# This Week in Virology

*with Vincent Racaniello, Ph.D. and Saul Silverstein, Ph.D.*

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# Episode 5: Herpesviruses

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**Vincent Racaniello**: I'm Vincent Racaniello and I'm here with a guest today, Saul Silverstein, who has been a colleague of mine at Columbia for more than 25 years.

**Saul Silverstein**: About.

**Vincent**: Dick Despommier isn't with us this week. He's off to PopTech, which is a conference up in Maine, to promote vertical farming. We're here to talk about herpes viruses today. Saul is the expert virologist in contrast to Dick who is not a virologist. Saul is a virologist, more so than I am; far more intelligent and learned than I am. It's great to have him today. We're going to talk about herpes viruses which is his specialty, isn't that right?

**Saul**: We are certainly interested in them. They are fascinating little beasts.

**Vincent**: We'll have plenty to say about herpes viruses, but before we do Dick passed along to me several articles that he found in various Indian newspapers yesterday. Last time we were talking about rabies and rabies virus. It turns out that rabies is a huge problem in India. Did you know that?

**Saul**: Yes. You know there are lots of different sources of rabies. We keep finding new ones and one always looks at sources or resources, such as bats, which can be almost anywhere; they're a constant provider of new infections.

**Vincent**: Bats are a huge source. It turns out that in India they have 25 million stray dogs, which contributes to 96% of the country's rabies. Thirty thousand people die of rabies each year in India. The main problem is that they can't immunize these stray dogs because it's too costly. The cost is around 500 rupees each. Any idea how many dollars that would be, 500 rupees?

**Saul**: It's not as much as you would think. The real problem is probably not just paying for the vaccination, but getting the vaccine to these infected individuals and recognizing that they have been bitten by a rabid animal.

**Vincent**: Right. So one of these articles is written by a veterinarian who says the animal birth control plan in India, which was meant to control dog breeding, is a flop. India is the only one in the world that spends more money on maintaining stray dogs than on anti-rabies vaccines for human patients.

**Saul**: It doesn't sound like a good investment, does it?

**Vincent**: It sounds like a problem. Clearly in many countries rabies is a huge issue because there are so many animals that are not immunized. In the US it's not an issue because our domestic pets are all immunized, cats and dogs actually. Most of the rabies in the US is due to

wild animal sources.

**Saul**: Found in high-density populations; frequently there are lots of rabid raccoons and they have the ability to pass that virus on to domestic animals, such as your dogs and cats. That's why it's important to maintain those vaccinations.

**Vincent**: Did you maintain your pets' vaccinations?

**Saul**: Absolutely, even on the one we don't let out of the house.

**Vincent**: In case it did get out of the house.

**Saul**: Or in case one that is out of the house came in.

**Vincent**: OK. Moving on to herpes virus, which is one you have worked on for many years in your laboratory and continue to do.

**Saul**: And we continue to do so. When I first came to Columbia University I was very fascinated by a virus that actually infects predominately primates, as we know it. These are viruses that infect New World monkeys. These are small monkeys and there were two viruses that were very interesting. One was called *Herpesvirus saimiri*. The other was called *Herpesvirus entellus*. I was interested in them because they had been shown to be viruses that were indigenous to the primate population, but were able to transform cells in culture and were perhaps responsible for a form of leukemia and lymphoma in these animals and I thought it would be a great opportunity to begin to correlate expression of various virus genes for the development of these lymphomas. That was back in 1974. It was a project I started right out of my post doctoral fellowship and I received some funding from the NIH and a local foundation for it and we began to study these viruses, but that got interrupted by something more interesting which was our ability to demonstrate that we could take a gene that had been isolated from herpes simplex virus and that gene encodes an enzyme called thymidine kinase. We could introduce this gene into animal cells and this became a technology which is now widely used in very many different applications for looking at how genes function in introducing proteins in animal cells, proteins that can't be either synthesized chemically or produced in bacterial cells because the bacterial cells lack enzymes that modify these proteins that give them either extended life after injection or actually afford properties to them that they require so various protein modifications are necessary for activity of these agents or compounds.

