Explaining the Human Condition: Problems and Prospects

Presentation by Ajit Varki, M.D.

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VARKI: The first point that I was going to make was actually already made by this Foundation, and that is that if you want to know where you are going, you have to know where you came from. We need to know what makes us what we are, how we got here, and where we came from. It's the totality of this information that's going to, eventually, allow us to try to answer this question.

I also realized that the Foundation had a broad view when I picked up this quote from your brochure where Walter Kistler says that “the purpose of the Foundation is to bring some light into the dark cave, so that humanity really sees and understands its surroundings and its own place in the universe.”

Let's just zoom right into that region of evolution that gave rise to us, the origin of primates. There's extensive molecular evidence now showing that our closest cousins are the rodents, not dogs or pigs or whales or anybody else, but the rodents. So, we actually picked the right species in terms of research – mice and rats – next to primates. Then, of course, we have common ancestors with prosimians, New World monkeys, Old World monkeys, lesser apes, and great apes. My work is focused on the hominids. It's pretty clear now that we shared a common ancestor with the orangutan about 13 million years ago, with the gorilla about 8 million years ago, and with the chimpanzee and bonobo, or so-called pygmy chimpanzee, about 6-7 million years ago. Now, the remarkable fact is that while we classify all these species as great apes, the mean amino acid difference between our proteins – between humans and the bonobo/chimpanzee clade – is less than 1 percent, and we’re closer to the bonobo and chimpanzee than any of us are to the gorilla.

In fact, the correct classification now is as follows. I won't go into details, but basically we are classified as Homo along with Pan – these two species under hominids. So, is it wrong that we call all these species “the great apes”? I've always wondered about this, and I feel that we've gone too far overboard in the other direction, going from saying that humans are totally unique and different to saying that the politically correct view is that we're just a third chimpanzee (although I really like that book by Jared Diamond of that title).

Over the years, then, I have collected these features of humans that seemed to me to be somewhat different from great apes. This is just a part of a very long list, an amateur list – I'm not an expert on this kind of topic. You all know about brain size, the adduc-tive thumb, and body hair, but some of you may not be aware about the chin, skeletal muscle strength, the descended larynx, the penis bone, concealed ovulation, breast tissue in virgin females, a different chromosome number, ear lobes, frequency of third molar impaction (wisdom tooth impaction), and so on. This list does not have cognition, consciousness, language, or any of those things on it. Chris Wills saw this list of mine sometime in the late 1980s when he was writing a book. He took this information and put it into one of these phylograms. And he put it in his book [Children of Prometheus: The Accelerating Pace of Human Evolution, Perseus Publishing. 1998], saying, we stick out like a sore thumb, or like a fishing pole.

There is something unusual about us... How do you have a group of species that are a relatively conservative clade, then you have this unusual species emerge?

There is something unusual about us, and I don't think it's purely anthropocentric. I think it's an interesting
question of evolution. How do you have a group of species that are a relatively conservative clade, then you have this unusual species emerge?

[Referring to slide] This is my daughter when she was born in 1984. About ten years later I was flying across the Pacific on a long flight with her and trying to keep her busy, so I took out a dictionary that she happened to have and I said, “Check entries in the dictionary under each letter from the top. Stop when you reach the first one that you think is unique to humans, and I’ll help you out.” In very short order, we came up with abbreviating, bag-making, calculus, darts, etc., and hit zeroing pretty soon. We finished up in an hour. Then I said, “All right, take the letter S and scan all the entries under the letter S and record all the ones that you think are unique to humans.” And we started with sacrificing, sack-making, saddling, and went on and on. By the time we reached the middle, spending, we were already tired so we jumped to the end to surfing. The point of all this is that there is something unusual about us humans, and I think it’s worthy of study and it’s not an anthropocentric point of view. There is something to be studied and it’s quite big.

The most obvious difference is cognition. There are many areas of cognition: the arts, the humanities, and the sciences. My expertise is in the sciences. [Referring to slide] Here we see C.P. Snow’s great divide of the natural and social sciences, but actually I see the sciences somewhat differently: that is, engineering and computing sciences, physical sciences, and biological sciences being quite distinctive, and I’ll explain why. Over the last century, all of these sciences have made major inroads into each other, although I would daresay that while the social sciences and biological sciences are beginning to merge, there’s still somewhat of a gap.

