

An Introduction to Evolutionary Biology

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Week 12 Lecture 50

Applications of Evolution: Part 1

Hi, when it comes to the word "evolution," Most people think it is all about fossils and things that happened millions of years ago. However, toward the end of our last discussion, I explicitly told you that Nothing can be further from the truth, and there are several ways in which evolution impinges upon our contemporary lives. So, that is the topic of today's discussion: evolution through the lens of application, particularly modern-day applications. Now, perhaps the biggest application of evolution is in agriculture and animal husbandry. As we already saw in our last discussion, when humans developed agriculture and started domesticating animals, That completely changed the way we lived and further shaped our own evolution. However, that process of getting hold of animals and other plants and making them you know, work for us from an economic perspective; that is something that has not really ended. In fact, it is, if anything, right now, given that the population of the world is increasing and given that, you know, we are kind of hitting. Some kind of barrier in terms of increasing our agricultural and livestock production, research in this particular area, you know, Breeding animals and breeding plants to make them more economically viable, research in this area is absolutely booming. So, just to give you some examples, here are just a few of the national-level plant breeding and animal breeding institutes of India alone. And these are national level, which means that at the level of each state, there are many, many other such institutes. Many universities also work on this topic, and this is just in India; you know, such things are happening all over the world. So, this is just to tell you the scale at

which people are using principles from evolutionary biology. breeding and other stuff in order to improve our crops and animals. However, this is not what I am going to talk about today; this is a very specialized subject.

What I am going to talk about in a little bit more detail is evolution and health. How exactly has evolution ended up affecting the practice of medicine in a rather big way? And there are two or three major topics here. But the first topic that we are going to take up is in the context of antimicrobial resistance. Now, what exactly is that? So, antimicrobial resistance refers to the ability of microbes to resist the chemicals that can otherwise kill them. I mean kill the anti you know bugs.

So, depending on which kind of organism we are talking about, antimicrobials come in different types. and therefore, the corresponding agents you know resistance is of different types. So, depending on the organism, for example, if it is a bacterium, then the kind of drug That we use to kill them, they are all called antibiotics; therefore, you have antibiotic resistance. Similarly, for viruses, you have antivirals and antiviral resistance; for parasites, antiparasitics; and for fungi, antifungals. Now, very often the reason I am making this distinction to you is that when we say antibiotic, We tend to think of all microbes, but that is not really true.

Antibiotics are only for bacteria; you have all these other classes of organisms. which requires very different kinds of chemicals to kill them. But together, these chemicals constitute antimicrobials, and the resistance against them is antimicrobial resistance. Now, in 2021 alone, there were about 1.14 million deaths that were directly attributable to antimicrobial resistance.

And it is estimated that by 2050, this number will be about 1.9 million annual deaths. I mean, that is a huge number. And these are the only places where things are direct. If you look at the indirect effects, they are obviously much larger, but More worrisome in this context is a prediction about how these deaths are distributed globally.

And this is the predicted death rate per 100,000, or per 1 lakh, attributable to AMR for all ages in 2050. And essentially, this is the color code. And you can see the deeper the color, closer to you know red, the worse it is. The highest category is this one, and this is in India. So, what is predicted is that you know about burying this one place in South America.

India is probably going to have one of the highest rates of death due to antimicrobial resistance. And right now, it is an absolute living nightmare for most hospitals in this country. If you tend to go to a hospital and catch a, you know, bug that is antimicrobial resistant, Then getting rid of that bug can sometimes be extremely difficult. Now, why exactly do we have this problem? Now, in this context, whatever I discuss, I am going to focus primarily on antibiotic resistance because that is what has been best studied. However, the major things that I am going to talk about are applicable across all the classes of drugs that we discussed.

Now, many antibiotics that we have to realize are natural chemicals. They were associated, you know, isolated from bacteria, and they have evolved by bacteria essentially to fight other bacteria, right? So, because of that, there is always some level of antibiotics in the environment, which means that even without us humans Doing anything, there is always a baseline selection happening among the microbes to fight each other. And there is a baseline selection for increased antibiotic resistance. Now, of course, because of this and because of the fact that the bacteria have been around for millions, if not billions, of years, There are many ways in which bacteria can end up evolving antibiotic resistance. For example, you know that for any antibiotic to work, it has to be able to go through the membrane.

