critical role in determining whether the embryo develops in that case as a female or a hermaphrodite. But that's more for lecture two.

13. Discovery of how sex chromosomes operate in humans (20:14)

Well, in 1923, sex chromosomes were discovered in our species. And as in fruit flies, a nicely matched pair of Xs in females and a mismatched pair, XY, in males. So... what would you have thought in 1923? Only seven years after the first issue of Genetics announced that it was the number of X chromosomes in flies. Well, in 1923, it was quite reasonably assumed that if sex in fruit flies was determined

by the number of X chromosomes, then the same should be true in humans. Well, these extrapolations often prove to be valid in biology, but this one didn't hold up. But it wasn't until 36 years later, in 1959, that the role of the human sex chromosomes was clarified. Human geneticists reported that some females have a single X chromosome and that some males have two X chromosomes plus a Y. The conclusion coming out of these studies was that in humans, the sex-determining signal is the presence or absence of the Y chromosome independent of the number of--independent of the number of Xs. OK. The same was demonstrated in mice, another mammal to which we'll return in a couple of minutes.

14. XX males and XY females suggest key genes for sex determination (21:41)

So, in human embryos, then, how does the presence or absence of the Y determine the fate of the bipotential gonad? Well, geneticists love to discover and study exceptions, and there are apparent exceptions to the rule that the Y is sex-determining, and these are cases called XX males and XY females. Now, XX males have testes and male structures, despite the presence, as judged by light microscopy, of two X chromosomes. XY females have ovaries and female structures, despite the presence of a Y chromosome. Now, it turns out that XX males occur about one in every 20,000 males;
XY females, perhaps at a comparable frequency. Now, we and other scientists had suspected that XX males might carry a portion of the Y chromosome, a testis-determining portion that was not detectable by light microscopy. And using Y DNA probes, this proved to be the case. At the top of the slide is a normal Y chromosome that's found in a usual XY male, so you have the short arm of the Y, the centrum here, the long arm. The XX males turn out to carry terminal portions of the short arm of the Y chromosome. You see here that they form a nested series. Now, that suggests that the testis-determining gene or genes on the Y might be in this region that they carry. That was dramatically confirmed by findings in XY females. Some XY females are missing precisely the part of the Y chromosome that is present in the XX males. So that suggested that this, that the region in common that is present in the XX males and absent in the XY females might contain the critical genes. The critical gene or genes.

15. *SRY,* the sex-determining gene, in transgenic mice (23:38)

And it turns out that within that critical region there is only one gene, and it's called SRY. It encodes a DNA-binding protein that probably turns on or turns off other genes in the bipotential gonad. And let's look at the definitive experiment that proved that SRY is the sex-determining gene in mammals. This involves making something called a transgenic mouse. We're going to begin with fertilized mouse eggs. So we have an XX fertilized egg flushed from the reproductive tract of a recently mated female. Now at this point, this egg is destined to become what? Female. OK. But what we're going to do is inject pure DNA--we're going to inject not just any DNA, but the mouse SRY gene--the mouse Y chromosome's counterpart to the human SRY gene. We're going to inject that gene, and it turns out that it will integrate into a mouse chromosome randomly, and therefore most likely into an autosome, generating a transgenic egg bearing the SRY transgene. Now place the transgenic egg in the uterus of a foster mother, where the egg will develop as an embryo for 20 days--that's how long it takes for mouse development-- and birth, leading to birth--and the birth of a transgenic mouse who's XX + SRY. Lo and behold, this mouse has testes and is a male. Doesn't make sperm. The XX males don't make sperm. The XY females also don't make sperm. And this led these researchers who produced it to proudly announce on the cover of "Nature," again, displaying the external genitalia, that it is a boy. And I'd like to stop at this point and see if you have any questions.

