million of carbon dioxide in the atmosphere. So you would require an enormous amount of processed energy to be able to get enough carbon dioxide to make the quantities of fuel we need.

The other broad class of technological solution would be, perhaps you could create some kind of enzyme—or whatever you would call it—but take advantage of the huge surface area of the oceans, and you could then put it into the ocean, and then it would take carbon dioxide out of the atmosphere and convert itself into oil. But then we would have the problem of the oceans being covered with oil, another undesirable solution.

VENTER: They're thoughtful questions. The first, about the concentration of CO_2, is relatively easy to deal with. The K_Ms of the enzymes and these organisms that exist throughout our planet are able to capture CO_2 out of the atmosphere, out of the water. But we don't need to rely on that. We have two phenomenal and, soon, a third point source of carbon dioxide. The two largest are power plants and cement factories. If we could simply capture back the CO_2 from those two point sources, it makes it very easy, because of the incredible concentrations you have there, and will eventually get in a cycle of a renewable source from that. We also have a third. It's a clustered carbon dioxide from a variety of sources to be pumped down into oil wells or coal beds. So, we are working in one of our programs with BP, trying to look at converting that CO_2 back into methane, so you could constantly be in a recycling mode. Once you sequester CO_2, we could use that as a source of energy instead of constantly taking more out of the ground. So we have so many incredible point sources of CO_2 production right now that that's the least of our worries.

BROCKMAN: Thank you. Thank you all for coming.

10
The Nature of Normal Human Variety

Armand Marie Leroi

[March 13, 2005]

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The question that interests me, as it does so many other people, is how to go about making a human being. It's a very difficult problem. Roughly what it boils down to is this: It's often said that the genome is something in the nature of a book. It has words, a grammar, a syntax, and of course those words have meaning. The only problem is that we don't know actually what that meaning is. So the question is, How do we decipher that? And turning that question around, looking at it from the point of view of the human body, what do those genes mean to the construction of the human body?

Of course I don't actually work on humans; they're just too inconvenient. I work on worms. This worm is *Caenorhabditis elegans*, for which Brenner, Sulston, and Horvitz won the Nobel Prize in 2002. And the reason why I and a thousand other scientists work on this worm is that, for all of its marvelous properties, it's easy to keep thousands of them in petri dishes, and it's easy to find mutants. And that's the critical thing. We find mutants that interrupt particular genes, and that tells us what those genes do and what they mean to the body of a worm.

Developmental biologists have been doing this for a long time—once a field has its Nobel, you can be sure it's reasonably

mature. What people haven't done, however, is to do this for the human body. The reason is obvious: you just can't go out and generate mutants in humans. For humans, you've got to go out and find those mutants. But they're out there. There are thousands upon thousands of mutants out there—no, more, millions—no, actually billions. This is because we are all mutants. That's one thing you don't expect but which happens to be statistically true. Each of us carries mutations that interrupt particular genes. So if you can just find who is a mutant for a particular gene, and examine what those people look like, you can then work out what those genes do.

This raises a question: What exactly is a mutant? Worm biologists and fly biologists—geneticists generally, working on model organisms—use the word "mutant" in a particular way. In worms and flies, there is an arbitrarily defined strain that we call the "wild type." But in humans there is no arbitrary wild type. So can you, in fact, speak of mutant humans?

You can, but the definition of what is a mutant in humans is necessarily more roundabout, because we have such an extraordinary amount of natural variation in our species. If you go around the world, you see tall people, short people, red-haired people, brown-haired people, people with curly hair, people with no hair, and so on. Given all this variation, what exactly, and who exactly, is a mutant? It's an important question, because to say something is a mutant is to make an invidious distinction. This is to say, something is not just different but actually abnormal in some fashion. Yet despite the fact that there is so much variation in our species, it is possible to speak in a coherent way of mutations and of mutants in humans.

Roughly, the reason you can do so is as follows: if you look at the coding sequence—more precisely, the protein sequence—

produced by any given gene, it's the case that for most genes nearly everybody has the same version. True, there are some genes that are polymorphic—variable—and these are genes that give us our natural diversity. But they actually constitute a very small fraction of the genome. Most people have the same functional version of a gene. Given that fact, you can define a mutant as somebody who has a rare variant of a gene—moreover, a variant that harms him in some fashion. And if you look at it that way, it's clear that we all carry rare variants that do us harm in some way, and that we are in fact all mutants.

