

***The Making of the Fittest: Got Lactase?  
The Co-Evolution of Genes and Culture***

**[WELLS:]** Only a small number of human beings live like this today. But from the time our species evolved some 200,000 years ago, until the not-too-distant past, all of us lived as hunter-gatherers. Then, around 10,000 years ago, people started domesticating animals for food, living in settlements, and cultivating crops. These cultural changes had profound biological impacts on our species. And you're about to encounter one surprising example. It has to do with a familiar food. I'm talking about milk, the main ingredient in some of our favorite things. Almost all of us can digest it as babies. But the story of how many adults can use it as a food is a fascinating case study-- a study of the co-evolution of human culture and biology. All infant mammals can digest milk. In fact, producing milk for babies is a key trait that distinguishes mammals from all other types of animals. The main sugar in milk-- lactose-- can't easily pass through the intestinal wall. So cells here make an enzyme called lactase, which breaks lactose into glucose and galactose. These two simpler sugars can then enter the bloodstream where they can be used for energy. Around the time young mammals stop drinking milk, almost all of them stop making lactase, so they lose their ability to digest milk. They become "lactose intolerant." What typically happens when an adult mammal drinks milk? It's not pretty. The lactose goes undigested straight through the small intestine to the large intestine. Here bacteria eat the sugar and can cause cramps, gas, and diarrhea. It's a bad idea to offer a bowl of milk to an adult cat. We only know of one mammal species in which some adults can drink milk without getting sick. Yes, it's us. Not all of us, but worldwide, about a third of adults can digest lactose. This minority is called "lactase persistent" because their ability to produce the enzyme that breaks down lactose persists beyond childhood, and in fact throughout their lives. How did lactase persistence come about? Why does it occur only in some people? I've come to University College London to start my quest to find out. Geneticist Dallas Swallow will show me how to figure out whether someone can digest the sugar in milk.

**[SWALLOW:]** You're going to do a lactose tolerance test.

**[WELLS:]** I am.

**[SWALLOW:]** The idea is to look to see what the level of glucose is in the blood of the volunteer before the lactose load has been taken.

**[WELLS:]** After measuring my baseline glucose level I now have to chug a liter of milk.

**[SWALLOW:]** You're allowed to breathe in between, it's all right!

**[WELLS:]** If my body is still making lactase, my blood glucose will shoot up. After I drank the milk, here's what happened. No doubt about it: My lactase enzyme is still working.

**[SWALLOW:]** Where do your family come from?

**[WELLS:]** Britain on my father's side, Denmark, Holland on my mother's side. But kind of northern Europe.

**[SWALLOW:]** Northern Europe, OK.

**[SWALLOW:]** You can see first of all that most people in Europe are lactase persistent.

**[WELLS:]** My family background makes sense. In only a few regions is a large majority of people lactase persistent. In other parts of the world few adults easily digest lactose. What exactly is different about people who are lactase persistent? To get a clue, researchers looked at DNA. They first compared the part of the lactase gene that encodes the enzyme across persistent and non-persistent people. They didn't find a change in the DNA that distinguished the two traits. So what could explain the difference? We know that genes, including lactase, are regulated-- turned on or off, dialed up or down-- by other pieces of DNA that act like switches. In search of a possible mutation in a lactase switch, a research team identified Finnish families that had members who were lactase persistent, as well as those who weren't. Statistical geneticist Joe Terwilliger was part of the team.

**[TERWILLIGER:]** We then looked to see if they shared DNA around the region where the gene was that we knew was affecting the metabolism of lactose.

**[WELLS:]** On chromosome 2, in and around the lactase gene, a number of shared markers in the DNA allowed Terwilliger and his colleagues to home in on a segment of DNA likely to contain the lactase persistence mutation. By comparing this segment base-by-base, across lactase-persistent and non-persistent individuals, they discovered the critical one-base difference-- a T instead of a C at one non-coding position. The researchers had made an important discovery. They'd found a mutation that causes lactase persistence in Finns and other Europeans. Do all lactase-persistent people carry this mutation?

**[SWALLOW:]** I thought there would be one mutation, and that would be it. So we went off to study samples from Africa, and to our surprise, we found that the mutation barely existed.

**[WELLS:]** Was a different mutation at work on this continent? Then a young professor, geneticist Sarah Tishkoff traveled to a number of African countries to find out.

**[TISHKOFF:]** We've now looked at Tanzania, Kenya and the Sudan, and Ethiopia. And so we've really looked at a broad range of groups and... mainly in eastern Africa at this point.

**[WELLS:]** In one population, the Maasai, Tishkoff and colleagues found a different lactase persistence mutation from the one in Europeans. The two mutations had arisen independently in two different populations, in each case providing adults with the ability to digest milk. Tishkoff was more than pleased.

**[TISHKOFF:]** Thrilled. Excited. You know, you rarely... right? It's so unusual to actually find a variant that appears to be correlated with such an interesting trait.