Now, I had the good fortune, as I mentioned, of having come from a background in biomedical sciences. This is a “shotgun marriage,” the one field where we cannot afford to say there’s social science or natural science or physical science or biological science. There’s only one science—it’s only science—and we have to use information from all the fields. This gives me the advantage of having a central view in terms of many of these problems.

If you look back at these different sciences, engineering and computing are highly precise. Well, we created these sciences; we know the rules. Unless somebody loses the code, we know exactly what we’re doing there. In the physical sciences, we didn’t plan it that way, but it turned out that there are almost universal laws in most of the physical sciences. So, there’s a tendency to believe that biological sciences fit in here as a form of a highly precise type of science, as opposed to, as some people would try to argue, the social sciences. I would say that’s wrong. The central dogma of molecular biology that Francis Crick enunciated in 1958 is: “DNA makes RNA makes protein.” It’s a wonderful and almost digital dogma, but there’s a tendency to then think, as this student put out on the Web recently, that DNA makes RNA—she recognized various kinds of RNA—makes proteins; add some chicken fingers, and you get me! In other words, protein makes cell makes organism. In other words, DNA makes the organism.

I organize some meetings on human origins in San Diego, and the last time I heard Francis Crick speak, this is what he said, “There are no laws in biology—only widgets.” Widgets, as you know, are little mechanical devices that are useful for little things. What Francis was saying is, “Now I see that biology is just a huge collection of widgets.” We have all these little things that do little things. We conglomerate them in various combinations to achieve things that seem to work. So, really, I think the physical sciences have to get used to the idea that there are no laws in biology. But perhaps there is one and that is this famous statement of Dobzhansky: “Nothing in biology makes sense except in the light of evolution.” But I think we need to be very careful. I like the statement of John Coffin: “Although no biological explanation makes sense except in the light of evolution, it does not follow that all evolutionary explanations make sense.” So, you have to be very careful, but that should not inhibit us from speculating and thinking along those lines.

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The other point I’ll make, since I’m in Seattle, is that we have our creationalists and we have our evolutionists, and we think that they are in two different camps altogether. Of course, the creationists now
have come up with the idea of Intelligent Design. I realized in medical school that we train people how to take care of one species – humans – but we teach nothing about the evolution of that species. Actually, most medical students think that evolution results in optimal design, that everything is perfectly designed and optimal, when in fact, what we are right now is a snapshot in the history of this complex process called evolution. "Survival of the fittest" was not coined by Darwin, and "survival of the luckiest" could happen just as well.

Let's go back to the central dogma [DNA -> RNA -> protein -> cell -> organism], and I'll give you a couple of other reasons why the dogma is inadequate. Obviously, DNA is meaningless unless you express DNA, and the physical environment has an impact. The biological environment – there's a huge impact of microbes, particularly, on the expression of our DNA. And in some species, we have cultural environments where we can alter each other's DNA expression. In the case of humans, we've expanded this cultural environment to take over all these other environments, so I daresay that humans are a major cause of gene expression on the planet today, in many, many, many species, including ourselves.

But there's another reason why this paradigm is incomplete, and that's a molecular one, which is really my area of research. Besides DNA, RNA, and proteins, there are two other major classes of macromolecules that got left out of the molecular biology revolution. One are lipids – fats – that form membranes, without which you don't have a cell. The other very major one is called glycans, or sugars. This is not carbohydrate diets and energy, and so on. If you were to approach a cell, it would look like the Amazon Jungle, and everything that was green would be sugars. That entire area of biology just got left out of the molecular biology revolution because it was too hard to study. I stumbled on it coming from a background in hematology and stuck with it, and it now has a name. It is called glyobiology, which is really a variant of molecular biology.

[Referring to slide] Here I'm showing you two cells, and it's not an exaggeration that I've drawn there in terms of the thickness and complexity of these glycans. So really, we have proteins and enzymes, glycans and lipids, glycoproteins and glycolipids, giving rise to cells and matrices, tissues and organs, organisms. Of course, things do signal back to DNA, although it turns out that a lot of what we thought was "junk DNA" is, in fact, very, very functional. But, of course, don't forget diet, microbes, parasites, physical environment, and, of course, in an organism like ourselves, cultural environment.

