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Advances in Viral Immunity Stemming from the 1918 Flu Pandemic

Preparing for the future by studying the past, researchers are now able to resurrect antibodies to the 1918 influenza pandemic from elderly survivors. How does technology use to do this potentially lead up to antibodies for other viruses. Can we be sure this immunity is not generated by recent exposure to similar strains. You are listening to ReachMD, The Channel For Medical Professionals. Welcome to The Clinician's Roundtable. I am your host, Dr. Mark Nolan Hill, Professor of Surgery and Practicing General Surgeon and our guest is Dr. James Crowe Jr., Professor of Microbiology and Immunology and Director of the Vanderbilt Program for Vaccine Sciences at Vanderbilt University School of Medicine. Dr. Crowe is the Senior Author on research published in the journal Nature on the cultivation of antibodies from survivors of the 1918 influenza pandemic.

DR. MARK NOLAN HILL:

Welcome Dr. Crowe.

DR. JAMES CROWE JR.:

Thank you its great to be with you.

DR. MARK NOLAN HILL:

Dr. Crowe, could you give us a quick overview of your research with respect to the efficacy in mice?

DR. JAMES CROWE JR.:

Sure, well we were able to isolate antibodies from the pandemic survivors in a way that we had single antibodies in our hand, these are termed monoclonal antibodies. So the antibodies only recognize 1 target and that target is hemagglutinin or HA protein on the surface of the 1918 flu **(01:30)**. So having that highly specific reagent which is almost like a biological drug, we were able to get these antibodies to Dr. Terry Tumpy at the Centers for Disease Control and at a high security, high biocontainment facility there, he infected mice with the resurrected 1918 virus, a virulent virus and he did it in a way at a dose that would surely kill them and the untreated mice all died, but at 24 hours or a day after exposure, he was able to treat mice with each of the antibodies that we isolated and the antibodies reduced the amount of virus in those mice and actually saved them and at the appropriate doses, each of the antibodies could save all of the mice that were challenged.

DR. MARK NOLAN HILL:

And how do you compare these strains to 1930 swine outbreak or 1943, 1947, 1977, 1999, all of these outbreaks, are there similarities, is this useful.

DR. JAMES CROWE JR.:

I think we are all aware that flu comes around every year typically in the United States, it's a winter epidemic and so we have all had experience with year after year hearing about or seeing flu every year. There are changes in the influenza strains each year and that is why we all have to be re-immunized every year, immunized with a new vaccine, that's because the viruses have mutated slightly and this is called antigenic drift. There is a slow drift, but every 30 or so years, a major change in influenza occurs and a new type of virus comes usually into the population from birds and this would be called a major change or an antigenic shift **(03:00)** When you get a shift, everyone in the world is susceptible because no one has ever seen that virus and that is when we get everyone being infected or that is called a pandemic. So when we got the antibodies to 1918, we went back to look at other viruses that had causes pandemics in the 50s or 60s and then we also looked at representative viruses throughout the 20th century that were the same type as of the 1918 and really we did not find a lot of cross reactivity between these antibodies, they really only seem to recognize the 1918 virus and the 1930 virus which was a similar virus in 1918 because these viruses circulated for several decades in the early 20th century.

DR. MARK NOLAN HILL:

Well do these viruses, these very virulent viruses occur every 30 years, I mean, why?

DR. JAMES CROWE JR.:

Well there appears to be an accumulation of immunity in the population to the circulating influenza that is around at any one time and right now we have 3 types of influenza circulating, H3N2, H1N1, and B are the names of the 3 types that are circulating and these are 3 that are in our annual vaccines and once you accumulate enough immunity, there seems to be a tendency to lose susceptibility of the population to that particular flu, but there are many types of flu that are in birds and animals, dozens of them and if we go into bird populations right now, we can swab birds and find lots of different flus **(04:30)** and we also find flus in pigs and other animals and we think what happens is, a human being that is exposed to some type of bird flu that is already there in the birds becomes infected and either that virus mutates or can infect people or actually mixes and matches with a human virus that is in that person at the same time and 1 way or the other by mutation or by a mixing even we get a new virus that has never been in the human population and it spreads like wildfire.

DR. MARK NOLAN HILL:

Now why birds, why not an animal that is much closer to us, like a pig or other animals, why a bird?

