Evolution: Constant Change and Common Threads
Lecture Four—From Butterflies to Humans
Sean B. Carroll, Ph.D.

1. Start of Lecture 4 (00:18)

[ANNOUNCER:] *From the Howard Hughes Medical Institute. The 2005 Holiday Lectures on Science. This year's lectures— "Evolution, Constant Change and Common Threads" will be given by Dr. Sean B. Carroll Howard Hughes Medical Institute investigator at the University of Wisconsin, Madison, and Dr. David M. Kingsley, Howard Hughes Medical Institute investigator at Stanford University School of Medicine. The fourth lecture is titled "From Butterflies to Humans." And now to introduce our program, the Grants program director of the Howard Hughes Medical Institute, Dr. Dennis Liu.*

2. Introduction by HHMI Program Officer Dr. Dennis Liu (01:09)

[DR. LIU:] Welcome to the Howard Hughes Medical Institute and the final lecture in our series on evolution. Those of you who have watched the previous lectures have probably noticed that David Kingsley and Sean Carroll really like Charles Darwin. Charles Darwin was a fascinating individual but of course he's a biology hero because of his great idea this big concept that he was able to formulate called evolution. Now, working on evolution today, Sean Carroll, our next speaker has a lot of advantages that Darwin didn't have and those have been covered in the previous lectures. The fossil record has grown enormously including lots of important transitional forms and Darwin, in fact never even heard the word gene and now we understand a lot of details about how genes work and in fact every human gene has been sequenced. In his lecture Sean Carroll will go from the genetic control of spots on butterfly wings to the evolution of human brains and he's going to argue that the mechanisms are very similar if not the same.

3. Introductory interview with Dr. Sean Carroll (02:25)

[DR. CARROLL:] The best things about my job are, I have never, ever been ambivalent about anything that I've done. I work with the most talented and passionate people you can find. I meet incredibly interesting people from around the world that do all sorts of things that I could never have imagined but they're available there to teach you, show you, take you out into the field tell you what drives them. So it's a very intense, continuously mind- expanding experience. I think the most unexpected things that have happened in my laboratory have been, there've been moments of eureka, even reflected by some of these images where you step up to the microscope, you don't really have a notion of what you're going to see but when you look through the microscope, that flash of data instantly changes what you were thinking and simplifies, clarifies all the muck that was running around your brain. I think the ingredients to being a good scientist part of them are intellectual and part are probably emotional or psychological. On the emotional/psychological side we have to be patient. Most things we do don't work. Most things we test, most experiments, it's not that they fail out of stupidity, but they don't reveal what we hope for them to reveal. It's a long-term process, so this is definitely a marathon. You need more the mentality of a marathoner than a sprinter here. I think intellectually it takes tremendous curiosity. The rewards in being a scientist come from having your mind open to new ideas, constantly being curious not looking for preset answers. Sort of being prepared for the unexpected. Well I would just ask any student why they want to pursue a career in science and if that's because they love it, it's because they can't imagine doing something else, that's a good enough answer for me. And so all they really need to do is get exposed to as broad a menu as possible and find out what things on that menu really hit them harder than others. See what that stirs up and eventually just follow your gut to whatever area seems to drive you the most.

4. Darwin's theory helped in understanding new discoveries (05:04)

Good morning, welcome back to the final lecture. I applaud your stamina and your curiosity. One of the common threads running through David's and my lectures are a connection of 21st century science to 19th century science, zigzagging through a bit of the 20th century. In the 19th century it was an extraordinary period of scientific exploration and discovery, a lot of mind-opening discoveries, a lot of mind-opening works such as Darwin's. But what we're looking for here in the 21st century are deeper explanations, deeper understanding and still sometimes some new revelations, things we couldn't have imagined before. Not all great discoveries of the 19th century were Darwin's or Darwin's alone, but his theory provided the essential framework. In the context of his theory new discoveries could be understood. In my final lecture you're going to hear about two more pioneering naturalists, both close allies of Darwin and how mysteries that first captivated them from the beautiful markings of butterfly wings, to the riddle of human origins are now being addressed with 21st century technology, 21st century knowledge.

5. Henry Walter Bates and his trip to the Amazon (06:20)

The first person I'm going to talk about is Henry Walter Bates. He left to travel in the Amazon, to explore the Amazon. In 1848 he was Alfred Russell Wallace's traveling companion. These two gentlemen were friends in England. They, like Darwin, dreamed of visiting the tropics and when they got the chance to go, they went off to the Amazon, and their plan was to make a living as collectors and to earn money to support further work by shipping their collections home and being paid for them, and Bates was a fantastic collector. He spent much longer in the Amazon than Wallace. They parted, Wallace returned to England briefly and then went on to other parts of the world, but Bates stayed in the Amazon which not only gave him a tremendous amount of time, 11 years in total but he lived among its indigenous people and he had a tremendous fondness and a tremendous bond and rapport with the various tribes living in South America and he learned a lot from those indigenous peoples about the local wildlife and the local plants for example medicinal purposes, things like this. So finally he came back to England after 11 years. He came back a little worse for wear. He'd experienced lots of tropical diseases, he'd been robbed, abandoned by assistants and servants malnourished, who knows how many insect bites or worse.

