Interview with evolutionary biologist Paul Ewald

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Paul W. Ewald is an evolutionary biologist, specializing in the evolution of infectious disease. He received his Ph.D. from the University of Washington, in Zoology, with specialization in Ecology and Evolution. He is currently director of the program in Evolutionary Medicine at the Biology Department of the University of Louisville.

The first recipient of the George R. Burch Fellowship in Theoretic Medicine and Affiliated Sciences, Ewald's publication of Evolution of Infectious Disease *is widely acknowledged by doctors and scientists as a watershed in the emergence of the new discipline of evolutionary medicine. He has been featured in The Atlantic, Newsweek, Discover, and Forbes.*

Professor Ewald is also the author of a groundbreaking book, Plague Time: How Stealth Infections Cause Cancers, Heart Disease and other Deadly Ailments.

How do the concepts of evolutionary biology support the idea that pathogens are to blame for most diseases?

When we consider the possible causes of disease, it's important to make sure that at our starting point, we put all categories on the table. I believe the most useful way to do this is to think in terms of three main categories:

- inherited genes
- parasitic agents (this includes bacteria, viruses, fungi, protozoa
- non-living environmental factors (too much or too little of a particular substance, radiation, exposure to a chemical etc.)

Once we have this spectrum of categories in mind we ask, "Have all three areas been investigated?

At this point scientists tend to make an error. They decide that if they have found enough evidence for categories 1 or 3, that category 2 is not playing a role. This is a fundamental problem that has led the medical community to misunderstand the cause of most debilitating chronic diseases.

So, which of the three categories is overlooked? Category 1 certainly isn't – once scientists figured out the structure of DNA and the nature of mutations they were extremely eager to show their relationship to disease. Category 3 hasn't been overlooked, largely because of the fact that we can sense environmental causes of disease. We suffer from a stomach ache after eating contaminated food or feel the pain from a sunburn.

But, if we look back at every decade, there has been a lack of research on category 2 relative to its actual importance in causing disease. Our track record shows that we have consistently failed to fully understand the role that pathogens play in causing disease and this trend has continued up until 2008.

There are many examples of how we have continually overlooked the category of infectious disease. I'm not talking about acute infection – researchers were essentially able to work out the mechanisms of acute infection from 1880 to about 1920. I'm talking about chronic infection, and thus the role of pathogens in causing chronic disease.

Take the case of peptic ulcers. The idea that bacteria cause peptic ulcers was first solidified in the 1940s, then independently investigated and solidified again by Marshall and Warren in the 1970s. It took over 20 more years before the relationship was finally accepted by mainstream medicine. Now, when people look back on previous theories about the cause of peptic ulcers they think, "Oh, isn't it surprising that we didn't understand the cause for so long!" or "We should have known better!" But

when they proceed to hypothesize about the cause of other diseases, they go right back to the dogma. They haven't learned the lessons from the peptic ulcer story.

Instead, they should think in an opposite fashion. If we find that one disease has an infectious cause, we should learn from that information and seriously consider the same possibility in other diseases.

Think about syphilis. In 1913, it was discovered that the disease resulted from infection with the bacterium *Treponema pallidum*. Soon, the disease was dubbed the "Great Imitator" because its symptoms often resembled those of other diseases, particularly in the later stages. I think syphilis should be called the "Great Illustrator," because it's a disease that imitates a whole spectrum of other diseases. This suggests that we should be actively looking for a pathogenic cause in these other diseases as well – especially since so many illnesses are still considered to be of unknown cause. Back in the day, the psychoses associated with syphilis and schizophrenia were grouped together into a single category of illness. But as soon as syphilis was found to have a bacterial cause, we separated syphilitic insanity from what is now called schizophrenia, and assumed that schizophrenia was not caused by infection. Rather than just separating the two diseases we should have actively pursued the hypothesis that schizophrenia also has an infectious cause. The information we can gain from these kinds of relationships is far more enlightening than any genetic data.

That's one of the realities of medicine – researchers tend to deny associations. Denial plays a major role as scientists love to hold on to the current dogmatic explanation. This suggests that in order for pathogens to be fully tied to chronic disease we will have to wait until the current powerful people pass away and a sufficient number of young people entering the arena without these vested interests mature into positions of influence, to tip the balance of expert opinion. This is something that Charles Darwin, Max Planck, and Thomas Kuhn all agreed with.