16. Student question: What are the symptoms of Turner and Kleinfelter syndromes? (25:39)

Any questions. Yes. A question in the house. You mention Turner Syndrome and Klinefelter Syndrome? Klinefelter Syndrome. Yes. What--I--I don't know anything about, like, what are the-- what happens to people who have those? Right. So--so what are Turner Syndrome, what are Klinefelter Syndrome? What are these syndromes? Well, so, Turner Syndrome--those are the girls and women who have one X

chromosome and have no second sex chromosome--those girls and women are-- are quite short. The ovaries actually degenerate to form so-called streaks. Those girls don't spontaneously go through puberty. And they will--they will not be fertile. There are some other-- some other parts of the body are sometimes affected. There can be some webbing of the neck, sometimes kidney anomalies and such. So, there are effects throughout the body. But here I was making the point that Turner Syndrome helps illustrate that it's not the number of Xs, but it's the presence or absence of Y that's sex-determining. Klinefelter Syndrome... Those males who are XXY, the major problem is they don't produce sperm. So they often show up, together with their partners, in infertility clinics.

17. Student question: What causes hermaphroditism in humans? (26:54)

Another house question? Yes. Were you supposed to be determining hermaphrodites as well? Ah, how about hermaphrodites? Well. So what is a hermaphrodite? We're going to hear about hermaphrodites in lecture two in the nematode C. Elegans. The way the term is used in... um, in humans... hermaphrodite refers to an individual who has both testicular and ovarian tissue. And such individuals do occur. To be honest, the geneticists have not yet figured out hermaphrodites very well in humans. We don't know what's going on. But those are cases where both testicular and ovarian tissue develop.

18. Student question: Why don't XX males produce sperm? (27:37)

Another question. Yes. If you all have determined that SRY creates the testes in the male, do you know what causes them to produce sperm, then? Ah. OK. So why is it that these XX males, both humans and the XX + SRY mice, why don't they make sperm? Well, we're going to actually come back to that in some detail. I'm going to come back to that in some detail in lecture four. But it turns out that those individuals and those mice seem to have two strikes against them. It looks like having two X chromosomes is somehow incompatible with producing sperm. And it also looks like other genes on the Y chromosome are required for producing sperm. So there are two reasons.

19. Student question: What makes XY females develop as female? (28:26)

How about another house question? Yes. Over here. SRY changes an XX embryo to male, right? That's right. What changes an XY embryo into a female? Ah. Well, so, in the XY female, we were missing--The XY female's Y chromosome was missing the SRY gene, OK? So the SRY wasn't present. We're actually going to come back in the second half of this lecture and reexamine that question of how does SRY come to be missing in an XY female. Great question.

20. Student question: Does *SRY* determine whether a person has testes? (29:03)

Yes. Is the SRY the--what determines whether they have testes or not? Yes, that's exactly... The question concerned is SRY the cause of the gonad--does it cause the gonad to develop as a testis? That is exactly what we think is going on. That the bipotential gonad is set, is poised, to become either a testis or an ovary, and if SRY is present, it follows the testicular path. If SRY is not present, it follows the ovarian path.

21. Student question: Can Y-chromosome activity be clearly observed in the human body? (29:39)

Ok, let's take a question from Moscow. Moscow Lyceum. I'm from Moscow Chemical Lyceum. It is common knowledge that even if there is certain genes, XX and Y is active at that time, you can observe the development of a male sex in the body. If there is no explanation, how do you explain for the activity of XY in the human body? I think the question concerned whether we can clearly see the activity of the Y chromosome in the human body. Much of what I told you about how we think SRY is acting comes from

studies that are carried out not in human embryos, where the research is difficult, but in mouse embryos. In other words, we think that we can use the mouse, and we'll hear much more about the use of other species as models for human development. We study the action of SRY in the developing mouse and then try to convey and transfer that knowledge and insight from what's happening in the bipotential gonad of the mouse embryo to our understanding of what's happening in the bipotential gonad of the human embryo.

22. Student question: Do XY females have male levels of testosterone? (31:03)

OK. We're going to turn to a last question from the house. If there are any more questions. Yes. In the back. People who have XY chromosomes, do they, do their gonads produce testosterone or estrogen? Do they have male hormones or female hormones? Ah. OK. So, these XY females who are missing SRY-- Are they really female, or do they have male levels of testosterone? Actually, tomorrow in lecture four, we're going to return to the question of testosterone and estrogen. But it turns out these XY females do not have male hormone levels. They have female hormone levels. So they are very much feminized. Again, the only problem is the absence, the inability to produce substantial numbers of oocytes. And, uh... and these XY girls will not progress spontaneously through puberty. So they often actually have to have some hormone replacements during adolescence and into adulthood. OK. I want to thank you all. Great questions.