6. Bates returned with 8,000 new species (07:57)

But he came back with a treasure trove for science and that booty included 8,000 new species. So of about 14,000 species in his collection, most of these new species were insects, so Bates—and you probably know the Amazon is an insect-rich place—Bates did a phenomenal job cataloging, collecting drawing, various insects and the insects that he's best known for are butterflies. Now Bates, when he got back from the Amazon, his timing was fantastic. He arrived in the summer of 1859 just months before *The Origin of Species* was published and after *The Origin of Species* was published he realized that a lot of his observations, a lot of his naturalist work could be better understood in light of Darwin's theory and he struck up a correspondence with Darwin. And in one letter to Darwin he wrote, "I think I have got a glimpse into the laboratory where nature manufactures her new species."

7. Batesian mimicry in butterfly markings (09:01)

And that glimpse, that flash of insight that Bates had was into a biological phenomenon called mimicry and a form of mimicry that we still name after Bates today called Batesian mimicry. What Bates identified going on in the Amazon with some of these colorfully-patterned butterflies, I'm showing you these as species pairs, each butterfly on the top and bottom is a different species and one of the pair is an unpalatable form, something that manufactures or contains in its body some alkaloid substances that are distasteful to birds and birds will spit them out when they sample them. What happens is that other species that are palatable that even don't possess these compounds, through the process of natural selection will come to resemble the unpalatable butterflies. In other words they're getting a survival advantage by looking like something that's distasteful to birds. And he saw this repeatedly in various groups of butterflies. So this form of mimicry when Bates explained it to Darwin, Darwin was absolutely delighted. He thought that Bates' paper on mimicry was one of the most remarkable papers he had ever read, and as Darwin's work unfolded in later years he would incorporate this additional work from naturalists into the whole fabric of evolution that he was describing.

8. Bate's book, *The Naturalist on the River Amazons* (10:17)

Now Bates wrote just one book called *The Naturalist on the River Amazons.* It's still widely available today, you can find it in paperback form. I encourage you to read books by these 19th century naturalists because they describe a world being sort of discovered at least by educated Western individuals for the first time. They also describe a world that sadly is not the same as it was 150 years ago. I have a little more to say about that later. Bates was also a little bit of a poet. He was a great artist and just as with Darwin, and I think somewhat influenced directly by his correspondence with Darwin, there were various passages in *The Naturalist on the River Amazons* that sort of waxed poetic about evolution. Here's one, Bates talks about how on these expanded membranes speaking of butterfly wings, "Nature writes as on "a tablet a story of the modifications of species."

9. Data from butterflies offers insight into our own evolution (11:10)

So I want to focus on, in the first part of my talk is that story. How are species modified? What can we learn, and we will in fact talk about the markings on butterflies, but I don't want you to go away thinking at all that this is just about butterflies. Just as with the stickleback work that Dave has described what we can learn from individual species like butterflies or fruit flies as you'll see, has general... offers general insights into the making of the whole kingdom the sorts of mechanisms that are at work everywhere and what scientists try to do is find the best models, the most tractable models that will give us these first principles. So we're going to focus on the question of how new patterns and how new features arise. And it's a little bit different than for example the hind fin reduction in sticklebacks. We're going to really ask not how something goes away but how something new evolves.

10. How did fruit flies and butterflies get their spots (12:05)

Now wings have been an evolutionary tablet throughout the insects, not just butterflies not just moths, not just beetles if you're familiar with things like ladybugs, but even in the more humdrum fruit fly world, wings have acquired all sorts of markings in the course of the evolution of these species. So you're probably most familiar with fruit flies as these annoying little nearly invisible things around your bananas in the morning or maybe you've had a chance to handle them in the laboratory and if you did probably the species you handled was not too colorfully marked. But throughout this group of flies there are some fantastic markings, albeit in black and white they have not discovered the color palette that butterflies have discovered, but they're nonetheless a great example of how new patterns arise continuously in evolution. So today I'm going to look at some simple patterns on insect wings, I'm going to look at spots and frame a simple question. How and why did fruit flies and butterflies get their spots? And we're going to look at a simple black spot that occurs on certain fruit fly wings, and some beautiful concentric colored rings of spots that occur on butterfly wings and get insights into how these new patterns have evolved and what that teaches us in general about innovation in the course of evolution. Let's look at a couple fruit fly species. These are two fairly closely related species. I'm showing you just the male flies, their whole body sort of looked at from the top down view on the left and their isolated wings shown over on the right. Well the obvious difference between these two species is that one has spotted wings and the other doesn't. In fact you'd be pretty hard pressed if you could examine the rest of the body of these flies to find almost any other difference. So there's this very pronounced difference. And these are the males of the species and only the males of the species and the bottom species called *Drosophila biarmipes.* Only the males have these wing spots. Before I get at the how, let's get at the why. And that's shown in the next short video.

11. Video: Fruit fly courtship behavior (14:05)

Look at the top of the fly with the spots and that's a little dance that he does in front of the female while he's pursuing her in courtship. So species that have these spots at the edges of their wings engage in this courtship display.

12. Sexual selection and courtship behavior (14:22)

Now a courtship display is really directly connected of course, to the process of mating and passing genes on to the next generation. So a courtship display is a form of what's called sexual selection, a term coined and described by Darwin at length in his 1871 book, *The Descent of Man.* So again, not just coral reefs, not just descent with modification, not just natural selection, sexual selection as well and because sexual selection is operating at that moment of mating, leading up to mating it's one of the most powerful forms of selection that goes on within species. Pigmented wings have evolved many times and this is the isolated wing of another *Drosophila* species called *Drosophila tristis* and we'll see in the next video that the idea's the same in terms of the courtship dance it's just the steps are a little bit different.