This is an overview of my thinking about the human condition. Our own specific research has to do with a finding that there was a molecular difference between humans and other animals. Basically, there is a molecule that's on that cell surface that sticks right out, called Neu5Ac – it's a molecule called sialic acid. We found that the other major variant of this, called Neu5Gc, was missing, specifically in humans, though present in all the apes and other animals. The reason for this is a specific genetic mutation that occurred about three million years ago in one chromosome in one individual somewhere, and is now fixed in the worldwide human population. We actually have evidence now that it was probably fixed a few hundred thousand years after the initial mutation.

Essentially, what we found is that as Ac is the precursor of Gc, so we're actually mutants, being unable to make this, but like any metabolic precursor, we accumulate this other molecule. So, we have two differences – one is a missing Gc on our cell surface, and the other is that we have an excessive Ac. This has raised a huge number of questions that we have been pursuing over the last decade: how, why, what, when, where. I'm not going to go through any of these except to say that it ranges all the way from studying fossils with Meave Leakey and Svante Pääbo to studying the brain with Rusty Gage to studying stem cells, or studying infections or malaria with people at CDC.

We're finding that a lot of this has had some impact on the human condition.

This slide is from a review ["An Anthropocentric View of Primate Gene Evolution"] I wrote recently about known genetic differences that have emerged over the last decade between humans and great apes. This is an anthropocentric view, starting with rodents and coming down to humans. These are genes that have undergone these types of different classes of changes. We initially found one genetic difference in sialic acid biology. The entire field of sialic acid biology involves about 55 genes, and out of all of these, we have now found 14 genes in which there have been significant changes in sialic acid biology. We think that this means this is a signature of some event that
occurred in human evolution that left its scars, so the sialic acid system has been shaken up in humans. That's what we're trying to study now.

So, how do you approach this kind of problem? Unlike most other fields of science, when it comes to humans, or, for that matter, great apes, 99 percent of the experiments you would like to do, you cannot do. You're left with taking a very different approach, for which I realized that my training as a physician was extremely useful — that is, the approach of making a diagnosis. If you went into the emergency room with a coma, the worst possible thing that can happen to you is to have the neurologist arrive immediately. The neurologist will immediately go to your brain and miss the fact that you've got a murmur in your heart or a spot on your toe and what you've really got is bacterial endocarditis, because you've had some infection that came from somewhere else and that's why you happen to be in a coma.

We need to make comparisons between great apes and humans and other animals — obviously everything we can find out coming from a common ancestor ...

The right way to proceed is to collect every possible piece of information and put it together before you try to make a conclusion. The point is: How do you proceed? The right way to proceed is to collect every possible piece of information and put it together before you try to make a conclusion. So, my view of approaching the human condition is that. It's fine to follow Sutton's Law and go for the brain, and to those that do it, I think that's wonderful; I commend you for doing that; but I think we may just as well find clues in the skin that lead us to the brain or elsewhere. It's not a surprise that Arthur Conan Doyle was a physician; in fact, many murder mysteries are written by physicians. Physicians are accustomed to being detectives, basically. I think that Richard [Klein] would say that sometimes it is sort of like a detective story that we're trying to figure out. So, this is our detective story for sialic acid biology.

Coming back to this issue of the different sciences, when I got interested in what makes us human, obviously I had to try to learn some anthropology and I tried to educate myself from Anthropology 101 onwards. As I said, my medical school education didn't teach me any of this. I found to my surprise that, as you all know, most of anthropology is classi-
We managed to convince the powers-that-be to put money into the Chimpanzee Genome Project. We held a symposium last year when the information in the draft sequence came out. It's still coming out. The bottom line is that things are far, far more complicated than we thought. There are many, many differences, many of which may be neutral. We are going to be searching for many needles in a very large haystack.

The other issue related to this is that apes are not mice. Having spent time with apes, I've come to realize they are very special creatures. So, we've argued ethical, legal, and social issues regarding this. We — my colleagues Pascal Gagneux and Jim Moore, who are primatologists, and I — have written an article entitled “Great Apes in Captivity: Ethical and Scientific Challenges in the Post-genomic Era,” which will come out in the same issue of Nature. [Editor's note: “The Ethics of Research on Great Apes,” by Pascal Gagneux, James J. Moore, and Ajit Varki, was published in Nature, 437 (September 1, 2005), 27–29.] We are sitting on the proverbial slippery slope where neither end likes us, but I think that is the place to be on issues like this. You have to be on a slippery slope sometimes.

