

The Making of the Fittest: Natural Selection in Humans

[NARRATOR:] Davaun and Skyy Cooper are brother and sister. Both of them have sickle cell anemia. Before the advent of modern medicine, sickle cell anemia almost certainly meant death before adulthood. Even today, young patients can suffer strokes and organ failure. Sickle cell anemia is a genetic disease. Parents of those who have the disease might not have it themselves, but both must carry the sickle cell character in their DNA. Besides some bone pain, Skyy leads the fairly normal life of a 13 year-old girl. But her younger brother Davaun, has suffered acute chest syndrome and has already had his spleen removed.

[NARRATOR:] Skyy and Davaun's symptoms arise from the fact that some of their red blood cells become misshapen--crescents instead of discs--preventing enough oxygen from being delivered to all parts of the body. It's not completely clear why symptoms are variable, but what is most perplexing about sickle cell disease is that it is not rare.

[DR. HEENEY:] So, in the United States, we think there are between 70,000 and 125,000 persons with sickle cell disease. However, that doesn't take into account immigration and other patients or persons coming from other parts of the world into the country.

[NARRATOR:] In fact, in some populations--African Americans, for example--the incidence is as high as 1 in 500, astoundingly high for a deadly inherited disease. Didn't Darwin teach us that harmful traits disappear from the gene pool through natural selection? Why is sickle cell anemia so prevalent, and why in particular among people of African descent? The answers to these questions began with a remarkable set of observations from an unlikely person more than sixty years ago.

[NARRATOR:] Tony Allison has spent most of his career as a medical doctor and molecular biologist in the U.S. and England. But he grew up in East Africa and he is quick to recall his formative years in Kenya.

[DR. ALLISON:] We lived in the upcountry, and we used to go to the coast every year in August for the holiday when it was a little bit cooler than at other times. So we had the trip all the way down, which was usually with a truck and a car. And, so we would camp on the way and, in Tsavo and there would be lions roaring around, so it was really quite exciting.

[DR. CARROLL:] These are the infamous Tsavo lions--

[DR. ALLISON:] The famous--

[DR. CARROLL:] Right?

[DR. ALLISON:] infamous Tsavo lions--

[DR. CARROLL:] Around 1950, biologists didn't know a lot about the details of evolution, because we didn't know really how heredity worked. The structure of DNA had not been discovered yet, genetic code had not been cracked. So, we know that while evolution was due

to genetic changes, we didn't know how those genetic changes took place whatsoever. So, there were holes in the whole picture of the evolutionary process, and Tony Allison was probably the least-likely person you would imagine, who would fill one of the most critical holes. He grew up far away from the centers of science in Europe and North America. He was really interested in natural history and he loved the Kenyan wildlife, and he visited archeological digs that were going on at the time. But it was a really circuitous and serendipitous route that led him to an enormous discovery in evolutionary biology.

[NARRATOR:] Tony first went to University in South Africa where he studied physical anthropology, then to medical school at Oxford. He had a deep interest in human origins, but not so much in ancient stones and bones. Tony was interested in blood. Could the common ABO blood types say anything about the evolutionary history of East African tribal people?

[DR. ALLISON:] And I actually learned just before going out about the sickle cell condition. Nobody really knew the frequencies of sickle cells in East Africa. So it was a barren slate, so to speak.

[NARRATOR:] Blood samples from people carrying the sickle cell character appear quite normal--until oxygen is removed. Tony learned that adding a chemical agent to the samples would quickly reduce oxygen and reveal sickle cells, if they were there. This gave him an easy test to score blood samples for the sickle cell character.

[DR. ALLISON:] But what was striking was that you had high frequencies of people carrying the sickle cell character in the coast and near Lake Victoria, and very low frequencies in the high country in-between, in Nairobi.

[NARRATOR:] What could possibly account for such a striking disparity? The sickle cell character was understood to be genetic, not environmental. Tony had grown up in the dry Kenyan highlands, but he knew the warm, moist lowlands were a breeding ground for the anopheles mosquito that carried the malaria parasite, *Plasmodium falciparum*.

[DR. CARROLL:] And it dawned on him, the places where there was a really high incidence of sickle cell was where there was a really high incidence of malaria. Bang.

[NARRATOR:] Now it was a burning question that confronted Tony: could sickle cell and malaria be connected? And if so, how? It was a radical notion that a genetic disease could somehow be connected to an infection.

[DR. CARROLL:] When you went back to Oxford--you had this idea of a linkage between sickle cell and malaria, but you hadn't published it? Did you know it was a big deal? I mean, did you...

[DR. ALLISON:] I was sure it was a big deal. Yes. That's why I wanted not to go off half-cocked. I wanted to have a really complete story.

[DR. CARROLL:] So, he decided he had to sit on this idea until he got a chance to test it

properly. So... and a key element of the scientific method is, to come up with a hypothesis, that's great. But you've got to test it in every way possible to see whether or not it can hold up to that sort of scrutiny. That's how science moves forward.