13. Video: Courtship dance of a difference species (15:18)

So if you see this male at the bottom is extending his pigmented wing, sort of in a matador sort of approach sticking out its left wing, she seems to be paying attention. She maybe was not as impressed as she should have been. Hey, hey, hey.... Now I know you're all laughing but you know, I have teenagers, and I've been to some of your dances.

14. Sports evolved via new use of old toolkit gene (15:57)

Okay, so this courtship dance is an important display that the males do and these sorts of displays are throughout the animal kingdom. Usually the male displaying for the females, sometimes comical, sometimes pathetic, and often unsuccessful. So how did these spots evolve? And the simple message is something very closely related to what David's been saying, the simple message is is that through a new use of a toolkit gene that these spots arise. So if you look at the left hand side, these are three different *Drosophila* species, the one in the center is the one you've been looking at that has these spotted wings on the males and on the right we're looking at the developing wings inside the pupal case of these flies using special techniques that allow us to see where a toolkit gene is being used. Not the blue stain that David showed you, but in this case the white pattern that you can see pointed out here with the arrow. That reveals where a particular toolkit gene is being used and you can see it's being used exclusively in this species at very high levels and this part of the wing is going to become intensely pigmented. Think of this toolkit gene as a paint brush and what this means is that there are genetic instructions in this species that instruct this paint brush to be used in a part of the body where it's not being used in other species. That's the novelty, that's the key change between these species, the spotted and the unspotted species.

15. Butterfly wing spots: An adaptation for survival (17:25)

Now let me just go to the colorful version of the same story. This is an East African species of butterfly. Now the spots in this species are being used for a different reason. These spots are not being used to attract mates or to impress mates, these concentric rings of pigmentation are out towards the edge of the wing, true but what they're doing is they're drawing the attention of predators, in this case, birds, away from the main body of the butterfly. The main body of the butterfly of course contains all its vital organs and its blood and if that was to be damaged it would probably be lethal. But the butterfly can tolerate attacks out at the edge of the wing and this is an East African butterfly photographed in the wild that has suffered an attack from a bird and what you can see is that a bird can take a pizza slice out of the wing, but the butterfly can continue to fly and all its vital organs are protected. So this is really sort of a decoy bulls eye, these false eye spots are to distract predator's attention away from the main body out towards the edge. So this is an adaptation for survival, not an adaptation for mating. Nonetheless it's real important to the selective advantage of these butterflies, the survival and reproduction of these butterflies.

16. Reuse of a toolkit gene creates the wing spots (18:38)

So what do we know about the making of these spots? Well, again, advances in developmental biology that have taught us about the sorts of genes involved in building body parts and patterning those parts have given us a whole tool kit of genes that are used in all sorts of species and we know about the use of some of these toolkit genes in the making of butterfly wing patterns. What I'm showing you here is on the right are isolated wings from two species, the Monarch butterfly which might be familiar to you in the upper right and this East African butterfly on the lower right and on the left we're looking at wings that have been stained in a special way to reveal where a particular toolkit gene is being used in the caterpillar. A week before those wing patterns would be visible to the naked eye, so this is an image you could only see in a special type of microscope to allow us to visualize where genes are being used. This toolkit gene in the Monarch butterfly is being used in all of the cells towards the edge of the wing and those white flecks of pigment you see at the end of the Monarch wing, those are not eye spots those are just little flecks of white pigment. But in the East African butterfly you can see there are seven spots where this gene is being used that don't have a counterpart in the Monarch butterfly. That's the novelty, that's the difference and if you want to understand the relationship between those spots and the spots in the adult butterfly, you can see this in the next animation. Each of these spots is made up of about 200 cells and I'll show you in the animation what those cells become.

17. Animation: Toolkit gene expression at center of wing spots (20:07)

So keep an eye on those bright green spots and over the course of about a week those spots of cells are going to be at the dead center, what we'll call the pupil of these eye spots on the adult butterfly wing. So this toolkit gene has taken on an additional job of marking where these eye spots are going to be in butterflies that have eye spots. That's only a subset of all species of butterflies.

18. Much of diversity is due to new uses of existing genes (20:34)

So what's the main message here from fruit flies and butterflies? The main message is that new patterns evolve when old genes learn new tricks, very old genes. The gene I just showed you we know is more than 500 million years old and possessed by most members of the animal kingdom. It has some very old jobs in, for example, building appendages but it's taken on a new task in these butterflies in terms of patterning these eye spots. So a lot of the diversities we see is not so much due to new genes, it's due to new uses of the same old genes. Okay, like a painter's palette, you don't necessarily need to invent new colors as much as you use colors in different ways. Okay,

19. Genes are reused in different ways via genetic switches (21:24) so how do they learn new tricks? How does a gene learn a new trick, and this is now going to connect with what you just learned about genetic switches in the stickleback case that David showed you. Well, those genetic switches govern how toolkit genes are used. It's mutations in the DNA sequence of those switches that change the function of those switches. And we can study these things by isolating these switches from different species and comparing how they operate. So when mutations occur in control switches novelty arise, variation arises and that's the material for evolution of form, evolution of novel spots for example in fruit flies and butterflies. So let me just show you this principle in a short animation.