23. Why does nature have two sexes? Are males really necessary? (32:15)

So, so far in this lecture, I've made a great deal out of a human embryo's becoming male if SRY is present or becoming female if SRY is absent. Now I want to consider with you an even bigger question. That's a pretty important one, are you a boy or are you a girl, but now I want to take on a much bigger question, which is why does nature bother with two sexes in the first place? To put the question more bluntly, since only females can give birth... why should nature bother with males? Or, are males really necessary? Now, wouldn't it be simpler, wouldn't it be more efficient, for our species or any other species to consist exclusively of females? To reproduce without sex?

24. Description of clonal reproduction (33:08)

Well, consider Dolly the cloned sheep. Dolly helps us frame the contest between sexual reproduction, and now I'm going to say sexual reproduction means having a mother and a father, versus asexual cloning, which is having only a mother. Now, in the interest of full disclosure, I should acknowledge that I am a father, and so you might suspect that I am biased. But that's too bad, because I'm giving the lecture. So, um, in Dolly's cells, in Dolly's nuclei, all the DNA came from one parent. So Dolly was generated by taking a sheep egg, an unfertilized sheep egg, in that case, taking an unfertilized sheep egg, removing the nucleus, and replacing it with the nucleus of a breast cell from an adult sheep. Now, that female that donated the breast cell nucleus became the one and only genetic parent of Dolly. So today, by today, goats, cattle, pigs, and mice have all been cloned by similar procedures.

25. Comparing cloning in Laredo striped whiptail with sexual reproduction in related species (34:17)

You may say sure, but these were experiments that were conducted by scientists in laboratories, and they have nothing to do with the natural world. So I want you to consider with me Dolly's wild and natural counterpart, which is the Laredo striped whiptail. This is a lizard living in the Rio Grande Valley of Texas and Mexico. Now, this species is a girls-only club. And the girls reproduce by cloning themselves. Now, there are some sister species, other whiptail lizards, that reproduce sexually. And so I want to compare the two reproductive strategies. So we're going to compare life as a female whiptail with and without males. Now, in species with males--over here--life is fairly routine. It's fairly dull. Females produce eggs, and males produce sperm. Fertilization occurs, and the male inclusive

life cycle is completed, but in species without males, life has, sort of, a different texture. Females produce eggs, but those eggs don't need sperm. Through parthenogenesis, which is a big word which in this case means we don't understand anything about what's happening, the unfertilized egg is capable of giving rise to another adult, which is always a female. So, I got some questions for you here. On the left, in the sexual species, these gametes--the egg and the sperm--these gametes have how many copies of each gene? They are haploid, or 1N, right? Now...so, what's the biological process that generates haploid cells? Meiosis, OK? So these are 1N cells generated through meiosis. Now, on the right, in the females-only species, did these eggs go through meiosis? Pretty sure about that? They didn't go through meiosis? Well, I agree. I don't think they went through meiosis, because one of the things you do in meiosis is cut your number of genes in half, and it wouldn't take too many generations over here to run out of genes, right, if you went through meiosis every life cycle. So, certainly we don't have any kind of meiosis that we're familiar with, at least, over here.

26. Meiosis is the defining feature of sexual reproduction (36:51)

So, the question, then, of are males really necessary--that is equivalent to the question to participate in meiosis or to abstain, to have sex or to clone, to have meiosis or no. So, meiosis, then, I'm going to argue, meiosis is the defining feature of sexual reproduction. Now, have you studied meiosis? Have you covered meiosis? So, you know you've got leptotene and zygotene and pachytene and dancing chromatids and homologues, and you can barely keep track of all these things. Well, today, I ask only that you keep track of two consequences of meiosis. So, one is gene swapping. Gene swapping is this process-- you know about recombination: reciprocal exchanges between paired chromosomes. That's a big consequence of meiosis. A second big consequence of meiosis, we've already mentioned briefly, is that you divide the genes by half. You divide them by two so that each gamete receives one of each chromosome pair, receives one of each of the paired genes present in the parent. Now, so, is this trio of males, sex, and meiosis really necessary? Well, not in an absolute sense, as illustrated by the Laredo striped whiptail lizard, so why bother?

