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Resurrecting Antibodies from 1918 Flu Pandemic Survivors

WHAT ARE WE LEARNING NOW ABOUT A VIRUS THAT HAS TAKEN MANY DECADES TO COMPREHEND?

The complete sequence of the 1918 pandemic flu virus was first published in 2005, but the story of how we have come to understand the virus began years ago in the remote Alaskan village and continues now in research across the country. What are we learning now about a virus that has taken many decades to comprehend?

You are listening to ReachMD XM 157, 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 & 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. HILL:

Welcome Dr. Crowe.

Dr. CROWE:

It is great to be with you.

Dr. HILL:

Dr. Crowe, would you just refresh our memories about the 1918 influenza pandemic? What was it all about?

Dr. CROWE:

Well, we are all familiar with influenza that comes around every year, which people would term seasonal influenza and when those influenzae infect a large number of people, typically in the United States 30,000 or 40,000 deaths occur and this would be termed an epidemic infection in the people by Latin, but every 30 or so years there appeared to be larger spread of fatal influenza or series A influenza, which spreads throughout the entire world and affects all age populations and these would be termed in Latin affecting all

people are pandemics, and so the 1918 was the largest pandemic that we are aware of in history and was an unusual flu that killed millions of people, the exact number of people is not really known, but it is estimated to be somewhere between 20 and 50 million people died in a very short period of time.

Dr. HILL:

Was that because of the virility of the virus or the lack of medical care?

Dr. CROWE:

Well, we do not really know exactly, there are lots of thoughts on why so many deaths occurred. One thing that is clear is that the virus is actually a bird flu. It crossed over from birds into the human population and therefore no one in the world had really seen this virus before and everyone was having their primary infection or they were not used to the infection and so there was no immunity, so that was one factor. The second is, now that scientists have reconstructed the virus. From archival and frozen tissues, scientists have been able to recreate the virus. We know if you put that virus in animals, it is very lethal, so the virus itself was very dangerous virus and then thirdly, recent studies have shown a lot of bacterial infections occurred after or during the infection and complicated the infection and so many of the deaths probably occurred due to bacterial infection, of course there were no antibiotics at that time.

Dr. HILL:

Tell us about the research in terms of greater than a decade ago in the remote Alaskan village. What you found, what you did, and how you did which you did?

Dr. CROWE:

The viruses that have been resurrected have been published by other groups including my collaborators and the thought was to find tissue that contained the virus and several places have been thought of in this regard. The military had collected tissues throughout the twentieth century and pathologist lead by Jeffrey Taubenberger at the Armed Forces Institute of Pathology were able to find tissues of soldiers who died very rapidly during the 1918 pandemic and it is very interesting because people who are housed together very densely died very rapidly and of course the military was involved in World War I at that time, so there were a lot of deaths in the military and it was an age group that was highly targeted by the virus. Dr. Taubenberger found some tissues in the military archives, but only got pieces of the virus out. When we work with the virus in the lab, we usually freeze the virus, deep freeze, negative 70 or negative 80 degree Celsius, and people started thinking where could you get frozen tissues and there were historical accounts of native Alaskans who have died and been very below the permafrost and therefore their tissues were thought to have been frozen at that time very rapidly and that turned out to be true, so scientists were able to recover lung tissue from many of persons who died rapidly and we were able to get other pieces of much of the virus genetics out of that and using those pieces scientists including Dr. Taubenberger and my collaborators at Mount Sinai School of Medicine reconstructed the virus.

Dr. HILL:

And what about the antibodies that have been found in the survivors of that epidemic?

Dr. CROWE:

Well, this is the work that we have just published in September of 2008. I have developed in my lab with my coworkers' technologies for generating antibodies from the blood of humans if we can get cells out and find the rare cell, the needle in a haystack that is floating around that specifies an antibody for any particular virus and it has taken us 10 years to develop these technologies. I had actually visited with the scientists at Mount Sinai in New York as a visiting professor and talked about our work with other viruses making antibodies and we sort of chatted, do you think it would be possible to make antibodies from survivors who are now 95 or 100 years old and my first reaction was absolutely not because it was so technically difficult to make antibodies from human cells. It is hard enough already if you have someone who has been recently infected, but these people had been infected in 60 to 90 years with this type of flu virus, but we tried it and it worked to all of our surprise.

Dr. HILL:

Were you pessimistic to being with?