We can even put some numbers on this. One of the surprising results in recent years, which comes from the comparison of the genomes of different species, is that every newborn child carries three novel deleterious mutations—that is, mutations that its parents didn't have. Not only that, but each child inherits at least some of the mutations that its parents have as well. It's estimated then—and of course this is just an estimate—that every newly conceived person has something like 300 mutations that affect its health for the worse in some fashion.

Of course, that number doesn't tell us a whole lot. We need to know not only the number of mutations we have but also the distribution of their effects. This is because some mutations have severe effects. They are the mutations that cause the big known inherited diseases—about 10,000 such diseases have been identified so far. But there must be many, many more mutations that do us harm but only subtly so. These are the mutations that give us weak eyes, bad backs, and the like. These are mutations we know very little about but that statistically speaking must be there. It's in these mutations that a lot of human health lies—or rather the absence of human health lies. At least it does once you have got rid of the contagious diseases.

When I speak of mutations that do somebody harm, what I really mean is not so much that they just affect physiological health; what I really mean is that they affect the Darwinian fitness, the probability that they will reproduce. It's an evolutionary definition. It's the kind of definition that can encompass an enormous range of impairments, and the kinds of impairments you see that are caused by mutations are sometimes of a degree and form that you just cannot conceive of.

If you go to teratology museums—literally "monstrosity museums"—in places such as Amsterdam and Philadelphia, you can see rows of babies in bottles. These infants, usually stillborn, are deformed in ways that are truly hideous, that represent the kinds of monstrosities you might expect from Greek myth. I mean this quite literally. They include children born with a single eye in the middle of their forehead, who look exactly like the monsters of Greek myth—Polyphemus in *The Odyssey*, for example. Indeed, it's sometimes suggested that the monsters of Greek myth were inspired by deformed children, and this seems to be a fairly remarkable correspondence, at least with some of them.

These infants, when you see them, are truly horrific. But very quickly, after you look at them, a sort of intellectual fascination takes over, because it's clear these children tell us something deep about how the human body is built. Take, for instance, the children with a single eye in the middle of their foreheads. The syndrome is called, appropriately, Cyclopia. Cyclopia is caused by a deficiency in a gene called Sonic hedgehog. Sonic hedgehog is named after a fruit-fly gene that, when mutated, causes bristles to sprout all over the fruit-fly larva, hence "hedgehog." When the gene was found in mammals, some wit called it Sonic hedgehog, after the video game character. If you get rid of this gene, bad things happen. You lose your arms beneath the elbow and legs

beneath the knee. The face collapses in on itself, such that you get a single eye in the middle of the forehead and the rest of the face collapses into a long, trunklike proboscis. The forebrain, which is normally divided such that we have a left and a right brain—the left and right cerebral hemispheres—is fused into a single unitary structure. Indeed the technical name for this syndrome is called Holoprosencephaly.

Now, all this is horrible, and that's just an initial list of things that can go wrong in infants that have no Sonic hedgehog. But what's really interesting about it is that by looking at infants of this sort, you can reverse-engineer and ask what Sonic hedgehog does in the embryo. Instantly it tells you that one of the things the Sonic hedgehog does is to keep our eyes apart, because if you don't have the gene the face collapses. It also separates the left and and right sides of our brains. And it's needed for the formation of our arms and legs. In fact, it is one of the most ubiquitous and powerful molecules in the making of our bodies.

And other, more subtle mutations tell more about it. For example, just as having too little Sonic hedgehog causes the face to collapse in upon itself, having too much causes it to expand. I was recently in San Francisco, in Jill Helms's lab at the University of California, San Francisco, where she's got a jar containing the head of a pig. Or is it two pigs? It's just not clear, since the jar contains a pig with two faces, two snouts, two tongues, two throats, and three eyes. It's not a Siamese-twin pig; it's just a pig with two faces. Chickens and pigs with two faces crop up periodically, as indeed do humans with two faces, or nearly two faces. There's a syndrome in which you have eyes widely spaced from each other and in which the nose becomes duplicated. You have two noses side by side in two varying degrees of development.