That's because powerful people tend to hang on to the opinions that made them powerful even if there is no longer sufficient evidence to support their views. It's a social problem that relates to the weakness of the mind. Human beings didn't evolve to be scientists. Instead they evolved to be competitive – to grab and hold onto what is theirs. Hence the name calling often observed among the medical community and the resistance among scientists to fund or support ideas other than their own, ideas that question the validity of current dogma.

From an evolutionary perspective is it possible that current diseases of unknown cause could all be genetic diseases?

No. Take schizophrenia again. Evolutionary biologists understand that if an allele (a sequence that codes for a gene) were to code for a disease it would slowly get weeded out of the population, particularly since people who are sick are much less likely to reproduce (especially people with a severe disease like schizophrenia). Yet a person's chances of getting schizophrenia are 1 in 100. The reality is that faulty genes cannot maintain this frequency. If schizophrenia was a genetic disease, then according to the rules of mathematics, it would only occur in about 1 in every 10,000 people. The current frequency of the disease is just far too high.

Some might try to rationalize the 1 in 100 number by saying that schizophrenia is influenced by environmental factors, but if this were the case the environmental factors would have to be widespread and consistent across much of the world which is highly unlikely. Yes, some populations do have a higher incidence of schizophrenia than others, but that variability is much better explained by the idea that some populations harbor more of the pathogens that cause schizophrenia then others.

This highlights another issue. The fact that illnesses tend to run in families does not mean that only faulty genes are at work. Family members could just be passing each other pathogens. If one member of a twin pair has schizophrenia, there is a 35-60% chance that the other member of the twin pair will have it. However, this may be just a reflection of the fact that both twins were exposed to the same pathogens in the womb.

Pathogens also possess the ability to evolve and adapt at rapid rates, meaning that even if the host acquires a defense against them they can often find away around it. As previously mentioned, genetic disease would gradually be weeded out of the population. But as soon as you hypothesize that a disease has an infectious origin, and that the pathogens causing it can adapt and evolve, it is possible to explain how diseases can be perpetuated indefinitely in quite severe forms.

So you support the idea that the genetic mutations picked up on by many scientists may be induced by pathogens?

Yes, it's possible. We know that some viruses and bacteria mutate and damage DNA. Similarly, the compounds created by the body in order to continually combat pathogens are often potent molecules that can also cause genetic mutations.

Give me some examples of diseases in which an infectious agent is certainly to blame.

Cancer is really a special case of the problems we have discussed. The same dogma has been driving how the disease is viewed for so long. But if people are able to recognize the dogma for what it is, they can take a better look at definitive evidence about the disease. Taking a look at the track record of cancer researchers is a good way to decide whether the consensus view is right or wrong.

Back in 1975, mainstream medicine agreed that about 0.1% of human cancer cases were caused by pathogens. When it came to the rest of cases, their view was that they were probably caused by a combination of inherited predispositions and mutagens. Then in 1985, the percentage of cancer cases they tied to pathogens was 3%, and they continued to make the same argument about the remaining cases. In 1995 the percent of pathogen-induced cancer cases was accepted to be around 10%. Now, we're at 20%. Still, mainstream medicine contends that the other 80% of cases do not have an infectious cause, but the questions is – do you believe them anymore? In this sense, the clarity of hindsight can help a lot. Between evolutionary instinct and plain common sense we can view the issues of pathogens and cancer much more effectively.

Or, take a disease like atherosclerosis in which noting patterns of infection is unavoidable. There are bacteria in the lesions of people with the disease and all kinds of inflammatory markers. What we need to do is take a step back, divorce ourselves from our predispositions, and look at these ideas together.

Modern medicine has done a poor job looking for clues of continued infection. This may be partly explained by the fact that in many cases, it's hard to link a pathogen to a disease because the pathogen grows and spreads so gradually. So the time at which a person becomes symptomatic may be years after the onset of infection.

Recognizing these patterns requires thinking broadly and deeply, but medical professionals and researchers have been trained to think narrowly. They've tried to follow a model that resembles a NASA undertaking for a great moon mission in which every person brings his or her own particular specialty to the table. But that model doesn't work for medicine. Instead medical professionals need to work together with a unified theory in mind. But at the moment, they don't have a unified theory, and without a conceptual model to guide them, researchers are only able to determine risk factors for disease rather than come to an understanding of the overall cause.