... a hypothesis I have come up with ... is that the major diseases of a given species are likely to be related to maladaptations during the recent evolutionary past of that species.

The genome, of course, is a diploid set of chromosomes. We know exactly what the genome is. We know how to go about defining it. A few years ago we published an article in Science suggesting that while we knew so much about humans, we needed to know more about chimpanzees and great apes, and we suggested the term phenome. It's still not in any dictionary but I just checked this morning and there are 113,000 entries in Google for phenome. It’s now being used in many different ways, but our original definition is: complete information about an organism's phenotype and relevant environmental influences. Here is the problem we face: We have the human genome at a 10X coverage. All that remains to be done is to find the differences between individuals, mostly. And we have a huge amount of knowledge about the human phenome. Over the millennia, we've accumulated so...
much information in so many fields of endeavor, so this makes sense. We can look at the genome and the phenome and its influence on the environment, and compare to the genotype and the phenotype.

The chimpanzee genome, by the way, is not complete. It's not polished. It will be polished in the next few years, and it will come up to the same preciseness as humans, although there's more genetic diversity among chimps. When it comes to the chimpanzee phenome, it turns out we know very, very little. So, we have suggested that this is where the big hole is, in terms of interpreting this matrix. One of the things we're trying to do is to create what we would like to call a Museum of Comparative Anthropology, where we will take all areas from ecology, complete including culture, to try to identify those things where either people know that there are differences between humans and great apes or that there are potential differences between humans and great apes - including the ones where it has been incorrectly claimed that there are differences between humans and great apes. This, we hope, will be a resource, although we're just beginning on this and it will be quite a while. The San Diego Supercomputer Center is helping us with this.

The second project is to try to develop materials and databases - just simple things like if you want a piece of chimpanzee skin to find out if there are genes that are expressed that are different from humans. It's not available. If you want a library of genes expressing a given tissue, it's not available, and so on.

[Referring to slide] This is Bernard Wood's version of the emergence of humans from a common ancestor after the common ancestor of the chimpanzee. But as you all know, modern humans are a very recent success story. While it's not clear exactly when things happened back here, the point is that a lot of things happened very recently. Why is this? Again, it seems to me that innovation and imitation are critical features. We have a very small number of innovators, but despite our common phrase "imitating like a monkey," we are the greatest imitators of all. Cycles of innovation/imitation can go a long way. Of course, this is not a novel concept.

[Referring to slide] Here is the diffusion of hybrid seed corn across two Iowa communities. There are 2.5 percent innovators and the laggards who didn't do it even after a long time, but it diffuses pretty fast. There are additional factors: population, communication, and instruction. As you increase your population, you can obviously greatly increase the availability of the actual number of innovators. Suppose we had two billion chimpanzees. I don't think it's fair to compare the studies we've done on five chimpanzees with four billion humans to see what their potential is. We do know that a chimpanzee doesn't have the capabilities of imitation that humans have, but this innovation factor can be great. Then, of course, you've got communication and instruction or teaching, which amplify this whole thing further.

Finally, I want to conclude with my favorite ... we all read Darwin and Wallace, and so on, and I'm still struck by this and somehow other people don't necessarily feel that there's a problem here, but I think there is one. As you all probably know, Alfred Russel Wallace was the co-discoverer of evolution, but toward the end of his life, he lost favor with science and sort of faded from history. A lot of that was because he wrote this article, "The Limits of Natural Selection as Applied to Man." What Wallace said is: "It will, therefore, probably excite some surprise among my readers to find that I do not consider that all nature can be explained on the principles of which I am so ardent an advocate; and that I am now myself going to state objections, and to place limits, to the power of natural selection." So, he became a bit of a spiritualist. Essentially he said, "I can explain everything except humans by natural selection. The origin of consciousness that developed into humans - there's something different about this." Again, what he's talking about is this phenomenon: How do you have an expectation that somewhere back here gives you a brain that is capable eventually of ... I saw my daughter a few years ago sitting in front of a computer typing, talking on the phone, listening to music, and talking to three people on AOL Instant Messaging - all of this at the same time. Granted that times were tough 50,000 years ago, but where did this come from? I'm not suggesting that there's anything more than normal biology, but there may have been some other kind of selective forces.