**Vincent**: This effectively diverted you from saimiri and back into simplex?

**Saul**: That took me out of the saimiri business and back into simplex.

**Vincent**: Simplex being, of course, a human virus.

**Saul**: Simplex was also a very interesting virus. It was a virus I had studied as a postdoctoral fellow and had really tweaked my interest at the time and this was back in early 1970, was the fact that it was a very very large DNA genome. It was my thought at the time that I could learn something about how animal cells function by studying this very large genome. I was of course very naive.

**Vincent**: As we all are.

**Saul**: Yeah. Well, it was a tough problem and I had my very first graduate student whose name was Yutaka Nishioka had come to the laboratory and was interested in working with me on problems with herpes simplex virus. And Yutaka discovered that shortly after infection with this virus a very interesting thing happened to the cell that was the host for that virus, and that was that it stopped producing its own proteins; not a hundred percent, but a very large percentage of

its own proteins were inhibited and we wondered what it was that was arresting protein synthesis. And Yutaka and I worked on this problem for about five or six years and actually opened up a new field and that was this field of what happens when a virus infects a cell, how does a virus subjugate the host to its own purposes. And what Yutaka identified was something in the virion itself, that is part of the virus particle, that when it infected the cell resulted in degradation of host messenger RNA and disassociation of host poly ribosomes and as you well know, Vince, ribosomes are the machinery that's important for synthesizing proteins. So for a virus to be able to attack this very important regulatory control element of the host that is how it makes its own proteins, to disassemble it without destroying the components laid ground for our understanding for how a virus begins to make its own proteins in the face of the host RNA. So virus mRNA are seen because the host mRNAs are degraded and they use host polyribosomes that have been disassembled by reassembling them with virus messenger RNAs. And that became a very interesting field, but we got sidetracked on that one, too. This very interesting discovery with TK really put me out of the virus business for about six years while we studied how to put genes into cells. It's just another example of how interesting viruses are and how they provide key tools for our understanding of how cells function and how proteins are made in cells. It was a wonderful, magical mystery tour. We had developed a technology that my colleagues, Michael Wigler and Richard Axel to put almost any gene into a cell and be able to ask what proteins does it make and can we express that protein. That became a wonderful tool for the pharmaceutical industry and they've used that to produce a wide variety of proteins.

But let's get back to viruses. Herpes viruses remained a very interesting area of study for the laboratory. While we were doing this research on gene expression and transferring genes into cells we developed a tool for us to look at individual herpes virus genes. We were very fascinated by discoveries that had been made in a number of laboratories around the world. I was particularly impressed with Hummas and Roisman in Chicago and subsequently by the groups in Glasgow in Boston that there were a family of genes that herpes simplex virus, and it turns out most herpes viruses elaborate; in fact just about all DNA viruses have a phase very early in their life cycle that their first genes that they transcribe and subsequently translate are very intimately involved with regulation of gene expression. So when we talk about virus gene expression, especially amongst DNA viruses, we frequently say that genes are temporarily controlled in a coordinate fashion. By that we mean that a gene has a specific time to which it's turned on and sometimes turned off and that the product of genes that are made first frequently go back to regulate the subsequently expressed genes from a virus and in work by a series of students -- Irwin Gelman and Adele Alcara -- we were able to demonstrate that herpes elaborated a series of immediate early gene proteins, two in particular that seemed to be very important, one called IPC0 and it's naught for nothing that we call it 'zero' but 'zero' is a protein not obligatorily required by the virus for replication yet without it the virus grows very very poorly, and we were able to demonstrate that this virus gene product activates transcription from a wide variety of virus and cell genes. That was a very interesting phenomenon and we and a group in England, Roger Ebert, and group in Johns Hopkins headed by Gary Hayward and another one in Boston headed by David Knight were the very first to demonstrate that this gene product was a transcriptional activator. And then this work proceeded to demonstrate that we could use this gene in concert with other virus genes to further augment regulation of virus genes. That became a very fruitful area for research for a while and it was one we followed because we were really interested in dissecting how virus genes are regulated, what turns them on; what turns them off.