DR. JAMES CROWE JR.:

Humans and birds use different types of receptors to bind influenza. There are sialic acid which are carbohydrate molecules that survey the receptors to which influenza binds and they are linked differently in birds and humans. So there is an alpha 2-6 chemical linkage

which differ in the birds and humans, so the details aren't really important and suffice to say that they are different. So typically we would think bird viruses would infect birds and human viruses would infect humans. Some times, we see that there are rare islets that appear to bind both types of receptors and this may actually occur best in pigs, sort of a mixing because pigs actually have both alpha 2-3 and alpha 2-6 receptors. So one thought is that birds, in fact, pigs and human farmers or other people on farms infect pigs. **(06:00)** If a pig is simultaneously infected with a bird flu and a human flu, they can sustain both of those viruses, because they have both receptors. It may also be that some bird flus can just jump directly and that is what you hear about in the news right now with H5N1 bird flu that has been threatening to cause a pandemic the last few years. This is actually a bird flu that just crosses directly from a bird to humans.

DR. MARK NOLAN HILL:

Do you think that that is a real possibility of a pandemic?

DR. JAMES CROWE JR.:

Experts disagree on the likelihood of whether the H5N1 virus will cause pandemic, right now we know that with close exposure and a lot of virus in a bird, certainly humans can get infected. There has been over 300 cases documented in the world so far and two-thirds of those have been fatal cases. So this is what raises concern. The good news is the virus does not appear to efficiently spread from person to person, it just spreads from bird to person. So that is why we have not had a pandemic and experts disagree on what is the likelihood that a virus will get into a human being and mutate and become a virus that can spread person to person. If a virus did that then we would have a pandemic and that is what people are worried about.

DR. MARK NOLAN HILL:

And how does the bird virus get into a human?

DR. JAMES CROWE JR.:

Well people who are exposed to birds very frequently in the markets in Hong Kong, many types of birds are closely housed and human beings are around those birds. So farming individuals or markets where live birds are sold, this is where you get this kind of exposure. **(07:30)** Now interestingly, birds are infected with flu in their GI tract, not so much in the respiratory tract. It is really a gastrointestinal germ and really they are pooping out virus into the environment and so if you look at Hong Kong even in the water that is used to wash down these markets, you will find the virus on the floor in the water and furthermore live birds have these viruses and they will sit down in the bodies of waters. So there is a lake in Hong Kong where you can go sample the water and you will find the H5N1 virus in that lake water. So close exposure to birds is the predominant way it is transmitted, but these birds are spreading virus all over the place. So it is possible to have an environmental or a foami transmission from an object that is contaminated with bird feces.

DR. MARK NOLAN HILL:

If you have just joined us, you are listening to The Clinician's Roundtable on ReachMD. I am your host, Dr. Mark Nolan Hill and our guest is Dr. James Crowe Jr., Professor of Microbiology and Immunology and Director of the Vanderbilt Program for Vaccine Sciences at the Vanderbilt University School of Medicine. We are discussing advances in the viral immunity stemming from survivors of the 1918 influenza pandemic.

Dr. Crowe looking at the big picture and your incredibly interesting research, what information will you learn that might help us in viral diseases in general?

DR. JAMES CROWE JR.:

One of the most important things we are learning from the antibodies we have isolated is the fundamental process by which antibodies actually flu viruses. **(09:00)** So we gave our antibodies to our collaborators Dr. Chris Basler at Mount Sinai School of Medicine in New York and he was able to treat viruses with the antibodies that were displaying the 1918 protein and find viruses that would mutate and escape from our antibody and when we tracked down and see where those mutations are, that is the footprint of where the antibodies actually bind. So we have been able to figure out where on flu proteins should we direct antibodies. What part of the virus is vulnerable to killing and so even though the antibodies have regenerated 1918 and that virus is not circulating now, we are learning lessons about how to kill flu viruses in general and we are trying to incorporate this knowledge into strategies for new vaccines for the seasonal influenza that are around every year and also for the bird flu that are threatening pandemics today.

DR. MARK NOLAN HILL:

Will we be learning any information that may relate to treating HIV?

DR. JAMES CROWE JR.:

Well actually it is interesting that you would ask. We have just recently received several million dollars to use the same technology that we are using in flu to isolate antibodies to HIV and we have been able to do so.

