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The Deadliest Flu: The Complete Story of a Virus Influenza Pandemic (?)

Dr. Anab Whitehouse

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BREWER, MAINE

The CDC article: “The Deadliest Flu: The Complete Story of a Virus Pandemic Influenza” – minus the parenthetical question mark which I have added for the title of this essay -- begins with a Transmission Electron Micrograph of the alleged virus that, supposedly, caused the 1918 pandemic known generally as “the Spanish Flu” despite not necessarily having its origins in that country. However, the micrograph does not constitute proof that the bodies depicted in the image are either infectious or lethal.

A micrograph, after all, is a static rather than a dynamic depiction of something about which claims are being made. This remains the case even if one were to concede that the bodies being depicted in the micrograph actually constitute a virus or even if one were to concede that the entities in the image constituted the same virus that many individuals believe was so lethal in 1918, and this latter contention is not necessarily a foregone conclusion.

The CDC article operates on the assumption that the proper explanation for the 1918 phenomenon is that it involved a viral agent that was both highly infectious and highly lethal. As a result, the CDC article argues that the 1918 event provides valuable data and insights concerning how to prepare for future viral pandemics, and this assertion is also not necessarily tenable.

Early on, the CDC article maintains that “an unusual characteristic of this virus was the high death rate it caused among healthy adults 15 to 34 years of age.” Such a statement makes a number of assumptions.

For example, the foregoing statement presupposes – but does not prove -- that the people who died in 1918 all died from the Spanish flu virus (and there is considerable evidence to indicate that this might not be the case). Moreover, the aforementioned claim also operates on the assumption that the people who died were actually healthy individuals … as opposed to individuals who were outwardly apparently healthy but who might actually have had underlying health problems of one kind or another which had not, yet, shown up in the form of symptoms, and, therefore, while a viral agent of some kind might have played some role in the demise of certain individuals, there may have been a number of factors aside from the presence of a given virus which was responsible for the death of various people.

According to the CDC article, a dedicated group of researchers were able to: “ … search for the lost 1918 virus, sequence its genome, recreate the virus in a highly safe and regulated laboratory setting at CDC, and ultimately study its secrets to better prepare for future pandemics.” The CDC article purports to be a “complete” account of the history to which the foregoing process of research gives expression.

The story being provided through the CDC paper begins with a small, ocean-side Alaskan village known as Brevig Mission. In 1918, the village contained approximately 80 adults, consisting mostly of Inuit indigenous people.

The article goes on to say that there has been some degree of controversy concerning just how the inhabitants of that village became infected. Some individuals believe that the virus was transmitted by a local member of the postal service, while others contend that the virus arrived in the village via one, or another, trader who travelled to Brevig Mission via dog sled.

Notwithstanding the foregoing considerations, if one doesn’t know how the virus was introduced into a community, then, one can’t necessarily be sure that the virus is what

killed those individuals. All one can say is that something happened in 1918 which resulted in the death of 72 of the 80 inhabitants of that village, and one does not necessarily know why the 72 individuals who died were vulnerable to whatever happened, or why 8 people were able to survive.

One also one does not know if the latter eight individuals got sick and, then, recovered, or whether they ever became ill. Furthermore, if the latter possibility is the case, then, why didn't they get sick?

What one does know is that all of the deaths took place within a six day period, lasting from November 15th to November 20th in 1918. The bodies were all buried in a mass grave near the village and remained that way until 1951.

In 1951, Johan Hultin, a Swede, was doing doctoral research in microbiology at the University of Iowa. He sought, and received, permission from village elders in Brevig Mission to excavate the bodies from 1918 because he believed that he might be able to find remnants of the 1918 flu in tissues of the bodies that had been buried and preserved in a frozen state while having been entombed in the permafrost for more than three decades.

Hultin was able to procure lung tissue samples from five of the excavated bodies. Nonetheless, back in his laboratory at the University of Iowa, he was unable to induce what he believed were viral entities to become active when he injected his collected lung tissue samples into chicken eggs in order to try to get the virus to grow.

In 1997, nearly a half century later, Hultin read an article by Jeffrey Taubenberger, and others, that appeared in the journal *Science*. The article was entitled: "Initial Genetic Characterization of the 1918 'Spanish' Influenza Virus."

Taubenberger is a molecular pathologist who, at that time, was working within the Armed Forces Institute of Pathology in Washington, D.C. . He, together with other members of his research team, had been able to obtain a lung tissue sample from an apparent victim of the 1918 flu who had been stationed in Fort Jackson, South Carolina at the time of the alleged pandemic.

The soldier had been hospitalized on September 20, 1918 with a diagnosis of influenza and pneumonia. He died less than a week later on September 26, 1918, and a sample of lung tissue had been taken from him and stored for possible subsequent examination.

Before proceeding further, perhaps, the following observation would not be inappropriate. More specifically, making a clinical diagnosis of influenza gives expression to a judgment that is made by a physician with respect to various symptoms that are being observed.

What is causing those symptoms is a separate, although, obviously, not an unrelated issue. However, electron micrographs that were capable of capturing images of possible viral-like entities would not be possible for nearly another two decades, and, consequently, to maintain in 1918 that symptoms of influenza or pneumonia were caused by a viral infection would be an entirely speculative perspective (This is a point that is touched upon in passing toward the latter part of the CDC article being discussed here.) .

Physicians treat the clinical presentation of symptoms. The cause of those symptoms might not ever be known until an autopsy is performed, and, perhaps, not even then.

Furthermore, the issue of autopsy findings is somewhat of a moot point in 1918. Very few autopsies were performed in conjunction with determining the cause of whatever might be causing the deaths that transpired in 1918.