A little bit later another cohort of students, Eric Liam and Bob Solomon and a postdoctoral fellow Christos Panagiotis began studying another gene that was expressed very early in expression. This turned out to be another virus gene with many many functions as we see over and over again where virus genes interact with the host and change the way the host regulates its metabolism and of course makes it more available for the virus. This virus gene product was called IPC27. It was a small protein of about 63,000 molecular weight that was phosphorylated and when we looked very carefully at the hypothetical structure of this protein and its DNA sequence we realized that it contained regions for nuclear localization, bringing the protein into the nucleus, nuclear export, taking the protein out of the nucleus, and RNA binding motifs and we

began to think what does this protein do and I think we were the first ones, but I really don't remember now, demonstrated that this protein shuttled, that is it moved from the nucleus into the cytoplasm and back to the nucleus. That was a very interesting observation and perhaps the most important thing that we learned about this was that this protein had a cargo and that cargo was virus mRNA's and subsequent work has demonstrated -- and this is work by groups in Britain, and on the West Coast, Russ Andrew Goldman -- has demonstrated this protein has just a whole lot of other functions and those functions include interacting with the polyadenylation and the machinery of the cell, and poly(A) tracts, or things that are added to the end of messenger RNA's, very important for regulating their half lives and getting them out of the nucleus. So this protein interacts with a wide variety of host specific proteins and protein machines, those that are involved in export from the nucleus, things that recognize the nucleopore, which is that that big hole in the nucleus which allows exit, and for apparatus in the cytoplasm which disassociate the protein which is a transporter, from its cargo. You want to do that because if you are bringing in very specific RNA's you want them to be translated -- there's a reason for it. Then of course the protein is released and it has to get back into the nucleus and it does that using its nuclear localization signals.

**Vincent**: Does ICP27 only bind to viral mRNAs?

**Saul**: That's a very interesting question. It's probable that it sees some host RNAs as well and I don't think the answer for that is clear. The other thing that is clear is that it doesn't bind all viral RNAs. There are some late RNAs that it sees and some that it doesn't appear to see. The binding is yet to be elucidated, how those two things interact. Some things that we do know that it binds are factors proteins are used for splicing and the splicing machinery of the cell that is very important generating host messenger RNAs is not used very much by most herpes viruses, not just herpes simplex, but the Epstein Barr virus, cytomegalovirus, various varicella viruses. These guys don't have a lot of genes that are spliced and the recently discovered Kaposi's sarcoma virus has a lot of CDNA-like copies of human genes, so the introns been removed and it's plausible that this results because many of these viruses have an IPC27-like function. It's one of the most conserved genes in the herpes virus family.

**Vincent**: Now for someone who is not intimately familiar with herpes simples viruses why is it important these various ways that you've described by which the virus basically takes over most host functions for its own purposes?

**Saul**: Well, there are a bunch of interesting problems with viruses. One of the most interesting problems is their proclivity for forming latent infections. By that we mean the first episode of virus infection usually results in some form of overt lesion. Not always; the cytomegalovirus viruses and Epstein-Barr virus primary infections are not generally overt and you don't see a wound.

**Vincent**: But for simplex you see a lesion I'm sure.

**Saul**: You see an ugly little lesion.

**Vincent**: It happens very early in life.

**Saul**: Most people are infected with it in the first ten years of life and many children are born with herpes simplex virus, either intrauterine or when they exit the womb through the birth canal. And those are serious infections especially for a young child who does not have an active immune system and they must be treated very aggressively. When we think about treating infections we look for targets. There are some very potent drugs that work well with herpes simplex, Epstein-Barr virus, human cytomegalovirus, varicella zoster virus. And these anti viral drugs target generally the viral thymidine kinase, which is a protein that's unique to the virus and very different from the cell kinases, or the viral DNA polymerases. Polymerases tend to be highly conserved, not just among virus families but across the spectrum of all organisms, the active sites that are used to add nucleotides to make chains of nucleic acid, be they DNA or RNA, are very much the

same from organism to organism. It's the other proteins that are important for differentiating between host and virus, and virus and virus. So those drugs, while efficacious, tend not to have quite the efficacy of the kinase-specific drugs because there are conserved elements and you have to be careful. We see that over and over again with HIV.

**Vincent**: So if the child has acquired herpes infection at birth and it's very serious they're treated typically with what kind of antiviral?

**Saul**: They're usually treated with an antiviral called Acyclovir or Penciclovir. These are various forms of the same drug that are actively taken up in the cells that are in infected because the cells have the viral thymidine kinase and only those cells that have the virus take up the drug. So that provides a great therapeutic index, that is uninfected cells don't incorporate the drug. And the second feature is that these drugs are now used by the viral polymerase and because they cause chain termination, that is no new synthesis of virus genome can occur, they are very effective at limiting the spread of infection if given early enough.