27. Is sex, in an evolutionary sense, good? (38:20)

So the question I put to you, then, "Is sex good?" In an evolutionary sense. What is the long-term value of meiosis, of sexual reproduction? Yes? Genetic diversity. Genetic diversity, OK? We're going to come back to that idea. Yes? Recombination maintains the chromosomal stability of each gene. Maintains the stability of the genes. Let's get some more ideas out here. If you only have things that are asexual, eventually they're not going to be able to breed, then you wipe out an entire species. You don't think they're going to be able to breed too well. OK, yes. The asexual, you think, are not going to be able to breed too well. Another thought? The ability to adapt to a changing environment. Adapt to a changing environment. Ok, so, I'm hearing-- it sounds--You're all pretty convinced that it is a good thing to have sexual meiosis, to have sex, to have meiosis, to have this recombination, this shuffling of genes, because it's going to allow you to adapt to a changing environment, perhaps to put together nice new beneficial combinations of genes. Well, I want to come back to this question of, "Are males really necessary?" and I want to look more closely at the relative advantages of asexual cloning.

28. Demonstration: Fresh fruit and rotting vegetables (39:51)

We're going to do a head-to-head contest between asexual cloning and sexual reproduction, and I'm going to need--perhaps you've been wondering what these fruits and vegetables are for, up here on... You've noticed these? Ok, so, I need four volunteers. I need four volunteers. I need three females and one male. Don't worry, this is not--I'm not running a dating service or anything. Ok, so, one woman up here and one here and one back there, and I need--OK, sir, yes. Why don't you join us? Ok, so, if you'll come down front and take your positions behind the table here, we will put you in charge of your genomes. Um, OK, so, sir, why don't you stand here? And I'm going to have--yeah, why don't you come over here--and if you

could be here and there. That looks great. OK, now... I'm going to explain that,
you didn't know it when you took these positions, but I see, actually, the asexual experiment is over here on the right. Now, remember, on the cloning--on those when we reproduce by cloning, we have female-only species. All right? And we have over here the gene shufflers. This is the sexual recombination team. OK? And we have each of these members of these two species--the sexual species here, the clonal species over there--each of the members of these species has three different genes, two copies of each gene. Right? And it looks like-- I want everyone to verify that this contest is starting with a level playing field. Everybody has got-- would you please confirm--would you agree that you all have the same set of genes to begin? OK. You can inspect any of these fruits and vegetables if you feel that you might be shortchanged. I want everybody to start feeling good about their genes and their genomes. OK, so, now, the trick is--I've got to express some of the rules. So, first of all, each female can have one offspring per reproductive cycle. Males can have no offspring. I'm sorry about this, but this is just the way it works. Now, the clonal reproducers-- the clonal reproducers--you are going to pass all of your genes to each of your offspring, OK? You are going to pass all of your genes to all of your offspring. You got that? OK, now, over here on this side, you are going to pass one of each of your genes to your offspring, and you are going to contribute, so the two of you are going to have to create sort of a tray when we carry this out. OK, so, let's go through the first cycle. So, you two are just going to have an offspring--You're going to have one offspring with these genes, one with these. You two need to make choices and put one of each of your genes onto the tray in the middle. OK? One of each of your genes. It's not a good idea to stop at one chromosome. You've got to do the whole thing. OK, now...OK, so who wins in this first generation: the sexual or the asexual? The asexual is ahead 2-to-1, right? This looks--oh, man. Sex is going to quickly run out of--OK, would you disassemble your offspring? We're going to try this again.