20. Animation: Paintbrush gene switch in the fruit fly (22:05)

Let's compare two flies, one without spots which is the humdrum *Drosophila melanogaster,* one with spots on the male, *Drosophila biarmipes,* there's a gene we're just going to call it the paintbrush gene that's coding sequence is shown here in yellow the same sort of schematic arrangement that we showed you for the stickleback. Well, there are switches for this paintbrush gene that govern how it's used in the body. Well, both animals' genomes contain these switches and these switches govern the use of this paintbrush gene to fill in the color on the abdomen of the fruit fly. But in the spotted fruit fly there's an additional switch a switch that draws a spot in the wing so should the paintbrush is also used, in addition to its other jobs in drawing a spot on the wing of these fruit flies. Same principle is applying to butterflies.

21. Evolution acts by gain and loss due to chance mutations (22:55)

So what we understand here is the process of evolution involves both gain and loss. In the case of the spotted fruit flies a new switch has evolved that draws a new pattern. It's expanded the role, expanded the number of jobs of a toolkit gene. In the case of the reduced pelvic sticklebacks a job has been abandoned. The *pitX* gene is no longer used for hind fin development in the species that have adapted to these lakes and lost their pelvic skeleton. The gene still exists and other switches still exist for that gene, but the switch has been inactivated in the sticklebacks. So this is the broad picture of evolution we get from understanding these switches and understanding how genes are used. Gains and losses are happening. Evolution is not a steadily progressive process. Pieces of genetic machinery, pieces of routines that are used in building animals are set aside or abandoned other new ones evolve. So whether we're talking about sticklebacks or butterflies or in fact virtually any other animal in the kingdom, the message is the same gains and losses are happening in the course of descent with modification. So, wondering where do these new tricks come from we have to reinforce the message of yesterday. The animal does not conceive of this new trick. Mutations arise at random that will create variation in form. Mutations in switches arising at random. Nature, either in the form of a mate or a predator nature acts as the art critic that selects the better forms and patterns.

22. Q&A: Are the switch regions turned off or deleted? (24:32)

So let's stop there and see if there's some questions before we move on. Yeah, in the green shirt.

[STUDENT:] Is the switch for the hind limbs in the stickleback and for the eye spots in the butterfly, is it turned off or is it deleted all together? And if it's turned off, how?

[DR. CARROLL:] Okay, so in the case of the switch, let me just explain. For the butterfly, there's a new switch there so it's turned on. In the case of the stickleback the switch has been inactivated. I don't think we know yet at the level of detail you're asking whether it's been inactivated by a small number of changes or by large chunks missing. That's work that's in progress right as we speak. But it could be, and

I know other cases of switches that have been inactivated by just a few changes in the DNA code, not complete erasure of the switch. Okay, so this ought to be exciting, see if we've still got an arm. Oh, it's going right! Okay.

23. Q&A: Spots the only difference between fruit fly species? (25:38)

Okay right here in the white shirt.

[STUDENT:] I was just wondering earlier you said that you had the two different flies listed and you said that they were almost identical but they were still different species because one had a different wing. The marking on the wing, but if it's only the males that show that then are the females of both those species the same?

[DR. CARROLL:] Well they're not exactly the same. I can tell you that these species separated from a common ancestor 15 million years ago. I'm saying from the human vantage point they're virtually the same. Flies for example, in their courtship rituals, use lots of other cues in addition to this visual cue of extending the wings. They tap out a song. And the periodicity of that song is species specific. They also use pheromones. They also don't necessarily inhabit the same habitat. So some flies will prefer rotting fruit some will be on cactus, some will be on leaf litter, this sort of thing, so they are distinct species not for the sole reason of the spots being different, they were distinct species a long time ago, their lineages diverged a long time ago and today, if co-mixed, there are so many different cues, the males of one species would have no success with the females of the other species. If that's what you're driving at. We're going to have to move on so just save some of those questions, thanks for that one.

24. T.H. Huxley in 1863 on human evolution (27:03)

So we're going to move to perhaps the question of questions. Our species. What is all this talk of sticklebacks and butterflies and fruit flies and the fossil record and all of that what does that have to do with us? And I think you can appreciate that culturally this has been the thorny point. You may not know that Darwin really didn't deal with the question of human origins in *The Origin of Species.* He dodged it, he knew he had enough trouble coming. It was much later that he took up the issue of the origin of humans. But his foremost and most formidable ally Thomas Henry Huxley, or T.H. Huxley, he didn't dodge it at all and shortly after *The Origin of Species* he wrote a book called *Man's Place in Nature*. Let me just read a brief passage. "The question of questions for mankind, the problem which underlies all others and is more deeply interesting than any other, is the ascertainment of the place which Man occupies in Nature and of his relations to the universe of things." In the sketch at the bottom you may have seen various forms of this, but that's the original frontispiece from Huxley's *Man's Place in Nature.* Huxley, like Darwin, had undertaken a long voyage as a ship's naturalist. Unlike Darwin, Huxley grew up with very humble origins he was a really "up from the boot straps" sort of guy. He was a very intense man, he was a great scientist he was a great anatomist, and he was quite an expert on both human anatomy and on ape anatomy. As apes started arriving in England from Africa Huxley was one of the first to make lots of accurate descriptions of their skulls, their anatomy, et cetera and understanding the relationship between apes and humans.