**Vincent**: So Acyclovir and its derivatives were discovered quite a few years.

**Saul**: A long time ago.

**Vincent**: Have there been any new anti-herpes, anti-viral drugs developed?

**Saul**: Most of the new herpes antiviral drugs have been derivative.

**Vincent**: Of the original Acyclovir?

**Saul**: Yes of the original Acyclovir or analog, yes.

**Vincent**: Correct me if I'm wrong: I remember a story of a new drug developed against the topoisomerase-polymerase or an unwinding protein of the virus that was very good but was never brought to market because it simply wasn't better than Acyclovir even though it was a new target and it was quite specific.

**Saul**: Topos have been targets for a number of drug companies for a long time. And interestingly enough none of those have made it to market to my knowledge. I don't know why that is. The efficacy must not be as good when put into the patient as when it is put into the test tube. You frequently going from the test tube to the patient is a long road of discovery and refinement.

**Vincent**: Do companies continue to look for new antiviral against these viruses or do we think that the Acyclovirs are sufficient for what we need.

**Saul**: We know the Acyclovirs are not sufficient because there are a large number of drug resistant variants that arise and they arise because of the unfaithfulness of the polymerase. There isn't quite as much editing functions in most polymerases as the host has and that results in a finite number of mutations and these mutant viruses can escape. They are resistant to the effects unless of course they are in a cell that has another virus that's making the legitimate kinase. There's not a lot of work in the herpes field at this point.

**Vincent**: So if you're infected and you develop resistance to Acyclovir what's done next?

**Saul**: They usually use is one of the variants, Vancyclovir, Pencyclovir; and again there are slight differences; they use the second line drugs.

**Vincent**: Now if you're infected at a young age and your infection is cleared, uneventful infection presumably now you develop an immunity to the virus. Yet later on if you have some sort of

stress, as you know, you develop fever sores which are the reactivation of the original infection.; the virus has stayed with you for years. So why is that it in the face of the original infection that this can occur over and over again?.

**Saul**: There are two elements to what we cal recrudescence, the virus coming back. When I used to lecture to medical students I would end with a slide that is a picture of the heart with an arrow that went thru it and said "Herpes is forever." The reason for that is that primary infections always result in latent virus. The virus goes and hides in the your dorsal root ganglia which are those nodes along your spine and it sits there as a big plasmid, a big circle in the nucleus of neurons and there are some very very peculiar things that we note about that. The first is that very little is going on. The virus is not expressing virus specific proteins.

**Vincent**: Which is good since those cells might be cleared.

**Saul**: That's an interesting problem because clearance in the brain is subject to the action of different cells than clearance in the body. The cells that cleared in the brain are astrocytes and microglia; these kinds of guys. We don't know much that immune system at all.

**Vincent**: We also understand that the body would rather not clear cells from the brain

**Saul**: I think most of us need as many cells as we have. It's not too good to lose too many of them. But the virus has found a way to put multiple genomes in a single cell. It's not just one copy of the virus genome, but as probably as many as fifty and that's a very difficult thing to understand. The reason that I say that is that if a virus enters a cell and we think it is going to become latent we think, and of course this is wrong, that not much is going to happen. And yet we get one virus particle with one genome that appears to result in fifty genomes so there must be some replication in that virus. The enigma is that it is doing it in a cell that does not replicate by itself. These are neurons. These are cells that are done replicating. So the enzymatic activity that is required to replicate virus as we know is not available. The other enigma is that as the virus goes thru its replication cycle we say there are three phases of virus replication: immediate-early, early, and late, and the early phase is when the DNA is synthesized and we have always believed, obviously incorrectly, that this order is maintain under all circumstances, but it's not possible to occur and still have these virus genomes present in the neurons. Now to come back to that question you asked awhile ago and that is shouldn't immune surveillance help keep these guys down on the farm. What we know about herpes simplex virus is that the virus is constantly testing the host and many people have what we call silent infections. We know that because they transmit virus in the absence of overt lesions, so they are shedding virus with no apparent infection.

**Vincent**: Where is it shed from, typically?

**Saul**: It's most often shed from the sex organs. We know that partners engaged in sex can transmit the virus without an overt infection. It's more difficult to monitor in women than in men but we know from studies done in Seattle by Korey and Holmes that women who are surveyed over repeated periods of time will show that virus has been shed and we know that are active carriers and we know that is also true for men.