29. Demonstration: Fruit and vegetables with mutations (43:48)

We got to see if--we got to somehow help this crew. OK, so, what-- Actually the claim was made
that recombination, that sex creates diversity.
What actually creates diversity?
What is the source of the raw materials for evolution?
It's not just recombination. You have to have another process. -Mutation. -You got to have mutation.
So, now some mutations are beneficial and create interesting diversity. So, for instance, we are going to trade--Would you mind if I...OK, OK. Now, just to keep things fair, we're going to have some mutations arise that are equally beneficial in creating diversity over here on the--And would you like to trade one of those heads of lettuce? OK, great. And would you like to do the same? Thank you. OK, so just to show that we're being fair in the rates of mutation in these two... OK, so, if we now carried out recombination in this group, you could see that these two could put together an interesting combination.
And so, well, maybe we'd be thinking that the sexual species is starting to catch up, but it turns out that most mutations are not beneficial. Most mutations actually diminish gene function or cause genes to work a little less well. They essentially cause genes to rot. So, I have to bring the bad news now, which is, well, there's a little bit wilted lettuce, and I'm afraid I'm going to have to--you're going to have to hand over this nice fresh one and replace it with the wilted, and just to be fair about this, we'll do the same over here. If you don't mind. OK. I'm sure you were quite happy with this. And then it turns out that this process just continues. Deleterious mutations are far more common, and, so, unfortunately--Audrey, would you be willing to trade? OK. And... I'm sorry, this is the way it works. Ok, so,

30. Demonstration: Meiosis can weed out rotten genes (46:19)

now I'd like to see, looking here over on the clonal species, the clonal species has no choice but to convey this mixed bag--we got some good diversity, but we got some rotted-out stuff. And now I would like the sexual species to choose wisely among their genes, and create a healthy basket of fruits and vegetables to be passed to the offspring. Excellent. Excellent. You really got this down. It only took a couple of generations to figure out how to do this. Good. So, the point is that clonal reproducers win

in the short term. OK? If you're starting from a level playing field, the clonal reproducers win in the short term, because everybody can have offspring. Mutation provides the raw materials. Some mutations add beneficial diversity, but most mutations actually mildly diminish--gradually cause the genes to rot. And sexual reproducers--sexual reproducers have the advantage only in the long run because they get the opportunity over an evolutionary time frame to pass the beneficial mutations together. You guys could have put this orange in here. I'm going to help you a little bit more. See, you have a really nicely mixed tray there. You get the opportunity to combine the beneficial mutations without the drag of the detrimental. And so we see, then, that meiosis serves as evolution's swap shop. Right? We got the swap shop over here. And males essentially provide spare parts. For swapping in. OK? And, so, what I'd like to do is--I think we should all acknowledge the great contributions of our volunteers, and.... And you are free to take back with you any of the fruits and vegetables that you'd like. Now, it looks like everybody's going meiotic right now. And I also have for you M.I.T. T-shirts. Thank you very much. Thank you all. OK. Great. All right.

31. Animation: Meiosis (48:47)

Now what we're going to do is watch a video that connects two of this morning's themes: meiosis and sex determination. The question is by what mechanism does an embryo come to carry a Y chromosome or a second X. The answer is found in meiosis, in the father. So, in this video of human male meiosis, I want you to look for two things. Guess what they are. Gene swapping--the swapping parts of paired chromosomes. And dividing by two--halving the number of chromosomes per cell. So, you'll remember that human cells have 23 pairs of chromosomes, but to illustrate the principles, we're just going to show six pairs here--six pairs of chromosomes. And we're going to look in detail at two pairs. We're going to look at the XY pair here and a pair of autosomes. And you see that we have--we have it arranged so that mom's chromosomes--You got half your chromosomes from mom, half from dad. We have it arranged so that mom's chromosomes are on the left in red and chromosomes you got from dad are in blue on the right. And what's the first thing that happens in meiosis? The very first step is--you actually don't divide by two. You multiply by two. You double all the chromosomes, double all the genes, so at the first step in meiosis, you go to 4N, to a 4N stage. That's where we're beginning. Let's roll the video. Ok, so we've got-- we're now going to blow up and focus on this pair of autosomes on the left, and you see there that recombination can occur at any point along the length of this autosomal pair. Let's see what happens when recombination occurs at a particular point. There's the swapping. We've just swapped a bunch of genes. The same can happen on the other arm of that pair of autosomes. Now, we're going to turn over to the sex chromosomes. That's where the SRY gene is located on the Y, and it turns out that the X and the Y can recombine only within--they normally recombine only within their ends. Let's see how the swap occurs in detail. So we've just swapped parts of some stuff from mom and dad down at the other ends like so. So, at this point... At this point, how many copies of each autosomal gene does this cell have? Four. We still have four. We have two copies of the X and two of the Y and four of every autosome. Ok, and what we're going to see is--What do we have to do now? We got to go from four copies down to one per cell. So, we're actually going to have two rounds of division, and you're going to see the X up here is going to go to two cells on the top. The Y is going to go to two cells on the bottom. We're going to get four sperm out of this one cell. Let's roll the video. OK, here comes the first division. The cell on the top has two copies of every gene. The cell on the bottom, two. Now comes the second division. Remember, we've got the Xs in the two cells on the top, the Ys on the two cells on the bottom. These are going to go on to mature into sperm. So, we will now have X-bearing sperm on the top and Y-bearing sperm on the bottom, and now these sperm have to go in search of eggs. Let's roll the video. Now they're fired up. On the experiment on the top, the X-bearing sperm in purple are going to win, down below, the Y-bearing sperm. We end up with an XX-fertilized egg,