The gene for this syndrome has recently been cloned, and

guess what? It turns out to be the gene that controls Sonic hedgehog and in fact switches it off. People with the syndrome have too much Sonic hedgehog, just as infants with Cyclopia have too little. So by looking at a range of these kinds of syndromes, you can put together a complete picture of how a gene like Sonic hedgehog controls one particular feature of us, the width of our faces. It's a mundane thing that you'd hardly think about but that seems to be controlled by this genetic system.

There are many other disorders that are equally informative. The star at the Mütter Museum at the College of Physicians of Philadelphia is Harry Eastlack, a man who had a disease called fibrodysplasia ossificans progressiva. It's a disorder in which supernumerary bones form. The Mütter Museum has his skeleton, which he donated at the time of his death when he was in his forties. The skeleton is essentially not one man's skeleton—it is, as it were, one skeleton encased in another. What happens in this disorder is that wherever you get a bruise or a wound, instead of normal cells moving in to regenerate the skin and the flesh and heal the wound, bone forms. So every bruise turns to bone. The children are born relatively normal, but as they go through life, bone accretes all over them, such that they can no longer move. They become rigid, locked into place. You can cut it away, of course, but as soon as you make an incision and that incision heals, more bone forms. So it's a vicious circle. We don't know which gene is mutated in this syndrome. But it's almost certainly got something to do with bone morphogenetic protein, a protein that is, as the name suggests, normally involved in making bone in infants. It's just that in most of us this gene switches off. In these people, this protein keeps on being produced throughout life, especially when there's a wound. It's another marvelous instance of how a given mutation can tell us something important

about how bones are formed. FOP is a very rare disorder, and the reason the gene hasn't been cloned is because to identify genes, to clone genes, you need to have big pedigrees—at least, it helps. But these people just never have children.

People sometimes ask what developmental biology is good for. We can identify genes that are responsible for making this or that part of the human body. But in humans, of course, there's a pressing question: namely, How can you fix the deleterious consequences of these mutations? It's one thing to go into a clinical genetics ward, a pediatric ward, and study kids who are seriously deformed, and say, "This is just terribly interesting. Your son is highly informative about the function of the Jagged-2 gene." But that's not a great deal of comfort to the parents, who actually have to deal with raising children who are variously deformed and may die or, at the very least, have to undergo a great deal of surgery. That, of course, is the problem. The molecular biology is beautiful, but when it actually comes to curing people, you just have surgery—which is little more than a rather sophisticated form of butchery.

The great promise, of course—and it's been a promise for years now and will remain so for some time—is that by learning about what genes do and how organs and tissues are constructed we can reconstruct them as we wish. By working out the program, we can take cells, put them in a test tube, and rebuild tissues. You don't have cartilage in your larynx? We can build it for your child, and we can fix it. You don't have a breast? We can rebuild that, too. And so on. This is a whole new area, called tissue engineering. There are big institutes devoted to it now, where engineers, materials scientists, and molecular biologists are all working together. So far, it must be said, it's more institution-building and propaganda than real results, but it'll happen. That

is when the justification for this whole science will ultimately come.

There's no doubt that when you see some of these children who are so terribly deformed, it's very difficult. It's shocking, it's heartbreaking, and if you spend any time with them, whether they're alive in pediatric wards or they're just babies in bottles, it takes a real psychological toll. I certainly don't ever get completely hardened to it. But what is also true is that the intellectual fascination of seeing what has gone wrong in these unusual bodies takes over. This is especially the case when your eye is attuned to perceiving the differences in detail, once you see that it's not just arbitrary deformity, once you understand that what you're really looking at are the outcomes of the laws that regulate and make the human body. When this happens, deformity acquires a real beauty. It's a beauty that emerges from answering one of the oldest questions in biology: namely, How are we put together?

But that's intellectual beauty. What of human physical beauty? This is something that interests me greatly. I'm not interested in the general aesthetic question here, but in ourselves. Some people say that beauty is uninteresting and just a matter of taste. I don't think so. I would say, and there are others who would agree with me, that we have a general psychological program from which stems a universal notion of beauty. Incidentally, this idea that we all perceive certain features to be beautiful is one that Darwin would have disagreed with. Darwin believed that the perception of beauty was particular to particular peoples in particular times and places. He was probably wrong, or at least he was only partly right. I won't attempt to justify that answer, but I think it to be true. These days, the general thinking tends to be that there's a

universal notion of beauty which is true for people around the world. And the question is, What is that and what drives it?