**Vincent**: Again in the face of an immune response.

**Saul**: In the face of an immune response how can it be. Shouldn't there be neutralizing antibodies. We know that if you sample fifty people that between forty and forty-five of them will have antibodies that will neutralize the virus, so what's the mechanism that allow for the transmission of the virus in the face of the circulating immune system. Tough question. But we think that what happens is the virus gets reactivated in a small of neurons in the infected ganglia and I don't think it has to be too many. And this virus travels down the long ganglia of the nerve and then exits thru the same path that it enters, the dendrites, those little tiny feeders of the

neurons and then where is it sitting, it's sitting right in the dermis and the epidermis and those are the layers that form the skin. The immune system doesn't survey itself very well, there.

**Vincent**: Nor within the neuron itself. That explains it.

**Saul**: That explains some of it. We always think or we always think and again it may or may not be correct, that a cell that's infected with a virus expresses virus proteins on its surface. I don't know how carefully that has been studied, but there are now systems where that should now be under study. Certainly the work Lyn Enquist and his colleges at Princeton are doing with pseudorabies virus and animal herpes virus. They have the chance to look at where virus glycoprotein, which are important in neutralizing epitope, that is things that are seen by the immune system and important to neutralize the virus. Do they go down those long neural tracts? Are they found in the dendrite? Somebody has to address that question to help us understand that. It's really a black box.

**Vincent**: You mentioned not too long ago that sexual partners can transmit the infection in the absence of the one knowing they have any virus at all. If the recipient in that case had been immunized against herpes simplex would that prevent infection?

**Saul**: That's a tough one. We know, for example, that there are individuals who are infected with more than one strain of virus because we can differentiate virus strains using what we call restriction fragment micropolymorphisms which differentiates virus subtype A from B from C. So we know that can happen and we know this happens to people who are immune, that is have circulating antibodies. So the answer is that there is evidence that that can happen although you would think that somebody was protected. The reality is that most people don't acquire type 2 herpes virus, which is the one that is associated with genital lesions sexual. Until later in life and are more often are infected with herpes simplex 1 which tends to reside above the waist.

**Vincent**: The reason I ask is because as you know there are some efforts to make vaccines against simplex viruses. So I'm wondering who the target would be for those vaccines and would they be effective if natural infections don't confer any protection anyway?

**Saul**: That's a very difficult question to ask. We know for example that we can make an effective vaccine against the herpes virus because we have a very effective vaccine against varicella zoster virus and that vaccine is a live attenuated virus. The vaccines that the pharmaceutical industry has been trying to manufacture for the most part have been subunit vaccines. To me it's unclear what the appropriate target is and I'm not sure anyone else is either.

**Vincent**: I assume you're not investing in these companies then?

**Saul**: It's not where I'm putting my money. We could digress a moment and talk about varicella which is another interesting virus.

**Vincent**: Which I recently harbored for some time.

**Saul**: And I'm sorry that we didn't have a chance to sample you in great detail.

**Vincent**: This is an interesting segue to varicella zoster. Four or five weeks ago I had an itching feeling on my chest which developed into a rash that I initially thought was poison ivy until I realized I don't get poison ivy and I then thought it must be zoster. It spread from one level of my rib around to the back and eventually because a nice rash, which was painful, went away but continued to hurt.

**Saul**: Does it still continue to hurt?

**Vincent**: Now it's starting to subside.

**Saul**: So we're about five weeks out.

**Vincent**: So one thing maybe you can explain. We say that the virus comes back in a single dermatome. So what is a dermatome?

**Saul**: A dermatome is a region of your body that contains nerves that arise in a single ganglion.

**Vincent**: So in those ganglia is where the zoster was since childhood. The initial infection that I had when I was less than ten years old was chicken pox. The same virus: in a kid it causes chicken pox and in adults it's zoster or shingles.

**Saul**: In an adult it's a reactivated infection. Chicken pox is the primary infection. Chicken pox is a relatively mild disease. When we were kids people used to have chicken pox parties. You wanted kids to have it so you got it out of the way. It was a very seasonal kind of an infection.