So, many bacteria can end up making all kinds of modifications at the membrane level. such that the uptake of the antibiotic itself is prevented. Similarly, there are all kinds of pumps available in the membrane, which actively expel whatever antibiotic has been taken. And when I say actively, I mean that you know it is in exchange for energy. So, this is the energy-consuming process.

And these efflux pumps, sometimes they are very specific; that is, they will only work for one kind of drug, but many times. They are pretty broad-based, which means that one efflux pump can actually throw out many kinds of antibiotics. Then, of course, bacteria have evolved different kinds of enzymes that can degrade antibiotic molecules. And sometimes what happens is that you know each antibiotic when it goes inside the bacteria. It typically ends up having some kind of target site.

So, some work on, let us say, topoisomerase; some work on the gyrase molecule; some work on the ribosomes; and so on. So, what the bacteria can do is modify the site at which the antibiotic will go and bind. And thereby, it can prevent the drug from binding, essentially making the drug ineffective. Now, very interestingly, some of these mechanisms are very, very specific. So, for example, target site modification is a very specific thing that typically works only for antibiotics that will bind there.

But some of the other mechanisms, for example, this efflux pump mechanism that I talked about, is a generic mechanism. which means that they are not only important in the context of antibiotics, but they can be used by the bacteria to fight other chemicals. For example, heavy metals, etc., which are entering the body of the bacteria or thus inside the cell of the battery. Now, this particular piece of information is actually very crucial, as we are going to see in the next slide.

Now, what are the selection pressures for antibiotic resistance? Now, obviously, the biggest selection pressure is an increase in the levels of antibiotics in the environment. That has happened over the last four or five decades. Why has that happened? One major reason is climate change. Now, we know that, because of climate change, there has been a warming of the environment all over the world. And because of that, the number of bacteria that are growing has actually gone up in many places.

Why is that? Because we know that you know many bacteria—I mean, almost all bacteria will have an optimal temperature range. In which they can grow, and when the world is

slightly colder, that optimal range is typically not reached. But because of climate change, there has been warming now. Many bacteria are finding that the climate is much more suitable for their growth. And they are, you know, as this study points out, increasing the number of taxa of bacteria that are growing.

Secondly, obviously, human beings have been using and abusing antibiotics at an astonishing rate for the last 45 to 50 years. So, nowadays, if you go to any doctor, you know, okay, not just any doctor, but many doctors, They end up prescribing antibiotics without really thinking through whether those antibiotics are really needed. or whether the patient will be able to take care of the infection on their own. Cannot blame the doctors entirely because you know if a patient is suffering, they go to a doctor, and the doctor tells them, "Look," You just fight it through, you know, because antibiotic resistance is increasing; the patient will probably go to a different doctor. So, many times because of those kinds of social reasons as well, the doctors are forced to prescribe antibiotics.

However, the much bigger issue in the context of antibiotics is in terms of livestock. So, we know that our livestock, you know, the cows, the buffaloes, the goats, the sheep, etc., Most of them have been bred for higher productivity. And many of these, you know, bred livestock; their ability to fight any kind of infection has actually gone down. Because they have been bred for other properties.

As a result, in order to keep them healthy and alive, most of the time the livestock breeders, not the farmers, You know people who are farming, you know, dairy farming or wool farming, etc. they end up injecting their animals with enormous amount of antibiotics. And unlike the human scenario, where the use of antibiotics is somewhat controlled, In the context of livestock, the use of antibiotics is hardly controlled. As a result, most of these people, they end up pumping antibiotics at a high rate into their you know animals Most of these antibiotics do not get absorbed in the body. Most of it actually passes out through urine or fecal matter and ends up in the environment.

As a result, the environmental load of antibiotics goes up, and obviously, that creates a selection pressure even for those microbes, which are otherwise not pathogenic, which are otherwise not even inside the body of, you know, the sheep or the cow. Now, because of this, this is one of the biggest reasons for which there has been a great increase. The second, or rather the third, thing that also happens is the same stuff in the context of agriculture or aquaculture. So, nowadays, lots of people end up spreading antibiotics along with pesticides for their crops.