25. First Neanderthal fossil supported Huxley's ideas (28:51)

So he took this matter of human origins head-on and soon really almost in the same context, time context as *The Origin of Species* he had new material to think about not just the great apes coming out of Africa and arriving in zoos or anatomy labs in England. He had fossils. So again, imagine the coincidence that David described to you the discovery of *Archaeopteryx* right after *The Origin of Species*. I described to you the discovery of mimicry by Henry Walter Bates. Well, this fossil was dug up in 1856. It took a little while before scientists realized what it represented, but this is the original Neanderthal skull, the specimen for which that species is named. This was discovered in Neander valley in Germany. At first it was unclear what it represented. The leading German anatomist of the time did not accept evolution and reasoned away this skull as the diseased remains of a soldier from the Napoleonic wars. But this skull was found with some bones of ice age mammals, mammals that were extinct. So it was quite clear that it was of ancient origin and we are looking at an ancient hominid. Now I'm not going to walk through the whole fossil record of human evolution, but I just want to highlight a few of the most remarkable fossils so you get some sense of what has been discovered, but it is a much wider array than we're going to see today in my lecture.

26. 3-million-year-old bipedal hominid: Lucy (30:31)

Much older than Neanderthal, and there's many, many many more specimens of Neanderthal now, we know a lot more about its culture from cave findings and things like that. You may have heard of Lucy, known as *Australopithecus afarensis* Lucy was dug up a few decades ago in Ethiopia. At the time, the earliest upright, in other words, bipedal, hominid, a little bit more than 3 million years old, her skeleton is shown here on the right. But this record of fossil hominids now extends back roughly 6 million years. The inference that Lucy was bipedal comes from detailed examination of some of her anatomy,

27. Older evidence of bipedal hominids: Laetoli footprints (31:15)

but there's other evidence about the existence of bipedal hominids at this time span of more than 3 million years ago and I want to show you this example because personally I think it's one of the most spectacular fossil finds ever. At a dig site called Laetoli in Tanzania about 25 years ago a team discovered these footprints which are those of an upright walking hominid, adult and juvenile alongside each other, through what was a fresh ash bed. You may know that east Africa is volcanically a very active region, the so-called Rift Valley. Well, when there were volcanic eruptions, when that ash falls maybe a little rain falls with it, that has the consistency of wet cement, well, these two hominids were walking along and their footprints were made to be uncovered by another hominid more than 3 million years later. This is about an 80 foot long trail and I think you can see the foot impressions rather clearly.

28. Fossil record of *Homo sapiens* (32:11)

So in addition to footprints of ancient hominids we do have a lot of fossil evidence of our own species *Homo sapiens*. And just to give you a little bit more of a time context, the oldest specimens we have of *Homo sapiens* date to about 160,000 years ago. So our species is, depending upon your relative time scale, relatively young, perhaps younger than 200,000 years old and there's a fairly good fossil record of our history and we know from that fossil record for example that *Homo sapiens* and *Homo neanderthalensis*, Neanderthals, co-existed at various times and in some places on earth. But we're down to one hominid now, it's us so we're going to have to make do.

29. The evolutionary tree of hominids (33:01)

The evolutionary tree of hominids has been worked on quite a great deal. I want to give you some notion of what that tree looks like without burying you in some of the details but if you just look at this shaded region on the left and the red bars, the red bars represent inferred proposed, individual hominid species on our line and the length of the red bar represents the time frame that paleontologists think that these individual species spanned. So we have a rather bushy evolutionary tree. All lines but one have died out. We are closely related to the chimp and the chimp's close relative is the bonobo, another type of chimpanzee and then a little more distantly related to the gorilla and the orangutan. So if you trace these branches down the evolutionary tree you see that we shared a most recent common ancestor with chimpanzees roughly six to seven million years ago.

30. Problems with finding hominid fossils (33:58)

Now, just so you understand the nature of the fossil record there's been tremendous effort to uncover fossil hominids and hominids moved out into areas that left a better fossil record than the sorts of rainforests that things like gorillas and chimpanzees live in. So we could be fairly confident that if you knew what the chimpanzee evolutionary tree looked like it would be a bushy tree as well, but there's only one fossil species of chimpanzee known because where they lived and where they die is not a very good place for fossil preservation. So I don't want you to have some idea that there's a ton of hominid species but just for some reason these four apes have existed unchanged. When you look at a gorilla or you look at a chimp or you look at an orangutan, you're looking at also a product, a twig on that tree of life. There were lots and lots and lots of other species on that lineage that are no longer around today. Remember, extinction predominates the pattern of evolutionary history.

31. *Homo sapiens* are a very new species (34:53)

And of all those red bars, it's this one that's us. I just want you to get a sense of the time scale that the history of our species is only about 50% of the total history since that split from our common ancestor with chimpanzees six million years ago and the implications of that are that a whole lot has happened before the origin of our species. A whole lot of evolution was taking place before the dawn of our species. Ninety-seven percent of the time was elapsing but a whole lot of changes in body form, upright walking long proceeded *Homo sapiens*, et cetera. So the challenge to understand human origins better is to understand from the fossil record the order in which various characters appeared or disappeared and to understand a little bit of the lifestyles of those species if possible and then just sort of figure out what was going on, what makes us different from any other hominids, if anything, in the course of time.