So, Wallace says, "These can only be met by the discovery of new facts or new laws of a nature very different from any yet known to us." He lost favor because of saying this, but I think he was just being honest, saying: This is unusual. We need to go beyond simple natural selection to explain these phenomena.
The great majority of differences between humans and apes are in favor of apes, apart from our brains, our upper arm coordination, and maybe our striding, bipedal gait.

One thing would be that we seem to have relaxed selection for physical attributes — as Terry [Deacon] says: We're a degenerate ape. The great majority of differences between humans and apes are in favor of apes, apart from our brains, our upper arm coordination, and maybe our striding, bipedal gait. In everything else we are degenerate; we are much worse off than apes. Maynard Olson and I have written articles on the idea that throwing away genes may be a much better way to get sudden change than tweaking existing genes. Maynard likes this analogy: If you had a Lexus and the weather changed and you had to survive, you are not going to survive by tweaking the air conditioning and tinting the windows. You're going to rip the top off, throw away the air conditioner, and get a Jeep. That's how you're going to do it. Maybe something like that happened.

[Referring to slide] Here's a little thing I made up, just off the top of my head. This is definitely part of the story, but when it came in, I don't know: Prolonged Helplessness with Extended Nurturing Occurring with Maternal input during Extended Necotomy Of the Nervous System [PHENOMENON]. I think this is one of the features that contribute to our abilities.

I've barely talked about the brain at all, but I would say that we need to take a holistic view of the human condition because that will eventually lead us to the brain and, in the bargain, will help us in many areas of human endeavor. And when it comes to genetic modifications, I would say: Do what you like to yourself, but don't do it to the germ line, because you are going to affect other people. Thanks.

VELAMOOR: Thank you, Dr. Varki. Are there any questions from either participants or observers?

OBSERVER: When you said that the trees with the humans sticking up like a sore thumb, based on attributes, what would happen in that tree if you filled in from the fossil record all these other hominid species? Does it become a little more uniform?

VARKI: No, not really. Many of those attributes we have no evidence for, one way or the other, so it would be difficult. But I think you're making an important point that what we need to do is try to fill in as much information as we can on the other fossil hominids. The orangutan is so far away from us in molecular, genetic terms and in terms of speciation, and yet I would argue that classifying the great apes as a group is still a very useful thing to do because they have a lot of similarities.

The other reason human evolution is interesting is not just a case of studying human evolution, but how does one get evolutionary novelty out of a relatively conservative clade of creatures? That's my feeling. You can look at it from the physical viewpoint. Obviously, the moment you get into cognitive issues, there is no end to the number of things you can list.

VELAMOOR: Even though it's estimated, as you pointed out, that the difference between the bonobo and the human is about 1 percent or 1.4 percent, do all the differences you have listed add up to being within that 1 percent, even though it appears, when you consider the spectrum, that it is far greater than 1 percent?

VARKI: This whole 1 percent story was a useful thing to focus attention, but now I think we need to get away from it. As I said, mice and rats are our closest cousins, not whales or dolphins or dogs. The percent difference is no longer that interesting to me. It turns out, actually, that the percent difference that has been touted for so long is based on alignable sequences. If you have two pieces of DNA, you couldn't align them, you just had different parts of the genome. Now that we have the whole genome, it turns out that in the alignable regions, it's actually less than 1 percent in protein sequences. Twenty-five percent of our proteins are identical. But if you go to other regions of the genome, there are huge chunks present in a chimp and not in a human, and visa versa. There are all sorts of insertions and deletions, so the actual number is more like 4.5 percent, if you take the total. So, the number of differences is huge. A lot of that is in areas called "junk DNA," but as we've been hearing recently, a lot of that junk DNA is very active. In fact, in our system, two of our genes were taken out by so-called junk DNA landing there and killing them.

VELAMOOR: Given the fact that these are the differences and the magnitude is not great, taking all of the
junk DNA into account, what are the risks of the same argument being co-opted by Intelligent Design?

VARKI: I realize that it's an inadequate position, but I don't stay awake at night worrying about the Intelligent Design people. Sometimes - maybe in my lifetime, I hope - they will go away.

VELAMOOR: Not likely any time soon.