**Vincent**: Now everyone's immunized against chicken pox, at least in the US, right?

**Saul**: Almost everyone. It was a very long road to immunization. The original vaccine was developed by the Japanese, probably 25 or 30 years ago, and Takahashi took a virus isolate, passed it in guinea pigs where the virus replicates very very poorly and the virus that came out of that was attenuated, that is it didn't cause as voracious an infection as the wild type virus. Because it was thirty years ago he was able to put this virus into people to test it and the rather remarkable thing was that this virus to produce an efficacious vaccine. The biggest problem with vericella, though, is that it's extraordinarily difficult to grow. Unlike herpes simplex virus where we can isolate beautifully formed cell-free virus at very very high titers, we can't do that with varicella. In fact the major manufacturers of vaccines, Merck, Glaxo and I can't recall who it is in Japan, have a great deal of trouble making high titer virus. Therefore the vaccine is very expensive to produce.

**Vincent**: So if this is a rather benign childhood infection why was the vaccine developed and why are we now using it in all children?

**Saul**: So there are really two reasons. Like everything thing else that goes around in the world there is an economic reason. When your child contracts vericella they are highly infections. There's a respiratory phase of the virus, which we think is the most infectious phase actually. You get a mild illness and then a week later they break out all over their body with these pox which are full of infectious virus and as a result of that the child is forced to stay home. Otherwise he can spread it around the immediate population. That frequently means one or two parents has to stay home. If both parents are working, it's an economic burden. I think a better reason now, though, is the incidence of shingles, that second occurrence of zoster, seems to be decreased in people who are vaccinated. What we don't know is that if people originally infected by vaccination, that is originally vaccinated, will these people develop zoster.

**Vincent**: Why don't we know that?

**Saul**: We aren't far enough out. People live a long time. You didn't get your painful lesion until you were fifty-five. You were infected when you were under ten as was I. In fact last year I was vaccinated for varicella even though I had had chicken pox. The reason I did that is a series of studies demonstrated rather graphically that people vaccinated with this vaccine in their 50's had a 70% lower incidence of shingles over a five or ten year period. That's a big difference. Shingles as you know is not a fun thing.

**Vincent**: Yes, but in an older person it shouldn't have the economic impact.

**Saul**: Well that's not really true. You were lucky. You only had a mild case with one dermatome.

There are people who get it all across their face which is very disfiguring and causes problems with going out in public cause they are embarrassed. There are people who have multiple dermatomes that are inflamed and there are people who get shingles and are in so much pain. You talked about post herpetic neuralgia which is a very difficult to describe syndrome but essentially happens is you get this rash across that unique area of your body and everything heals. Then everything looks normal and yet you are in terrible pain and these people frequently can have this pain for years.

**Vincent**: So it can be debilitating and interfere with work.

**Saul**: Right and we don't know the basis for that at all. That's a very fascinating area of research and its another one of these area of research that combines people with different interest, people who are interested in pain, the physicality of pain, the neurobiology of pain, the interaction of infectious agents that result in this; how does the immune system moderate this. So there is a wide area of research areas to come together to address such a problem as this,

**Vincent**: So the vaccine you receive which was meant to prevent zoster, is that the same vaccine a child would receive?

**Saul**: No actually not; it's a much a much higher titer -- more virus present --and more expensive to make. Again the vaccine companies run up against this problem of being able to manufacture really high titer virus. We know this is something they remain interested in.

**Vincent**: So in another twenty or thirty years there will be some very interesting studies ongoing to see if the incidence of zoster is reduced in countries like the US.

**Saul**: We should be beginning to see those studies come out in Japan in the next ten years and try and identify that cohort that received the early vaccinations that did not have chickenpox and whether or not they developed zoster.

**Vincent**: So if you have not immunized as I was never and you have the zoster incident can you take an antiviral to dampen the pain?

**Saul**: What we know is that the antivirals if taken very early will help to sooth the pathway of infection. It won't completely prevent it because by the time you know that it has happened you have lots of infected cells, but it will keep it from spreading to adjacent cells and should dampen the infection, make it less severe. So you should be better off if you start that kind of therapy. You should heal and recover faster.

**Vincent**: So it's a good idea if have zoster, you should see a physician and perhaps get a prescription?

**Saul**: Absolutely.

**Vincent**: OK. So we've talked about herpes simplex viruses a bit and in the same family of viruses is varicella zoster, the same pattern of infection. Initially at a young age the virus hides in a nerve cell of some kind and then later on becomes active. In the case of simplex it's more frequently activated by various insults.