Dr. CROWE:

I thought the idea was crazy to begin with because generally we think immunity only last for a number of years, may even an decade would be thought to be a fairly robust immune response, now certainly been reported that childhood smallpox immunization and this is the immunity that can still be detected if you do a serologic tests where you just take serum, you will find antibodies there, but no one had ever dreamed that you could find the actual B-cells floating around and the cells are really the factories that would make the antibodies. So, those cells were not expected to be floating around this far after the infection and even I thought this really was crazy idea, but it worked and in fact we did look at the numbers, the numbers are on average about 1 in 4 millions cells that are floating around in these people over 1918, so I do not want to overstate the fact of the immunity. This is a rare cell that is flowing in these people, but still is present.

Dr. HILL:

Dr. Crowe, many times we think about the longevity of immunity such as tetanus that you have to give the injection every 5 or 10 years. How can these B cells still be able to produce antibodies after such a great length of time? Are they different than other cells?

Dr. CROWE:

Well, we were able to clone out individual cells from these survivors and because we were able to do so, we could actually obtain the genes in those cells that specify the antibodies and by sequencing those genes, we learned a lot about the antibodies made by these people and these antibody genes are very unusual and that they are highly mutated. So antibodies or antibody genes become mutated when you are exposed and then re-exposed to an antigen, so be idea of boosting, so getting more than one tetanus shot you will boost your immunity and during that boosting, you actually can mutate your antibody gene as well. The genes from these people were more mutated than almost any antibody we had ever seen. So, it suggest that these people were infected multiple times early in their life and we suspect that people throughout their life retained memory for childhood exposures quite well and actually as they become older, they become less capable of making new responses that are robust and in a way this is a sort of metaphor almost of the cognitive memory because people often remember their childhood memories very vividly, but they cannot remember where they put the keys and it seems to be same way in the immune system, in that these people have fantastic antibodies to think that they were exposed to multiple times during childhood and their early twentieth century and yet we know elderly do not make as robust in immune response to vaccines that we have give them now.

Dr. HILL:

Now, are these responses would you refer to as mutated responses, amnestic responses as we learned in medical school?

Dr. CROWE:

Absolutely, these are B memory cells and the sequences suggest that the memory cells have been actually restimulated a number of times early in their life.

Dr. HILL:

Now, if you took theoretically one of these survivors and infected them with this influenza virus, would their B cells be able to respond in therapeutic amounts of antibodies?

Dr. CROWE:

Well, that is a great question and the experiments that we have done so far obviously do not answer that we have not challenged individuals. The only way to know would be if a natural occurring pandemic swept across the world and we look it to see what age individuals died in such a pandemic. As a surrogate for this, what we did was to produce the antibodies in large amounts in a high security high biocontainment lab at the CTC, our collaborator, Terry Tummy, infected mice with virulent reconstructed virus at doses that are lethal, it is highly lethal virus and intreated the mice with each of antibodies individually 24 hours after to see if he could cure the mice and in fact all of the antibodies that we isolated individually they will cure the mouse, so the antibodies themselves are sufficient to be protective or curative, but whether or not the individuals would stimulate their B cells to make those antibodies in enough amount to protect them, which is really what you asked. We really do not know that, but basically have the antibodies there and have the cells there. So we suspect that they would at least be partially if not completely protected.

Dr. HILL:

I am curious and I am serious some of our readers are likewise curious. If you infected someone who is healthy today with one of these reconstructed viruses, what would you think would happen?

Dr. CROWE:

Well, we expect that it would be just like the natural virus in 1918, it would be a very virulent virus. There are different types of influenza and types are based on laboratory test directed at the proteins on the surface of the virus. So the 1918 viruses what is termed an H1 N1 virus and there are H1 N1 viruses that are circulating today. In fact, one of the three vaccines that is in the annual vaccine that we all get are certainly I hope all of our listeners as medical providers get an annual influenza vaccine. One of those components is H1 N1 virus and so it is possible that there would be some cross reactivity of current immunity against the 1918 virus, but it seems unlikely because we screened serum that we got from individuals who were 40 and 50 and 60 and 70 and 80 and 90 and we really only see high levels of antibody that kill the 1918 virus in subjects who were 90 and above, so although there is theoretically the possibility that the current H1 N1 vaccines or viruses would induce some cross reactive immunity, probable not.

I want to thank our guest Dr. James Crowe, Jr. We have been discussing the resurrection of antibodies from survivors of the 1918 influenza pandemic. I am Dr. Mark Nolan Hill and you have listening to the clinician's roundtable on ReachMD XM 157, the channel for medical professional. You should visit our website at reachmd.com featuring on-demand podcasts of our entire library. For comments and questions, please call us toll free at 888MD XM 157 and thank you for listening.