**[WELLS:]** What was special about both the Maasai and the early Europeans that might explain why they each independently evolved this trait? Both are pastoralists-- people who domesticated animals for food.

**[TISHKOFF:]** They adore their cows. They are very possessive of their cows. This is their monetary system. Their wealth is determined by their cows. The culture centers around the cow.

**[WELLS:]** Was the evolution of lactase persistence driven by drinking milk? If so, can we find evidence of early milk use in these cultures? In Bristol, England, organic chemist Richard Evershed is examining fragments of old pots to find out.

**[EVERSHED:]** These look like they were probably cooking pots, like the ancient saucepan. We actually select pottery from the body or the upper parts of vessels, because obviously fat floats on the surface of water when you start the cooking process.

**[WELLS:]** Evershed has examined the fats trapped in pots from ancient settlements across Europe and Africa to determine if milk was on the Paleo menu.

**[EVERSHED:]** It is quite wondrous to think that you are holding artifacts in your hands that were made and then used by people just like us.

**[WELLS:]** To figure out whether these pots once held milk, Evershed first had to find a chemical signature of milk fats. He started analyzing all kinds of fats from contemporary animals.

**[EVERSHED:]** We go to farms where they're using traditional farming methods, raising animals on natural grazes and pastures as far as possible.

**[WELLS:]** Comparing the ratios of two carbon isotopes, in two kinds of molecules in fats, Evershed watched the measurements pour in.

**[EVERSHED:]** I sat at my desk with one of my students and we were looking at some data; and we started to sort of see patterns in the data. Clustering in one part of the plot were body fats from pigs. In another region were body fats from ruminants such as cows. But there was more.

**[EVERSHED:]** I can remember the moment like as clear as day when we sat there. There were just these points disappearing off the bottom of the graph. They were the milk fats.

**[WELLS:]** Evershed now had a tool to look for evidence of milk in the ancient pots. He hoped that the tight pores of the pottery material would preserve the milk fats. To find out, his team grinds up potsherds... and analyzes them with gas chromatography and mass spectrometry-- just as they did with present-day animal samples. Evershed's detective work paid off. Right where contemporary milk fats showed up, there was now data from

ancient pots. They once contained milk. African settlements 7,000 to 5,000 years ago were using dairy. And potsherds from Europe and the Middle East showed milk use 9,000 years ago-- the oldest ever discovered. The dates reach back almost to the dawn of civilization. Geneticists can date the origins of mutations by analyzing DNA. Remarkably, the dates for when the European and African lactase persistence mutations first spread in populations are a good match with the archaeological evidence of when people first started using milk in these regions. How did dairying drive the spread of the lactase persistence mutations? Mutations, of course, occur at random. So before humans kept dairy animals, if a mutation arose that maintained lactase production, it could have vanished from the population. Without milk around, there's no known advantage to the mutation. But if such a mutation existed when we started dairying, then it could have increased in frequency in the population, because lactase persistence now provided a selective advantage. I spoke with Mark Thomas to find out just how powerful that advantage was.

**[THOMAS:]** Mind-bendingly strong. The estimates have put it at somewhere around 5 or 10 percent. Let's just say that it's 5 percent. What that means is that for every person... for every 100 people who would have survived without this trait, 105 would have survived with this trait.

**[WELLS:]** And multiply that over a few generations, and—

**[THOMAS:]** And that's every generation, it goes generation to generation. You know how quickly generations happen.

**[WELLS:]** And why?

**[THOMAS:]** I don't know. Look, I've got some ideas.

**[WELLS:]** So what are your ideas?

**[THOMAS:]** Naturally we have to start first with just basic nutritional facts. So, milk is very protein and fat-rich. Both are good for us. The protein in milk is of the highest quality. It's the only food that we're aware of that was produced with the intention of being consumed. All other foods generally want to avoid being consumed, whether consciously or otherwise.

**[WELLS:]** That's true, that's true.

**[THOMAS:]** Milk is a relatively uncontaminated fluid, and so it reduces the exposure to pathogens and parasites.

**[THOMAS:]** You have these populations, they're moving into northern Europe. They're primarily not lactase persistent. Now, imagine your crops fail. Now, you become entirely dependent on your milk. If you are in a famine situation, so you are borderline starvation, and you eat something that gives you diarrhea, you're probably going to die. And that's exactly the thing that's going to happen to these people, because they've got nothing else

to eat, and they're eating more and more effectively toxic foods. So I suspect that that's the real times that sorted out the lactase-persistent from the lactase-non-persistent.

**[WELLS:]** While the exact selective advantage of lactase persistence is still being debated, it's clear that the nature of this selection was unusual. It's a rare but powerful case of what's called gene-culture co-evolution.

**[THOMAS:]** To understand our biological evolution absolutely requires an understanding of our cultural evolution as well, and that means that the human story is more a gene-culture co-evolutionary story than it is for any other species on Earth.