VARKI: I have this view that bad ideas reach a crescendo before they collapse and right now we are facing a huge crescendo of fundamentalism in all areas. I think that's the prediction of a collapse. The question is when it happens, and hopefully it happens soon. The fact is that we shouldn't go exactly by numbers and percentages; we should go by actual genes.

One of the things the Genome Project has found is that there are so many differences, they don't know where to start. Meanwhile, we had a system of 55 genes and we had found eight that were different. Then we found a few additional differences. It turns out we found most of them just by nosing around in a gene-centric way. So, what should happen is people should pursue their little areas and make inroads into the genome as a resource, and that's how it will happen, I think.

DEACON: You mentioned the very big difference between gene variation within the chimpanzee clade, for example, and the human clade. Unfortunately you didn't show one of the nice tree pictures that give that sense of how incredibly small our variation is genetically compared to a species that has maybe 100,000 or so individuals in Africa. I always find it curious that we're terribly worried about the simplification of the chimpanzee genome when ours is such a vastly smaller variation. I think there are significant consequences for our future because of that. I would be interested in what you think.

VARKI: Pascal Gagneux did his post-doctoral on this and his thesis work was to show that one group of chimpanzees in West Africa had more genetic variation than all the humans on the planet. That's true - chimpanzees have a much wider variation. So, we are an unusual species and this fits the idea of some very small, common origin of peoples that spread out and, by sexual selection and environment, and so on, selected ourselves into so-called "races." I personally would advocate the complete abandonment of the term race, going instead to looking at peoples of different origin, which is a very interesting concept. If you want to talk about our future, I think that race is one of the most damaging words that is used.

The fact is it's not a matter of being politically correct. Everybody in this room is genetically more similar than a few chimpanzees in West Africa. That's just how it turned out. Now, having said that, on the other hand, when you take a particular gene and you look, you find many more polymorphisms in humans. You say APO-E, the worst allele to have for Alzheimer's Disease and heart attacks, both of which chimps never seem to have had. Here's the allele in chimps. We have APO-E2 and APO-E3 and various other things. Partly it's population size, but partly we came from a very narrow bottleneck and then subjected ourselves to enormous selection over a very short period of time.

So, I think we're going to see both: on the one hand, overall incredible similarities and yet we're going to see all sorts of little selections that occurred. It makes a huge difference whether you live on the Equator or in the Arctic - it's going to make a difference in how you get selected. There's been rapid evolution over the last 500,000 years but, because of the rate at which humans migrate and copulate with each other, a lot of that has been partially rehomogenized, which creates a big mess if you're trying to figure out what's going on.

CALVIN: Regarding the Intelligent Design problems, and, for that matter, creationism, these are beginners' mistakes. I think beginners' mistakes are always going to be with us because most of the population - even if they had the time that we have to study the issue, some of them will do that, but the people who are only ten years old or they stopped reading in this area at age 20, or whatever, are going to wind up with much simpler analogies to work from.
... the way I would speak to Intelligent Design people is to say, "Boy, you call this 'Intelligent design'? What a mess!"

VARKI: The point I was trying to make is that most biologists are unwittingly falling into that trap. We like to think that the systems that we study ... the system I study is wonderful! It's amazing in its precision and balance because it was honed by many years of evolution. But that somehow translates into biologists thinking everything is perfectly honed, and that gets co-opted by the Intelligent Design people. Instead, the way I would speak to Intelligent Design people is to say, "Boy, you call this 'Intelligent design'? What a mess!"

CALVIN: The other thing I wanted to say was that in terms of a lot of selection going on in the period of, say, the Mind's Big Bang 50,000 years ago or in that vicinity, in this period there's an enormous amount of the climate flipping around. When you go from a warm and wet climate to a cool and dry, dusty, windy climate, and then pop in five years back up to the other, what this means is an enormous amount of drought, an enormous amount of shrinkage of populations down into confined areas where there are not enough resources to make the trip to another population. So, you wind up with a lot of inbreeding, a lot of loss of alleles — and all different in each of the different groups. Even when they come back together, you've still got a lot of loss.

VARKI: There's no question that there's huge variation.

CALVIN: Particularly with the spread out of Africa at this time, you have a perfect setup for squeezing the populations down, reexpanding them, and when you squeeze them down, you lose a lot.

... my point is that the way that humans were classified was a social construct ... the convenience of using these old classifications is detrimental to society and our future.