Evolutionary biology is the most synthetic area of biology. It asks why things are the way they are, and integrates knowledge of how things work mechanistically. Evolutionary biology promises to be the most synthetic area of medicine for the same reason.

While we're on the subject of cancer, it and heart disease are now considered to be inflammatory diseases. Wouldn't the presence of inflammation be a red flag that pathogens are to blame?

Yes. And the immediate questions researchers should be asking is "What causes inflammation?" One thing that we clearly know causes inflammation is the presence of an infection. So, as soon as I hear the word inflammation I think, "What infectious agents are at play?"

That brings us to the concept of autoimmune disease – the idea that the immune system just "goes crazy." I think the fact that the concept of autoimmunity was developed in the first place is largely related to the fact that our brains have not evolved to think scientifically. People who have studied disease from their own point of view have recognized that the immune system is extremely important. But as we've learned more about the immune system, we've realized that it is an extremely complicated system – as complicated as the brain. Just like we can't look at one type of neuron and infer information about the entire brain, we can't try to understand the characteristics of only some immune cells and think we understand immune function.

So, over the years, as researchers have been daunted by the complexity of the immune system, it has seemed logical that such a complex entity has the potential to go wrong. Because they are limited by the power of their brains, they tend to simplify the issue and view the immune system in the same way they would view a truck that could break down. There are two problems with this type of thinking. For starters, we can't trust our intuition that something complex is likely to malfunction. The fact is, the immune system functions just fine in a large proportion of the population. The only logical way to explain the immune activation seen in patients with "autoimmune disease" is to suggest that there is some sort of agent pushing the immune system off balance. This argument is only strengthened by the fact that the same evolutionary forces that would cause a serious disease to be weeded from the population would also cause those people whose immune systems are prone to self-destruction to be eliminated from the population.

The concept of autoimmune disease has progressed to the point that now even researchers who previously dismissed the possibility of infection are accepting the possibility that "autoimmune" disease could be triggered by infection. This is some progress, but it's not enough. Especially since the concept of autoimmunity encourages doctors to prescribe immunosuppressive steroids to patients. But if persistent infection is involved these steroids may exacerbate the fire by allowing pathogens to spread.

Do you believe that pathogens could be involved in the aging process?

Aging is a super-category. We've gradually lumped together more and more symptoms under the category of natural aging. Many of these symptoms are the same as those caused by diseases that surely have an infectious cause. In that sense, you could view much of what we now call aging as an incapacitating illness that leads to a decrease in function. We know that inflammation and the interaction of the immune system with pathogens can destroy tissue. So it's not surprising that the tissues of a person who harbors a lot of pathogens would age earlier and alter their biological structure earlier in life. I do believe it is inevitable that people will eventually die of old age, but I suspect that this should generally happen when they are 80-100 years old. But we are increasingly seeing signs of aging-related diseases in people who are much younger.

What does evolutionary biology have to say about psychosomatic illness?

Personally, I believe that we label an illness as psychosomatic when we don't really know what's going on with the patient. It's a last resort diagnosis – a black box. If we knew more about what was causing their symptoms we could address the issue more clearly.

Looking at psychosomatic illness from an evolutionary viewpoint, you could say that those people who might exaggerate how sick they feel in order to gain attention and resources could have an evolutionary advantage. But if that's the truth, it only accounts for an extremely small percentage of cases. It's also true that often an illness will have both a psychological and physical component. But just because a psychological component is identified doesn't mean the physical component should be overlooked. Plus, most mental illnesses are probably the result of infection too. Chronic Fatigue Syndrome is a good example of a disease that up until recently has been dismissed as psychosomatic just because researchers couldn't figure out the cause. On the contrary, it's quite a serious illness.

What role do you feel the Internet will play in facilitating acceptance of an understanding of pathogens in disease?

I think the Internet plays an incredibly beneficial role as it can provide information to anybody who is willing to put in the time to learn terminology and information presented in the literature available on the Internet. I believe it will, and already is, changing the patient/doctor relationship and also the relationship of the general public with the government mainly because we can now check up on things and check up on them quickly. I can find information in half an hour rather than spending an entire day at the library – and think about the fact that this is happening all around the country.