And of course, you know people who are into aquaculture, such as fish culture or prawn culture, etc. Those people also end up using a tremendous amount of antibiotics. And finally, there is a lot of residue that comes from pharmaceutical manufacturing, and this also gets into the environment. And of course, when it comes to antibiotics, improper disposal of hospital waste happens to be one of the biggest culprits. Now, all these things taken together are happening simultaneously, right? So, taken together, these have increased the baseline level of antibiotics in the environment to an epic proportion.

However, they are not the only culprits. I mean, these five are probably the biggest culprits. But there are other things that also end up increasing the selection pressure on the bacteria. For example, as I told you, bacteria have these efflux pumps, which are active. Not only to throw out antibiotics, but also to throw out other heavy metals, chemicals, and so on.

Now, because of all kinds of manufacturing processes, the concentration of heavy metals and various kinds of industrial chemicals pollutants. These have greatly increased in the, you know, soil and atmosphere, and so on. Now, because of these, there is not a direct selection for antibiotic resistance, but there is an indirect selection for antibiotic resistance. So, whenever a bacterium encounters these chemicals, it is actually ending up among other things, increasing its efflux activity. And that, as a secondary first reason, can end up increasing its antibiotic resistance.

The other very interesting thing that we found out was, you know, related to a fluctuating

environment. So, this was an experiment that we did in our lab, wherein we took the environment's pH, salt, and so on. We just fluctuated the environment; we varied it unpredictably. So, the whole idea was that you know in the natural world, bacteria are always going to get an environment that is continuously changing and most often unpredictably.

So, how exactly did they end up combating that, and what we found was that when we changed this, you know? Environment unpredictably, the first thing the bacteria did was increase their efflux activity. And because they increased their efflux activity as a correlated response, they ended up gaining increased antibiotic resistance. Now, think about it; these were bacteria that were never exposed to any antibiotic, yet because the efflux activity had gone up, they had become more resistant to antibiotics. So, why is this critical? This is critical because if you look at what climate change is doing, it is not only warming up places. It is not only changing the pattern of precipitation, but it is also leading to a lot of increase in the variability in various, you know parameters, environmental parameters, and our work is showing that the increase in the variability alone. Under certain circumstances, it can end up increasing the bacteria's ability to combat antibiotics and others. Yeah, in the context of bacteria, it is antibiotics that matter. So, as a result of all these things happening together, there has been a massive increase in selection pressure. For antibiotic resistance in bacteria, not only the pathogenic ones, but all of them.

And this, in the context of bacteria, is a huge thing. Why? Because there are certain properties of bacteria that make them extremely potent against these kinds of selection forces. What are those? Number one, remember that bacteria have massive population sizes, and they also have extremely low generation times. They are, you know, multiplying very fast; they can multiply very fast. Now, because of this, there are certain advantages that a bacterial population has which, for example, a human population or a goat population will not have. Like what? Because the population size is very high, that means they are dividing continuously. They have a very high chance of hitting beneficial mutations. Remember, mutations by themselves will arise randomly with respect to their

fitness. Most of the mutations that will actually change fitness will end up being deleterious.

But in spite of that, even if there is, let us say, a 1 in a million chance or a 1 in a billion chance of hitting a beneficial mutation, That kind of mutation is much more likely to occur in a population that has a large size. And you know, it is replicating extremely fast compared to, let us say, A population like ours, although large in size, is replicating very slowly. So, the chances of getting the beneficial mutation are high, and more importantly, because the population size is so high, Remember, we talked about the selection-drift balance; we know that as the population size increases, the role of drift goes down and the role of selection goes up, which essentially means that. In bacteria, for high population sizes, selection is most probably going to be a very dominant force. And as we have seen, selection, anyway, is a very strong force of evolution. And it can lead to extremely high levels of change and a high magnitude of change rather quickly. So, if you have a scenario where selection is operating extremely well, that is a recipe for disaster.