VARKI: My point is not that there's incredible diversity in the human species; my point is that the way that humans were classified was a social construct. I think if you want to reclassify humans according to our current knowledge, I have no problem with comparing groups. The biggest problem I have is with the concept of white. I have no idea what white is. You could have a man from North India who comes to the United States and changes his name and has fair enough skin and he suddenly becomes a white, whereas some blonde-haired blue-eyed Scandinavian gets called a white. I think that if we got rid of that, to begin with, that would help a great deal.

Now, if you want to say, "My ancestry is primarily of Scandinavian origin or West African origin," that's very useful information, extremely useful biologically. I just think that the convenience of using these old classifications is detrimental to society and our future.

TOOBY: I was just wondering if you would talk a little bit about having identified the eight genes that might have glycoproteins differences. I know that all the consequences would come to a huge list, but do you have, from what you have studied, a functional interpretation of any of them? What would have been the selective force that would have driven it?

VARKI: Yes, one thing for sure: We have changed our susceptibility to certain infectious diseases because these are the targets for things like malaria and various livestock diseases, and so on. That is pretty clear.

The second thing that's pretty clear is that we are missing a molecule from our bodies that we are eating in our food. It turns out that it's getting into our bodies, incorporating into ourselves, and we're making antibodies against it. And it's also in stem cells, which is why our recent work on stem cells got all this attention because these animal molecules are getting into stem cells and antibodies are reacting.

From the point of view of the brain, it's all indirect right now. We have one molecule that has turned on in the human brain and it is not in ape brain, but we don't know what it does, so we're in the early days in that. The other is the particular molecule that is present throughout the body of the chimp and missing in humans. There's only one place where it's hard to find — it's the brain. If you go back all the way to whales, you find the same thing. There's some reason why you don't want this molecule in the brain; we find tiny amounts in every brain we look at except humans. So, our fantasy is that we finally 'got rid' of it. We've been trying for three years to make a mouse that overex-
presses this molecule in the brain to see what’s so bad about having this molecule in the brain. We’ve been unable to get a mouse so far, which is interesting, but unfortunately I don’t have any definite statements to make.

This has impact on biotechnology, on many other things: food, various diseases of humans, and so on. But it’s still in the early days.

**TOOBY:** So, one of them might be because bigger brain evolution, greater brain functioning in humans requires a lower level for that one?

**VARKI:** The timing is right. The mutation occurred and got fixed about two and a half million years ago, presumably by some infectious agent. It would have actually resulted in an immune system that is hyper-reactive, which we think is still not settled down. A by-product of that could have been some selection for some brain process. But we have a mouse now that has the same defect as humans, the exact same defect, and it’s certainly not walking around talking. It has a few funny changes – actually surprising things like balance – not things that we would have thought. The problem is that you’re talking about something that happened a long time ago, and we’re seeing the outcome right now. I think it’s too early for us to say much more than that.

**HOLLOWAY:** I’m interested in the possibility that the loss of the gene or the molecule that you were talking about might have to do with rationality. I find whales quite rational. I find even chimpanzees to be rational, and moose and caribou and all the rest. But I do wonder about humans.

**VARKI:** You’re wondering if we became irrational by losing this thing. That’s an interesting idea.

**HOLLOWAY:** In your talk, you mentioned Francis Crick and widgets. Do you really subscribe to the idea that there are no biological laws?

**VARKI:** When I say laws, I mean universal laws. In physics, there are universal laws; in chemistry, there are universal laws that, at least in this universe, are not going to change.

**HOLLOWAY:** With regard to the relationship between brain and body, there seems to be a very, very lawful constraint in which the exponent comes out to be .75, suggesting a relationship to metabolism.

**VARKI:** But I’m sure it won’t be very difficult to find exceptions to the rule, like humans. Take a law in chemistry: An oxygen atom, unless it’s in very, very unusual circumstances, is going to behave like an oxygen atom, and you can hang your hat on that certainty. That’s my point. Maybe I should change that to say that what Francis is really saying is that there are no universal laws in biology. There are little laws you can make when a certain bunch of widgets get together and do a certain thing, then you get a law of those widgets, which works for that zone, but won’t work in another biological circumstance.

**VELAMOOR:** Thank you, Dr. Varki, and thank you all very much. I think it was an extraordinary set of eight papers.