Of course, now there is so much information on the Internet that it's too much for an individual mind to keep up with. Sometimes you have to read quite a bit of literature in order to extract the relevant information. That's why we need people to team up and share information. What we need is small groups of people poring over information together. In this way they can develop a more thoughtful, broad outlook. This is in contrast to the current medical model in which doctors and researchers are trained to specialize in such a narrow area of knowledge. They know very little about issues outside their area

of expertise and have trouble seeing the big picture. Thus, what we need is for the NIH to put money into grants that foster interdisciplinary insights.

Do you think that the peer review system and pharmaceutical industry are standing in the way of understanding chronic infectious disease?

I think the peer review system is becoming less important because there are so many other outlets where people can put up information. So I don't see it as too big of a barrier.

When it comes to pharmaceutical companies, it's important to recognize that they are very good at some things and very bad at others. What they are good at is product promotion and marketing, and working in innovative ways when the resulting product can bring in lots of money. The problem is the products that make the most money are not necessarily the products that actually help people the most.

Basic economic principles first put forth by Adam Smith show that the free enterprise system does not work well under certain situations. Writing over two hundred years ago, he argued that free enterprise cannot be expected to generate an effective national defense. For modern society, pollution control would be another example. If we want to move in that direction there needs to be a profit driven motive, or we have to get the government to do the things that do not generate sufficient profit. Otherwise, it just won't happen.

If you think about it, there isn't very much money to be made off a vaccine because a person uses it once or twice in his or her life and that's it. Instead, think of the amount of money to be made off a statin when a person is going to take it every day of their life. There's just not much motive for drug companies to invest in products that are cures or very good preventatives. We don't have to condemn drug companies, just recognize this role that they are playing in drug development. If we want to develop a drug under a high priority situation that may result in a curative solution we can't count on the pharmaceutical industry. In cases where the free enterprise system doesn't result in a situation that may benefit the population the government has to step in and provide funding for the possibility at hand.

What kind of approach to research would best expedite the process of better understanding the role of infectious agents in disease?

Most experts in the health sciences advocate a building-block approach to the problem of causation. They try to understand the workings of disease at the cellular and biochemical levels, in hopes that solutions will eventually emerge. Even among infectious diseases, however, the fundamental achievements have occurred more through the testing of deductive leaps than by building-block induction. What it boils down to is that we need both types of development but we can't have one without the other. Working incrementally can be great as long as scientists understand the big issues and the larger concepts that need to be guiding their research. But right now we have way too many scientists working in building block mode, missing what's going on outside the box.

Why do doctors often have such a problem accepting the idea that pathogens are to blame for more diseases then commonly accepted?

Because it's not in the textbooks. They are trained to look at a patient and try to match them with something in a textbook. These medical texts don't consider the preponderence of evidence across the entire spectrum of possible causes of most chronic diseases. The evidence implicating infectious causation tends to be a casualty of this restricted perspective, leading to the result that consideration of infectious causation in medical texts is minimal for chronic diseases of uncertain cause.

So until infectious pathogenesis is accepted to the point that it is in the medical texts taught in medical school, they will continue to consult only the standard operating procedure. If they can't put a label on the patient's illness it falls into a bin of "unexplained phenomena" which goes back to what I was saying earlier about psychosomatic illness, since they have a tendency to speak dismissively about what's in the bin.

The problem is that considering a new pathogenesis or a cause that isn't in a textbook requires thinking hard about unknown problems. They just don't have the time or training to think logically and deeply about such issues. This is evidenced by the

fact that you can go to five different doctors, get five different explanations for your problem and be recommended five different treatment options.

What got you interested in this area of research?

My interest in evolutionary medicine began in grad school around 1977. I came down with a bad case of diarrhea and was thinking about whether I should treat the symptoms or let the illness run its course. At first it seemed like it was most logical to let the illness run its course because that seemed to be my body's way of eliminating the pathogen. But then I thought about the fact that the pathogens might be manipulating me. If I expelled them, they might be endowed with an evolutionary advantage that would allow them to persist and infect others. I realized that my intuition couldn't provide me with the answer. That led me on a long web-like series of connections. The more I started to consider medical problems in the light of evolution the more I realized that some diseases simply cannot be caused in a way they are explained by current dogma. So I've tried to look at disease in a balanced way, to put all possibilities on the table, and from there to figure out what's feasible and what's not.