32. Hominid skull evolution (35:53)

So what was going on? Well there were some obvious things going on. One of the most obvious things going on was skull evolution. So I'm showing you here representative skull... sketches of representative skulls from the chimpanzee in the upper left and from some ancient hominids and modern *Homo sapiens* here in the lower right and lots of changes were happening in the skull. If you pay attention in particular to the overall size of the skull, to the size of the skull apportioned to the brain case, to the jaw, et cetera. So *Australopithecus africanus* is a relative of this guy here, this is a cast of *Australopithecus boisei*. You can see for example, you might even say he has a little bit more ape-like appearance, broader face shallower nose, bigger jaw and the sagittal crest on the top of his head. This is *Homo erectus*, shown there on the lower right again a younger species but still a good hop, skip and a jump away from *Homo sapiens*. And Neanderthal, Cro-magnon, so there's been lots of changes in skull morphology but those of course reflect some interesting changes going on inside that soup bowl and that's with brain evolution. So whether it's just our own point of view or whether it's something if there was another type of naturalist on the planet that wasn't human, whether they'd agree that this was the most dominant feature of human evolution

33. Evolution of larger brain size in hominids (37:13)

clearly brain size has been changing and been changing in some dramatic ways. What I'm showing you in this bar graph, if you look back to the brain sizes of hominids on our line of the tree you can see that they have been ascending in size over evolutionary time, but we are talking about millions of years. You can see roughly from a little more than two million years ago to a million years ago almost a two fold step up. That was probably one of the more dramatic phases of change in brain size. It also happens to be a time when the earth's climate was changing quite a great deal and there's a lot of theories that one of the driving forces, one of the selective forces here for the increase in brain size was hominids, unlike their ape cousins, being out on the savanna and coping with the dramatic climate changes the droughts, the heavy rains, the migrations of animals remembering where fruit was, remembering where food stuffs were. More complex social behaviors and you needed a bigger brain to handle all those sorts of activities. So coping with a more dynamic climate probably played an important role in expansion of the capacity of our brains. But, just before you get a little too full of yourself I will point out that Neanderthals had bigger brains than we do, and they're not around anymore.

34. Traits that distinguish humans from other apes (38:30)

There are lots of other traits changing, and just as for the sticklebacks if you remember David's list of all sorts of behavioral, morphological and physiological traits that were changing, we know all sorts of things that distinguish us from other apes. Highlighting a few here, brain topology, all the folding of our large brain, we do have brains with a fairly different anatomy. Language, the evolution of speech and language of course a really important step in our biological and our cultural evolution. Reduced hair cover, a large relative brain size was already mentioned. Our skull is balanced upright on our vertebral column. Walking upright. Walking is a pretty clever invention and one thing it did of course was it freed these things up to do other things. Lots of other characters that have changed. So we can't just be thinking about brain size alone. In fact if you're going to have brain size changing some interesting things have to happen with our changes in lifestyle or our changes in life history, namely the length of time that we develop in the womb is going to change, pelvic size in females is going to change. Delivering big-brained babies is quite a challenge. So we're born relatively immature and require a long period of maternal care for our development. So lots of things are going on that are changing. Our diet is changing from more of pretty much a herbivore to more of an omnivore in later species and you see these changes for example in teeth morphology and teeth make great fossils so we know a lot about the record, or the evolution of our teeth.

35. What can we learn about human evolution? (40:08)

So if we try to understand human evolution at the level we're trying to understand sticklebacks and butterflies and fruit flies, what should we expect to find out? We should expect to find that what's true for those other species is true for humans. Some genes will have learned new tricks, other genes will have abandoned former tasks. The challenge right now, right now, and available right now is how can we tell what has happened? Well we've got some new tools to do that. And one important tool is we've got the complete genome of humans and now just this year the complete genome of chimpanzees, our closest living relative and that allows us to do some comparisons and some contrasts to say, okay, what's identical between ourselves and our ape relatives, and what's different and what's the meaning of what is different?

36. Comparing the chimp and human genomes (41:01)

So let me give you a little bit of a snapshot of what we can tell so far by comparing our DNA with the DNA of chimpanzees. Gene number. We have really roughly the same number of genes. Now I can tell you that a few years ago, there was the expectation before the human genome was sequenced in some quarters that humans would have more genes than any species. After all, are we not the pinnacle of evolution? Okay. Not only do we have about the same number of genes as chimpanzees, we have about the same number of genes as mice, okay. Again, the whole complement of genes is roughly the same between these different mammals. About 25,000 genes, most genes have a one-to-one counterpart. What about DNA sequence? Well you've probably heard a number like this, we've just gotten more exact by having the complete sequence but 98.94% identity. That means only one letter out of 100 in our DNA code is different from that of a chimpanzee. Now that's a pretty impressive similarity. That's a really close relationship, but there's three billion letters of code in our DNA, so a 1% difference still says, there's more than 30 million differences between ourselves and chimpanzees. Some of those differences mean nothing, perhaps the vast majority of those differences mean nothing. But some of them, of course, are the very stuff that makes us different from chimps, makes me able to have this conversation with you and to throw those t-shirts out into the crowd.