**Saul**: There's an interesting difference between the viruses. This relates to research that I did in collaboration with Ann Gershon, a pediatrician, who is one of two major people in the US along with a woman named Ann Arvin at Stanford who were really responsible for pushing the vaccine in this country and getting it through all the clinical trials. Ann and I looked at ganglia from people who died and had zoster at death. What we noted was that many ganglia from the cervical, which is all the way at the top of the spinal cord to all the way down to the lumbar and sacral area, contained virus DNA. That really recapitulates chicken pox. When you get chicken pox you

are covered from head to toe with virus and its easy to understand how every dermatome could become infected and in fact that virus is there in all of those dermatomes.

**Vincent**: So every dermatome probably has the virus, but when you have a zoster attack only one or a few…

**Saul**: People tend to have more than one and that's another mystery. You would think that second coming of varicella would really boost your immune response and the reason I say that's a real enigma is because if you think about the time span between the initial infection and the recrudescence, that the appearance of zoster, it's forty or fifty years. That's about the lifetime of what we call T memory cells. Oh, they're gone so now you're not being surveyed in quite the way you were before and maybe that's why you get zoster, but after you've had zoster you had zoster you should have boosted that response and you should be real good at it and yet people continue to get multiple occurrences, so we don't really understand that. Yet the vaccine is protective for zoster. Really there's a bunch of immunology that we don't have a handle on.

**Vincent**: So it's safe to say we need to work on these viruses for a long time.

**Saul**: I think if we want to study these guys and address the problem and help people who have these infections, yes we do need to study them more. We have been studying that problem and one of the things we have noted that is very different from herpes simplex, which makes no protein products that we can detect while it's latent, herpes zoster makes four or five protein products, and maybe these protein products are there in a symbiotic way to keep this guy down on the farm hidden in your ganglia and that they provoke the immune system just a little bit, but we don't know that for a fact.

**Vincent**: Right. One of the difficulties with these viruses is using animals to study them, correct?

**Saul**: Zoster only grows really in people and as you know that when we were studying ganglia here in Columbia in the mid 90's we had to have a lot of car accidents to get those victims. The reality is that we don't have good systems for studying these. We don't have good systems in vivo. We don't have good systems in vitro. That's really plagued our understanding of establishing latent infection and reactivating the latent infection. With simplex we have a better model with a mouse, which unfortunately most of the time doesn't react spontaneously which is what we would like. The rabbit does react spontaneously but we don't have the immunologic tools with the rabbit that we have with the mouse, so you give up something to get something else.

**Vincent**: So what about varicella zoster?

**Saul**: We've tried for a long time to establish a decent in vitro system and we've been plagued by our inability to reproducibly establish latent virus. Another problem with the in vitro system is that those nerve cells don't actually grow in vivo and divide; you can't keep them in culture forever. So we don't have what we need which is a reagent, which would be latently infected neurons that we could harvest at intervals. We can't propagate them so we constantly have to make new ones. We need a better model system. We need an animal model system.

**Vincent**: So all you budding virologists out there take note that herpes simplex and varicella zoster viruses need more people to work on them as long as we can convince our funding agencies to continue supplying the needed capital, of course. I think we can wrap this up today. Thank you for joining us. It was very nice of you. Is there any place on line where people can find out more about your work?

**Saul**: Actually, not.

**Vincent**: You don't have a web site?

**Saul**: I never got to the point of developing a web site, but if you go to the Columbia University web site and see a profile of what we do in the laboratory and there are references to some of the manuscripts we've covered over the years, maybe it's time to create a website.

**Vincent**: We'll put a link in the show notes to what you have with the idea that maybe you'll build it up. Today we've only touched on a few of the many more herpes viruses. We've talked about herpes simplex and varicella zoster, but of course there's cytomegalovirus virus, herpes viruses 6 and 7...

**Saul**: And 8.

**Vincent**: Eight; there's Kaposi sarcoma, Epstein-Barr viruses. So perhaps you'll come back another time and we'll have talk about those viruses and we'll have Dick Despommier.

**Saul**: I'd love to.

**Vincent**: Thanks for listening. Remember to send your questions and comments to TWIV at TWIV.TV. Come back next time. Thank you.

**Saul**: Thank you.



Transcribed by Jim Vandiver