DR. MARK NOLAN HILL:

Tell us about that.

DR. JAMES CROWE JR.:

Well in the last year, we have used a cohort of subjects at Vanderbilt that is followed by Dr. Spero Columns and these are termed long-term nonprogressors. So there are individuals who have been infected for say 10 years and have never taken anti-HIV drugs, but their viral load is very low. **(10:30)** So somehow they are controlling the virus themselves with their own response and we don't fully understand what is the basis of that, but one of the contributors maybe antibodies. So we have obtained circulating B cells from these long-term nonprogressor HIV-infected subjects and have obtained HIV-specific antibodies from them and we are already trying to study where on HIV do these antibodies bind and do these antibodies kill HIV efficiently and so on. So the viruses are very similar in that they change very rapidly. So flu changes in a population year to year. In HIV, this is accelerated. The change happens within an individual. So everyday the virus is changing. So the approach we are using in HIV is actually to obtain antibodies in the same individual over time, so we have to bleed them every 3 months or so and to make new antibodies and then to study them against their new viruses and to find out, can a person's antibodies actually chase the virus that is evolving within them.

DR. MARK NOLAN HILL:

Can they?

DR. JAMES CROWE JR.:

Well we don't know yet. We suspect that they do, but the research that has been done by others with serum testing suggests that the body's response is always about 2 months behind. So a new virus arises and that is almost like a vaccine event. So we see 1 to 2 months later, you get a nice response of antibodies occurring in that person, but by that time, the virus has already moved on. So this is a chasing event in which the person is always several months behind and what we want to learn is how to predict where the virus is moving. **(12:00)** Get out ahead of that virus and lay some antibodies down, sort of in an way that firefighters go ahead of a large fire and they will burn a corridor in front of that fire so that when the fire reaches, there is nothing to burn. That is what we want to do, is to get antibodies out in the direction in which HIV is moving. So that when the virus hit that point, it couldn't continue.

DR. MARK NOLAN HILL:

I want to thank our guest, Dr. James Crowe Jr. We have been discussing advances in viral immunity stemming from survivors of the 1918 influenza pandemic. I am Dr. Mark Nolan Hill and you have been listening to The Clinician's Roundtable on ReachMD, The Channel For Medical Professionals. Be sure to visit our web site at ReachMD.com featuring on-demand podcasts of our entire library. For comments and questions, please call us toll-free at 888-MDXM-157 and thank you for listening.

You are listening to ReachMD, The Channel For Medical Professionals. Welcome to the CDC's Flu view update provided by the Influenza Division of The Centers for Disease Control and Prevention. This week's featured speaker is Dr. Anthony Fiore, CDC Liaison to ACPI Influenza Vaccine Working Group.

The purpose of the advisory that CDC released on December 19, 2008, is to inform clinicians and public health officials about high levels of resistance to oseltamivir, the antiviral drug also known as Tamiflu among influenza AH1 viruses in the US this season so far and to provide some interim guidelines on the use of antivirals for this season. At this point in the season, there is only a low level of influenza activity so far in the US and as a result we only have about 75 viruses to look at. Of the 50 influenza AH1N1 viruses, however, 49 of them have been resistant to the antiviral drug oseltamivir. Fortunately all of them are sensitive to the drugs zanamivir and amantadine and rimantadine. There is no evidence these viruses are any different in terms of what sort of illness they cause or how easily they are transmitted and we don't know how many of these viruses will circulate in the US this year. So clinician's need some more options for antiviral treatment. They can look at information from the local or state health department about local virus surveillance. They can use laboratory testing to help them make decisions, but there is no easily available test that can tell whether a patient has a resistant virus or even which strain of the virus the patient has. So if influenza AH1 virus infection is suspected, CDC now recommends that that patient receive either zanamivir or a combination of oseltamivir and rimantadine and either of those 2 choices should work.. The good news is that these resistant strains are very similar to the strains that are represented in these season's vaccines. The vaccines are likely to be effective in preventing or reducing the severity of infection with the circulating H1N1 viruses regardless of whether or not they were resistant.

You have been listening to the CDC Flu View update provided by the Influenza Division of the Centers for Disease Control and Prevention. For more details on this week's show or to download the segment, visit us at ReachMD.com and tour the CDC's flu view web site at cdc.gov/flu.

Thank you for listening.