37. Loss of jaw-muscle gene could allow a larger skull (42:33)

So what biologists now want to understand is what makes humans unique and different? Well, we can learn some things, and let me just give you one example. By comparing DNA we can see some things that have happened in our DNA that didn't happen in the lineages of other animals and I'm just going to zero right in on a little chunk of DNA code of one particular gene and this is a gene that in other apes plays a job in building a big muscle, a muscle that moves the chewing apparatus of those apes. And in those other apes you can see that the code is absolutely identical between them and absolutely identical with humans except for where those two asterisks are. And where those two asterisks are, those letters of code have been deleted only in the human lineage. This actually inactivates this gene completely and the muscle whose formation is influenced by this gene is tremendously reduced in humans. But not other muscles. Remember how David told you yesterday about the modularity of bones in vertebrate skeletons. Well, remember the movement of those bones is controlled by muscles. Well, just as you have a modular skeleton, you have a modular muscle assembly and muscles evolve their size and shape independently of one another and some genes are devoted to building certain muscles and not others. This gene plays a huge role in the development of the so-called temporalis muscle that moves the chewing apparatus. Well, in comparison with other apes, our temporalis muscle is really reduced. We have, say compared even with ancient hominids like this guy, had a pretty big jaw, we have a really slender jaw. Our diet has changed a lot, we're not eating as much rough grain, we're eating meat that's been cooked and the interesting consequence of that may well be that now that we've taken a lot of pressure off the skull of holding this massive muscle in, which attached up to the sagittal crest here and you'll see that these other skulls don't have a sagittal crest, that this may free up some of the skull to expand in other ways. So rather than having a thick skull for holding this muscle mass on the side of our head, our skull is a little thinner and a little larger, and we're packing a little bit of the old brain meat in there. Okay? So some consequences, one of the advantages of more slender chewing apparatus may facilitate certain aspects of skull evolution that were important.

38. Modern genetics tries to find key evolutionary changes (45:04)

I want to just leave you with that notion is that what we're trying to do here is we're trying to pinpoint meaningful genetic changes in the evolution of the human lineage and correlate those changes with information from the fossil record, with information from comparative anatomy. We're not always going to be, we're not going to have the level of certainty, perhaps, that we had when we studied sticklebacks and fruit flies and butterflies that this is the exact change for this exact anatomical change because we can't do some of the experiments that would test that at the same level we could in model species. Nonetheless these correlations are really intriguing and they are no doubt signatures of things that have been happening in our lineage. So this is just the beginning of this era of discovery. This work is just able to be done right now. So you, perhaps, in the coming years, will have an opportunity to ponder human origins at a level Huxley could have never imagined, at a level Darwin could have never imagined. You'll be able to look at the precise changes that make us different from other species and even from earlier hominids and weave that into an understanding of our physiology, of our anatomy of our neural behavior.

39. Resistance to the theory of evolution (46:20)

That's possible, but will you have an audience for that research? Well, maybe, maybe not. I want to take a few minutes to address the general issue of the acceptance of all this evolutionary knowledge in our culture and particularly emphasize the importance of this knowledge in human society. Most polls conducted over the last several decades would come up with about this same ratio, of about half in America, about half of all Americans accepting that plants and animals have evolved from other species and about half of Americans not accepting that. So that's despite 150 years of science from fossils genes, and embryos. And you've seen a lot of evidence in the last two days that's been gathered in just the last few years and it goes down to the very fine details of DNA code changes that have occurred, independent evidence from fossils, genes, and embryos. Well, let me call upon two of Huxley's grandchildren to address this issue. The first is Aldous Huxley. You may have heard of him he wrote *Brave New World*. But he also pointed out in another one of his books that facts do not cease to exist because they are ignored and of course the facts of evolution are being ignored by that half of our society that does not accept them. Now you might say, "Look, this is just a personal philosophical matter." This is just something, this sort of differences of opinion that we can live with and we have to find some way "to accept those differences." I won't accept that. The denial of evolution is about the denial of 200 years of scientific work and it's not a merely philosophical matter. Aldous Huxley's brother—the Huxleys were kind of a gifted family—another writer points out almost five decades ago that "it is as if man had been appointed managing director of the biggest business of all the business of evolution and whether he's conscious of what he's doing or not, he is in point of fact determining the future direction of evolution on this earth. That is his inescapable destiny and the sooner he realizes it and starts believing it, the better for all concerned."

40. Darwin's "endless forms" are endangered (48:43)

Our destiny, and the destiny of the living things on this planet are very much dependent upon choices that we make and our understanding of science. Let's look at some of the choices we've made in the past. Those choices in the past have to tell us that the endless forms that Darwin wrote about are not endless. When commercial whaling started in the start of the 20th century, the original populations of whales were somewhere around these numbers shown in the left-hand column 100,000 right whales, 240,000 humpback whales. Those populations have now been reduced somewhere between 80% to 97%. Even with the moratoriums on whaling, some of which were enacted as early as 1935. So the large cetaceans, some of which you've heard about through David's lecture, are far fewer than there used to be. And you might say, "Okay, we don't depend on whale meat "anymore and there's whale watching and maybe those "guys are protected." But did we learn our lesson? No, we didn't learn our lesson. Let's look at the vanishing of large ocean fish. Cod for example. Cod which you may know played a critical role in the ability of sailors to sail the open seas and explore new worlds and to settle those new worlds. Cod that were so numerous off the East coast of the United States that sea captains complained of being pestered by the fish. Well, in 1992 the originally enormous Grand Banks fishery off the Canadian coast collapsed. Collapsed completely, the cod populations were absolutely decimated. And we know that rapid evolution in those cod populations preceded their collapse. Rapid morphological evolution, rapid changes in their reproductive rates and at the age at which those fish reproduced. Fishing is a form of artificial selection. Fishing is a selective pressure on fish populations if done without any consideration for the effect on those populations, it can backfire in our face and there's no more fish. Tuna, marlin, swordfish, similar story. Ninety percent of their biomass, meaning the total number of individuals and their total sizes has been reduced since the end of World War II. These are of course important food stocks. And there's byproducts of this activity. Sharks, for example, are caught in the nets or the long lines that are used for catching these other fish and you may not be too sympathetic towards this but nonetheless these animals play an important role in the ecosystems in the ocean and have for more than 400 million years. Hammerhead sharks, white and thresher populations have declined by more than