Many people think that beauty is a certificate of health; this is an idea that comes out of sociobiology. But it is more obvious than that. It's simply the idea that beautiful people are healthy people and we search for healthy mates. And that's probably true. Or at least it was. But is it still? In the past, health was primarily a matter of environmental conditions—your exposure to contagious diseases and the amount of food you had when you were growing up. Rich people had better environments, hence the positive association between beauty and wealth. But what of modern economically egalitarian societies, such as Holland? In such societies, does the ancient association still obtain? If the variance in beauty is due to the variance in the quality of the rearing environment, then it must be the case that the Dutch—who all eat much the same good food, live in much the same well-designed houses, and have access to much the same excellent health care—must all be equivalently beautiful. But is this so? The answer is, of course, no. Among the Dutch, you can find good-looking and not so good-looking people. And the question is then, why?

I would argue that the reason for this is that there is and will always be variance in beauty, because there is variance in mutational load. What is beauty fundamentally about? I would argue—and this is really just a postulate at this time but it is one that interests me a great deal—that the fundamental reason some of us are more beautiful than others is because of those deleterious mutations we all carry. We may carry 300 deleterious mutations on average, but there is of course a variance associated with that. Not everybody has 300. Some people have more, some people have fewer. If this is true—and statistically it must be true—then someone in the world has the fewest mutations of all. Someone

in the world is the least mutant human of all. Indeed, we can actually calculate, making some assumptions about the shape of the distribution, how many mutations that person has—and it turns out to be 191 versus the average of 300. This, to my mind, is surprisingly many. I would suggest that if we could find that person, he or she would be a good candidate for being the most beautiful person in the world. At least she would be, assuming she did not grow up in some impoverished underdeveloped nation. Which, statistically, she will have done, since most people do.

There's one more thing I should like to know about, and that is the nature of normal human variety. There are tens of thousands of geneticists around the world, all of whom are busy identifying the genes that cause human disorders of one sort or another. Historically they began with the really easy ones, the big congenital disorders, especially those that allow people to survive and produce children and so have big pedigrees that allow mapping of the genes. Now the emphasis has shifted to studying the genetic basis of more subtle and more complicated kinds of disorders—things like diabetes and cancer—that have lots of genes that underlie them, each of which has a small effect. This is a much more difficult task, but people are doing it because these are the inherited diseases that affect millions.

But there's one aspect of human inheritance that people are resolutely ignoring. And that is normal human variety. Or, to put it more crisply: race. If we look around the world, we find that people look very different from each other. These differences are manifestly genetic. They must be. That's why people's kids look like them. Yet we know nothing about that variety. We don't know what the differences are between white skin and black skin, European skin versus African skin. What I mean is,

we don't know what the genetic basis of that is. This is amazing. I mean, here's a trait, trivial as it may be, about which wars have been fought, which is one of the great fault lines in society, around which people construct their identities as nothing else. And yet we haven't the foggiest idea what the genetic basis of this is. Why is that?

The reason is twofold. The first—which is not such a trivial problem—is that skin color is not controlled by one gene. If it were only one gene, we'd know it. It's many genes—more than three but certainly fewer than thirty. It's a difficult problem, although, frankly, it's not such a difficult problem that if geneticists really wanted to solve it, they couldn't. It'd be easy enough to do if they put a fraction of the effort that went into discovering the BRCA1, the breast cancer gene. I'm not saying they should; finding the breast cancer gene is more important than discovering the genetic basis of white and black skin, but still, it's not a technically impossible thing to do.

But of course the fundamental reason why people don't do it is because it's race genetics. It's because of the long and sorry history of genetics and racial differences. And indeed, more than that, the whole thrust of genetics since World War II has been to argue that races don't exist and that they are just social constructs. This is very much the Harvard School—Dick Lewontin, for example, has been one of the big proponents of this point of view. The late Stephen Jay Gould was another.