To make life more, you know, interesting or scary, whatever you call it, we are also having a lot of zoonotic transfers. What does it mean? So, zoonosis essentially means the situation in which bacteria and other microbes They end up moving from their regular hosts to other organisms. So, in this particular case, we are talking about some bacteria moving from an organism to humans. Now, because of various reasons, there is a large increase in zoonotic transfers. So, for example, the biggest example that I can think of right away, although not in the context of bacteria, is viruses.

Zoonotic transfer from bats; we all know where it went. Not only do we have transfers from wild animals, but there is also a lot of zoonotic transfer happening from domestic animals. And that is a lot scarier because, as I told you, domestic animals are being continuously pumped with a lot of antibiotics. So many of these pathogens, which normally are not human pathogens, but let us say they are in the domestic animals, they are getting lots of antibiotics. So, they are becoming resistant and at some point due to

whatever mutation you know they end up shifting from those animals to us. So, for example, if you remember the bird flu and the swine flu, these are All examples of zoonotic transfers that are happening from other domestic animals to humans.

To make life even more surreal, you know, climate change also plays a role here. Because many times you end up getting stuff from permafrost. So, in 2016, there was a very major anthrax outbreak in Russia, and they could not really figure out why. It was happening until they figured out that, you know, due to global warming, the permafrost—so what is the permafrost? Permafrost is basically, you know, that part of the soil or the seabed which is permanently frozen. The temperature is permanently or for a very long time below 0 degrees Celsius.

Now, because of global warming, the temperature in many places in Siberia and, you know, other places with permafrost, The temperature is increasing. Now, because it is increasing, the permafrost is melting. Now, the permafrost actually ends up trapping a lot of microbes inside it. More importantly, in places like Siberia, it traps the carcasses of animals that died a long time ago, but were frozen before they decomposed. So, in this particular case, it turns out that some of those, you know, reindeer carcasses in Siberia, they were actually having very deadly anthrax germs and they had gotten frozen. And then you know this happened long, long ago, you know, probably hundreds of years ago. But when the permafrost froze, all these carcasses were exposed, and then all the anthrax came out. That anthrax was responsible for the 2016 outbreak is an absolutely scary kind of scenario. Now, obviously, if you have all these bacteria coming in, these are all new organisms.

And therefore, sometimes these new organisms can end up making life very, very difficult because they might have genes that Through horizontal gene transfer, genes can be transferred to existing pathogens, making them even more deadly. In the context of antimicrobial resistance, that is actually our lesser worry. Our bigger worry is that, because HGT is extremely common in bacteria, Suppose you know there are so many species of bacteria out there, right? The environmental load has increased. Suppose there

is a non-pathogenic species of bacteria that has ended up with the mutation.

This makes the bacteria resistant to some antibiotics. Then, from that non-pathogenic strain, that thing can end up transferring into the pathogenic strain. which can then become really, really problematic for us. And the issue is that we know it is happening, and it is happening at an extremely alarming rate. And the whole thing has been complicated even more because we, human beings, We obviously know that all the countries are connected to each other by commerce and travel. So, suppose let us say you know I am sitting here in Pune and I am, let us say, doing some farming, and in that farm, I end up, you know putting in some antibiotics, which causes some bacteria to develop resistance. And let us say I know whatever I create some crops and I do not wash my crops properly. That crop gets sent over to wherever, say Africa, China, or the US. And there that bacteria ends up transferring that gene to another bacterium in that country. And therefore, those guys over there who were never exposed to that antibiotic did not even use it.

Suddenly, they will find that you know people are not responding to antibiotic treatment in their country simply because. The thing that the resistance evolved in my country went over there through crops. So, this kind of scenario has made the entire thing a living nightmare. And to make it even more complicated, the one major thing that we are seeing nowadays is what is known as multiple drug resistance. What is that? So, when you have simultaneous resistance, also called cross-resistance, to multiple drugs.

Now, why should such a thing arise? There are many ways in which it can arise, some of which I am quickly telling you. So, one of them is supposed to be that you know you have a bacteria. But typically, you will get just one or two, you know, mutations happening in that. But suppose there is prolonged exposure to antibiotics; what will happen if you know the load in the environment is high? Because of that, the same bacteria might end up getting multiple mutations in multiple genes, or the same lineage can end up getting multiple mutations in multiple genes. which can end up making it resistant to multiple drugs simultaneously. Or, as I told you, you know, there is horizontal

gene transfer. Now, when there is horizontal gene transfer, remember that one of the things bacteria transfer is plasmids. Now, plasmids are, you know, circular DNA molecules, and they can contain multiple resistant genes at the same time.