75%. So if Bates was to go back to the Amazon, the parrots and butterflies that had enchanted him, some species would be gone, they certainly would be nowhere near as numerous as they were 150 years ago. If Darwin returned to the Galapagos today he'd find that the very symbols of the islands, the Galapagos tortoise ,as well as certain finches, are extinct on some islands. The endless forms are not endless. And it's not just species but entire ecosystems that have been exterminated or damaged.

41. The alternative to thinking in evolutionary terms (51:46)

So evolution is not just important for medicine it's important for nutrition, understanding, evolution is important for nutrition for human health and for our economic livelihoods. So I'm going to just close with one thought and it's a thought that comes from a Nobel laureate a few decades ago, Sir Peter Medawar, who said, "The alternative to "thinking in evolutionary terms is not to think at all." And I say particularly to your generation that that's an alternative our species can no longer afford. So let's take some questions.

42. Q&A: Why did some hominids last longer than others? (52:20)

Lots of hands, I'll just try to swing across the room let's swing over here to the right, yeah, in brown.

[STUDENT:] The chart of all the humans and when different species existed, one of the species stood out as having survived for a long time. Do you know what species off the top of your head that was and any reason why its span on earth was so long?

[DR. CARROLL:] Yeah. When you look at those red bars there's two things you have to take into account. These are estimates and sometimes they're an estimate as broad because we don't have exact dating on all of the fossils that may belong to that species. The second may be just what you're inferring is that the life span of that species or of sub-species that are so closely related to it that we can't distinguish them right now may have been fairly extensive. So *Homo erectus*, for example, seemed to have had a fairly long run. That may be partly due to the amount of territory that a species has covered. It may be in part due to the climate how harsh the environment was, how many upheavals that species had to confront, so there's a little bit of perhaps, luck factor, and some may be just how well adapted that species was. There's, I think, no textbook answer to your question. Those are really questions that the answers need to be worked on now. Far back right.

43. Q&A: Could some hominid species just be variants? (53:39)

In the tie, sorry behind you and I'll come to you next.

[STUDENT:] How do we know that like the different species of hominids were a different species not just different variants? Because, like, in an earlier lecture you said that if we found fossils of all varieties of dogs we had we'd classify them all as different species.

[DR. CARROLL:] Right. So paleontologists, and you can ask some on your own because I'm not one, but I'm going to represent their position, is that paleontologists are inferring fossil species from a variety of pieces of data. Some will be the time span, are these specimens coexisting at the same time at the same place? If they're separated by a fair amount of degree in time that's one piece of data. The other would be look at morphological characters look at, for example, brain size, skeletal form, et cetera. If those divergences are greater than the range of variation that you might see in living populations then the inference might be strong that these are a separate species. If they're found in different parts of the world that's also another inference. So this is an area where there's not a cut and dry answer. These conclusions are overturned quite frequently where something that may have been called two different species, it's now agreed by some further work that that should be made into one species or something that was as identified as a single species is now from the identification of more specimens, split into two. So it's a bit of detective work and it reflects the consensus of that dynamic process of testing ideas and generations of scientists wrestling with these ideas. There's been lots and lots of change in perspective in the human fossil record, the hominid fossil record over the past 150 years, especially as that fossil record grows and be prepared, you've probably heard there's been some spectacular hominid fossils found within just the last two years, which again have the potential for upsetting the apple cart of our notions of how this all happened.

44. Q&A: Gene or control region mutations more likely? (55:39)

Okay, let's go back left, gentleman there in gray or black, yeah. Right there.

[STUDENT:] I was wondering, you and Dr. Kingsley were talking about how there was a regulator part of the DNA and then there was also the protein coding part of the DNA and I was wondering if either of them are more likely to be mutated than the other?

[DR. CARROLL:] Great question. So the question is either one, non-coding or coding DNA more likely to be mutated. In terms of just that event of mutation, no. There's not a difference we see between the propensity of just DNA sequence wherever it is to be mutated. But in terms of which types of mutations are more acceptable or more tolerable in the course of evolution carry the smallest penalty with them, make certainly the best ratio of advantage to disadvantage, for the evolution of form it may well be that it's changes in these genetic switches, because they don't disrupt the function of the gene elsewhere, may be the much more common form of evolution in DNA sequence in terms of evolution of form than changes in coding regions. So that's not to say the sites of mutation are different it just says that what selection can use may be biased towards non-coding DNA in these cases. Gonna wrap up there, thank you very much.

45. Closing remarks by HHMI President Dr. Thomas Cech (57:08)

[DR. CECH:] Thank you Sean Carroll for a terrific final lecture in our series. To make the Holiday Lecture series it requires a lot of people and I want to thank the student audience for your terrific attention and great questions. Thanks to the production team and especially thank you to our speakers. From all of us at the Howard Hughes Medical Institute, happy holidays.