32. Animation: Picture sequence of human embryonic development (52:54)

an XY-fertilized egg, and then as we said, the first six weeks of human development are anatomically, histologically indistinguishable in male and female. We progress up to the seven-week stage, right here, and it's only at this point that the SRY gene fires... and leads to the birth of a male or female.

33. Animation: How does an X chromosome gain the *SRY* gene? (53:19)

OK, so, how do XX males carrying SRY arise? How do XY females deleted for SRY arise? I want you to remember that the XX males are carrying a terminal portion of the Y chromosome. The XY females are missing a terminal portion of the Y chromosome. We're going to see how that happens in a rerun of a part of this video we just watched. Let's run that video now. OK. So, here again we've got the six chromosomes that are representing our 23 pairs. Now we're going to look just at the XY pair, and we're going to watch an aberrant recombination or gene swapping. So there again is the SRY gene on the Y chromosome. Recombination would normally be restricted out at the very ends of the X and the Y, but occasionally, an aberrantly placed recombination event. Look! That one is too far down, and look what's happening. The SRY gene is being passed over to an X chromosome, and look, here's a Y chromosome that has lost SRY as a result of this misplaced swapping event. So, we end up with an X chromosome that is SRY+ and a Y chromosome that is SRY-. That's exactly how XX males and XY females in humans are generated. I want to stop there and take some questions again.

34. Student question: With a recessive mutation, would a clonal reproducer be better off? (54:43)

A question from the house on any topic we've discussed so far. Yes? What if a bad gene goes in? Wouldn't the clone be better? Oh, you're saying--The question is, "If a mutation arises "that causes a gene to be a bit rotted, "wouldn't the clone be better off?" If they had all good--Ah, you're thinking about recessive and such. So, of course, we do have two copies of all our genes, and so you'd say, "So maybe we can take one hit." Well, there are two ways that this might be dangerous. You're well set up now. What happens if you get a second hit in that same gene? You don't have any way to clean house, right? Meiosis provides you an opportunity to swap out for somebody else's clean copy. The other thing is that sometimes there are diseases that result from having just one defective gene copy. We can have dominant diseases or diseases where gene dosage is really critically sensitive. We're going to hear much more about the importance of gene dosage in lecture two from Barbara Meyer.

35. Student question: Is lizard cloning the same as cloning in Dolly the sheep? (55:56)

How about a question from our audience in Moscow? My question is, how do lizards multiply? By parthenogenesis or by the same technology as Dolly the sheep? Right. So the question is whether lizards have mastered the art of cloning by the methods used to produce Dolly. Well, the lizards pull it off naturally. They don't have the benefit of a laboratory. And, again, as I mentioned, it's by parthenogenesis, but we really don't understand how it works. So, cloning in lizards remains a mystery. I must admit that even the practice of cloning in mammals is as very much an art as it is a science at this point. I want to just thank all of our audience, a distance in Moscow and the audience here in the room for great questions, and I want to thank you and say good-bye at this time.

36. Closing remarks by HHMI President Dr. Thomas Cech (57:20)

Thank you, David, for a scintillating lecture. Now we're going to break for a half-hour, after which Barbara Meyer will tell us about sex determination in a very different experimental organism: the nematode worm, Caenorhabditis Elegans. Like mammals, C. Elegans has two sexes, but in this case, instead of male and female, they're male and hermaphrodites. I'm sure you'll want to return in 30 minutes for the details.