So, one plasmid can contain multiple resistant genes. So, in one shot, you can have a scenario where resistance to 3 or 4 genes is going to be transferred straight away. And obviously, that makes life very difficult. And the third thing that is happening, and this is what is making life even crazier, is the evolution of so-called super genes. So, for example, there is this group of enzymes known as ESBLs, extended-spectrum β -lactamases.

So, β -lactamase is a kind of enzyme that breaks down certain antibiotics. but this particular group of enzymes, you know, ESBLs, They end up allowing the bacteria to cut out many kinds of antibiotics at the same time. And because of this, it makes the pathogen resistant to a wide class of antibiotics, including the very recent fourth-generation antibiotics. And this makes this kind of resistance extremely difficult to treat.

And right now, ESBLs have spread to *E. coli* and *Pseudomonas aeruginosa*. I also think of staph and many other extremely hard-to-treat organisms. So, what does one do? How do you combat this? Obviously, the best thing to do is a more rational prescription of antibiotics and avoidance of self-medication. Now, the problem here is that this is something doable, but due to the social reasons I discussed, it is hard to do this. More critically, see that this is a community thing. As a person, I can say that, look, I will not take antibiotics; I will let the infection run its course.

Even if that means I will have to be in my bed for 10 days. The problem is, suppose my neighbor does not think that way; my neighbor ends up taking the antibiotic anyway. And therefore, the resistance develops in that neighbor, but remember this is a community matter. So, the resistance that develops in that neighbor does not stay inside the neighbor; it passes on to the environment. And therefore, even if I am not using antibiotics, I am not

immune to getting bugs that have gained their resistance from somewhere else.

Therefore, many people end up thinking that you know why to bother until and unless. The entire society signs up and very religiously does not use antibiotics; I am anyway going to get antibiotic-resistant bugs. So, why should I go through the pain of fighting the disease? Let me have the antibiotics as well. So, which is why, although it is very easy to say, it is very, very difficult to implement that first step. As I said, a huge amount of antibiotics is used in agriculture, animal husbandry, and aquaculture. So, somehow one needs to come up with good-quality policies to monitor and rationalize the usage of those antibiotics.

One thing that we have noted is that many times when bacteria end up developing resistance to one kind of antibiotic, They become sensitive to another kind of antibiotic. This is what is known as collateral sensitivity. So, one needs to monitor which mutation or resistance is associated with which sensitivity. And then, if possible, one can give drug combinations in such a way that you know, you let us say that resistance to antibiotic A makes you sensitive to antibiotic B. So, give a combination of A and B so that every time a bacterium tries to become sensitive to A, it ends up being killed by B. Of course, this is not very easy to do because these patterns of collateral sensitivity are themselves very labile. They end up depending on all kinds of epistatic interactions in the genome, but if one can take care of them, you know, This is one way in which, at least to some level, the spread of resistance can be stopped. Of course, the best thing is to prevent the infections and improve sanitation levels.

As far as practicable, vaccinate at least against the most common diseases. So, the whole idea here is to try to make sure that you do not even need to take antibiotics. That is what is going to reduce the overall antibiotic usage; easier said than done, of course. And finally, we have to step up our rate of discovering new drugs. Right now, there has not been any new classes of antibiotics for the last several years.

So, in 2025, they finally announced a new class of antibiotics after a gap of 30 years. This

is partly because antibiotics are very powerful. So, most of the time, although there are many candidates, you know when it comes to trials, human trials. Many of these candidates are thrown out simply because they end up having extremely high side effects. Which is why developing a new antibiotic is not easy, but somehow we have to do something to get more drugs. So, that was about how the evolution of microbes can create problems for us, but it turns out that Under many situations, our own evolutionary history can affect how we end up getting diseased conditions.

And that understanding and the corresponding, you know, medical practices, they form a very fascinating sub-discipline of medicine known as evolutionary medicine. But that is what we are going to deal with in our next discussion. See you then. Bye.