After World War II, when the enormities of Nazi science really hit home—which were in turn the consequence of a much larger racial science not just in Germany but everywhere—all right-thinking scientists made a resolute effort to ensure that science would not be bent to such evil purposes again. They were determined that science would never again be used to make

invidious discriminations among people. The immediate result of this was the UNESCO Declaration on Race in 1950—fronted by Ashley Montagu and backed up by geneticists such as Theodosius Dobzhansky—which affirmed the equality of races. Then, in the 1960s, Dick Lewontin and others discovered that gel electrophoresis could be used to survey genetic variation among proteins. These studies showed that humans have a huge amount of concealed genetic variation. What is more, most of that genetic variation existed within continents or even countries rather than among them. UNESCO said races were equal; the new genetics said they didn't exist. Finally, moving a few decades on, the out-of-Africa hypothesis of the origin of *Homo sapiens* comes to the fore and multiregionalism falls from fashion, as it becomes clear that humans are not only a single species—something we've known since Linnaeus's day—but a single species that has diverged into subpopulations only very recently.

The result of this history—which has been driven partly by data and partly by ideology—is that these days anthropologists and geneticists overwhelmingly emphasize the similarities among people from different parts of the world at the expense of the differences. From a political point of view, I have no doubt that's a fine thing. But I suggest that it's time we grew up. I would like to suggest that by emphasizing the similarities but ignoring the differences we are turning away from one of the most beautiful problems that modern biology has left: namely, What is the genetic basis of the normal variety of differences between us? What gives a Han Chinese child the curve of her eye? The curve I read once described by an eminent Sinologist as the purest of all curves. What is the source of that curve? And what gives a Solomon Islander his black-verging-on-purple skin? Or what makes red hair?

Actually, the last is the one thing we do know. It turns out that red hair is due to a mutation in a gene called MC1R, melanocortin receptor 1, which controls the production of eumelanin, black pigment, versus red pigment, pheomelanin. Rather marvelously, it also turns out that mutations in MC1R also cause red hair in red setters, Scottish cattle, and red foxes. But we don't know what causes brown eyes versus blue eyes versus green eyes. We know very little about the variation in normal human height. We don't know why some women have big breasts and some have small breasts. These are important questions—or at least jolly interesting ones—and we just don't know their answers.

The reason I love the problem of normal human variety is because, almost uniquely among modern scientific problems, it is a problem we can apprehend as we walk down the street. We live in an age when the deepest scientific problems are buried away from our immediate perception. They concern the origin of the universe. They concern the relationships of subatomic particles. They concern the nature and structure of the human genome. Nobody can see these things without large bits of expensive equipment. But when I consider the problem of human variety, I feel as Aristotle must have felt when he walked down to the shore at Lesvos for the first time. The world is new again. What is more, it is a problem we can now solve, a question we can now answer. And I think we should.

Of course, there will be people who object. There will be people who will say that this is a revival of racial science. Perhaps so. I would argue, however, that even if this is a revival of racial science, we should engage in it, for it does not follow that it is a revival of *racist* science. Indeed, I would argue that it is just the opposite. How shall I put it? If you want to prove, what most of us believe, that skin color does not give the measure of a man, that

it tells nothing about his abilities or temperament—then surely the best way is to learn about the genetics of skin color and the genetics of cognitive ability and demonstrate that they have nothing to do with each other. The point is that there will always be people who wish to construct socially unjust theories about racial differences. And though it is true that science can be bent to evil ends, it is more often the case that injustice creeps in through the cracks of our ignorance rather than through anything else. It is to finally close off those cracks that we should be studying the genetic basis of human variety.

11
Brains Plus Brawn

Daniel Lieberman

[October 17, 2012]

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I've been thinking a lot about the concept of whether or not human evolution is a story of brains over brawn. I study the evolution of the human body and how and why the human body is the way it is, and I've worked a lot on both ends of the body. I'm very interested in feet and barefoot running and how our feet function, but I've also written and thought a lot about how and why our heads are the way they are. The more I study feet and heads, the more I realize that what's in the middle also matters, and that we have this strange idea—it goes back to mythology—that human evolution is primarily a story about brains, about intelligence, about technology, triumphing over brawn.

Think about Greek myths like the myth of Prometheus and Epimetheus. Epimetheus, which means "hindsight," is the Titan who gave out all the gifts to the animals, and when he finished, he hadn't given any gift to humans. Prometheus took pity on these poor humans who didn't have claws and fangs and speed and power, so he gave humans fire. Of course, he got tortured by the rest of the gods for this. I think this idea—that humans are essentially weak creatures—is deeply woven into a lot of the ways we think about our bodies.