[DR. ALLISON:] The scientific method essentially means that you address a problem and try to find a solution. So you look at children of the appropriate age and find out whether they are, in fact, protected against malaria. And if that's the case, you predict that you will have high frequencies of sickle cells only in areas where malaria is endemic.

[DR. CARROLL:] He wanted to know that this correlation held, not just in Kenya, but everywhere.

[NARRATOR:] It would be important to look directly at the incidence of malaria and sickle cell in as many areas as possible. So, Tony went on a sickle-cell safari.

[DR. CARROLL:] He wanted to gather blood samples from all over East Africa to really test this correlation. And now he was a trained medical doc, so he had something to offer. So he would go into the market on market day, and offer to do checkups on children. And just take a little finger prick or a little heel prick to get a little sample of blood.

[NARRATOR:] The first thing he did was look at the malaria parasite load in each sample. Then he tested for the sickle cell character. He found that children carrying the character had a lower parasite count, as if they were partially protected against malaria.

[DR. CARROLL:] And when he examined the blood of about 5,000 individuals, a really massive study, the correlation was really clear. So clear, in fact, that he could really draw a map of East Africa, and shade in the areas of high incidence of sickle cell, and they were superimposed right on top of the areas of high incidence of malaria. Bang, that was it.

[NARRATOR:] The many samples and detailed maps made it clear there was a connection between sickle cell and malaria. But to understand how sickle cell might protect people from malaria required thinking about the genetics of sickle cell.

[DR. ALLISON:] What happens is the genes are lined up on chromosomes. And one has pairs of them with the exception of the sex chromosomes. And this means that you have two copies. So the copies can be the same or they can be different. And if they're the same, they're called homozygous. And if they're different, they're called heterozygous.

[NARRATOR:] When an individual finds a partner and reproduces, one of each pair of chromosomes is passed on. If the parents are both heterozygous, carrying one sickle cell and one normal gene, odds are one in four that the child will be sickle cell homozygous, two in four that the child will be heterozygous, and one in four that the child will carry two copies of the normal gene. In the absence of malaria, there is strong selection against the sickle cell gene. However, in a malarial environment, individuals born with two copies of the sickle cell gene, and those born with two copies of the normal gene, are both at a disadvantage. One gets sickle cell disease, the other is most vulnerable to malaria. Tony's brilliant insight was that those that

carried just one sickle cell gene had an innate resistance to malaria. Malaria tipped the selective balance in favor of heterozygotes. The evolutionary trade-off is that protection from malaria comes at the cost of more sickle cell disease in the population. The sickle cell mutation was not the best genetic solution you might imagine to resist malaria. That's not how evolution works. It was the most available--a simple typo, A to T, in the gene that encodes hemoglobin.

[DR. CARROLL:] Mistakes are made in the copying of DNA in every generation. You and I were born with about 40 or 50 mutations that didn't exist in either of our parents. It's just part of the nature of copying three billion letters in the process of reproduction. And when those mistakes arise, a typo arises in the globin gene... for most of us, that would be a bad thing. But if you live in a malarial area, it gives you an edge against the malarial parasite, so that mutation is retained.

[DR. ALLISON:] Well, fitness, essentially, is a measure of whether a particular gene is likely to be passed on to the next generation. And this means that for that to happen, the individual carrying that gene has to survive to reproductive age, and secondly has to reproduce.

[DR. CARROLL:] Now you had a sense that you had this explanation that was general to the prevalence of sickle cell and its correlation with malaria. But you didn't quite know the mechanism, right?

[DR. ALLISON:] That's right.

[DR. CARROLL:] So what did you do next?

[DR. ALLISON:] Well [laughs] I have to say I left that part of the story to others, because it's quite a complex story...

[NARRATOR:] A large body of subsequent research has shown that the sickle cell mutation compromises the ability of the parasite to reproduce. Thus, a mutation that creates one genetic disease can also protect against another disease.

[DR. CARROLL:] What Tony gave us was a fully-worked-out example of evolution by natural selection. And the amazing thing was, this was in humans. This is how natural selection was working on humans in real time in the real world. Tony's map of East Africa was a stunning achievement. But he could go further than that. He knew that there was a high incidence of sickle cell in Southern Europe, in Southern India, and in other parts of Africa. And it turns out, these were all malarial zones as well. And so, his map applied not just to East Africa, but that whole part of the world.

[DR. HEENEY:] When I'm explaining about the origins of sickle cell disease and its association with malaria to children or their families, they often look at me with incredulity. They don't understand, like, "You're kidding, right? This is all to do with a mosquito infection?" As our species has been able to move across the globe to areas with low malarial incidence, this gene is now really more of a nuisance than anything else. It's not really a clear selective advantage for them, in Boston, let's say. But it takes thousands of years for the population to

change and for genetics to change based on the pressures around them in the environment.

[NARRATOR:] What Tony Allison did, first with his sharp intuition and then with his rigorous research, will stand as a monument, bringing our own evolutionary process into the light.