Putting the foregoing considerations aside for the moment, Taubenberger's research group had been able to sequence nine relatively small remnants of single-stranded RNA chains from the aforementioned soldier's lung tissue sample. Those nine fragments were alleged to be from four of the purported eight gene segments that were theorized to make up the genome of the 1918 influenza.

One problem with the foregoing account is that since human cells – including samples from the lungs – often contain single-stranded RNA sequences of many different kinds, one cannot necessarily be sure that any given RNA fragment which one is able to acquire from a human cell is necessarily from a virus. Moreover, even if the single-stranded RNA sequence were from a virus, there is no guarantee that the segment will be from one particular kind of virus (i.e., 1918 Influenza) rather than from some other virus that might have been in the lung tissue of the soldier who died in 1918.

Virologists contend that the Influenza A viral genome consists of eight, single negative-strand RNAs that can range between 890 and 2340 nucleotides long. Each RNA segment is believed to encode one to two proteins … including the glycoproteins -- hemagglutinin and neuraminidase – which is where the 'H' and the 'N' come from in the H1N1 subtype that is believed by many virologists to constitute the 1918 influenza virus.

There are thousands, if not millions, of RNA fragments that are to be found within the cultures that supposedly contain the foregoing sort of virus. So, the question becomes, how does one know that the "nine relatively small remnants of single-stranded RNA chains from the aforementioned soldier's lung tissue sample" actually constitute fragments from the 1918 influenza?

Notwithstanding the foregoing issues, Taubenberger's research group maintained that the RNA which it had sequenced constituted a novel form of influenza A – namely, H1N1. This virus was alleged to belong to a subgroup of viruses that tended to inhabit pigs and human beings rather than birds.

After reading the Taubenberger article in *Science*, Johan Hultin, Hultin wrote to Taubenberger and inquired about whether, or not, Taubenberger would be interested in what might be discovered if Hultin returned to Brevig Mission and, once again, tried to obtain some lung-tissue samples from the interred bodies that had died during the 1918 phenomenon. Taubenberger said he would be interested in such a venture, and, consequently, Hultin returned to the village which he had visited in 1951.

During this return journey, and after, once again, receiving permission from village elders, Hultin unearthed the body of an Inuit woman who was buried some 7 feet deep in the mass grave. Her lungs had been extremely well-preserved due to the permafrost in which they had been entombed.

After placing the lungs in an appropriate kind of preserving fluid, Hultin later sent the excavated biological materials to Taubenberger. Word subsequently came back to Hultin from Taubenberger "that positive 1918 virus genetic material had indeed been obtained from" the lung tissues that had been sent."

Nothing is said in the CDC article at this point about what made the RNA sequences from the Inuit woman's lungs **positive** with respect to the 1918 virus. In other words, one

does not know what the RNA sequences from the Inuit woman's lung tissue cells were being compared against in order to permit someone to be able to conclude that, in fact, some of her RNA had come from the 1918 Influenza virus that supposedly had caused the woman's death.

Putting aside the foregoing sorts of issues, the CDC article proceeds to state that in February of 1999, a paper entitled: "Origin and evolution of the 1918 'Spanish' influenza virus hemagglutinin gene" appeared in the *Proceedings of the National Academy of Sciences*. The article was written by, among others, Anne Reid, who was part of Taubenberger's team of researchers and Johan Hultin had been given credit as being one of the co-authors of the article.

The Hemagglutinin gene is hypothesized to help make possible the entry of the influenza virus into the interior of a healthy cell within the respiratory system of a human being and, thereafter, go about replicating itself. The foregoing claim is actually only a **theory** about how a virus gains access to the interior of a cell since no one has actually seen or proven how the breeching process take place, just as once a virus is alleged to have gained entry to the interior of a cell – no one has seen, or knows how the virus is able to take control of the cell's replication machinery or how it sets in motion a series of events that lead to death. Everything which is said about such a virus – or viruses in general -- is part of an elaborate theoretical framework that is based, in part, on data, and, in to a large degree, on speculations concerning how to interpret that data.

At this point, the CDC article offers an illustration of what virologists believe the influenza virus looks like. One needs to understand that the illustration in the CDC article is someone's rendition of the virus since there are no electron micrographs that are capable of verifying that such an illustration is accurate.

The hemagglutinin – HA – protein that was the subject matter of the aforementioned Reid article is a surface protein which is believed to aid the virus to gain access to the interior of a human cell. Once inside a cell, the virus proceeds to infect a healthy respiratory tract, but, so far, nothing has been said in article to indicate how this infection process takes place or why it can be so lethal.

The fact that an entity of some kind might be able to gain entry into the interior of a human cell doesn't, in and of itself, prove anything. One needs to understand the dynamics taking place within human cells, but this is difficult to do in conjunction with objects that are the size that viruses are said to be, and, therefore, such accounts tend to be heavily theory-laden.

The aforementioned HA component is one of the features of the virus that is believed to be targeted and tagged by antibodies. One theory underlying flu vaccines is built around the idea of finding a way to target, and, then, neutralize, the HA surface protein of that virus, and, in the process, undermine the putative means by which such viruses are believed to gain access to the interior of human cells..

The CDC article goes on to indicate that the 1999 Reid – et. al. – study was able to put together a proposed sequence structure for the hemagglutinin surface protein. This structure was based on combining fragments from the lung tissue samples drawn from the woman unearthed in Brevig Mission, as well as from the soldier who had died at Fort Jackson, along with remnants from a service member who had been stationed – and who died -- at Camp Upton in New York in 1918.

The foregoing amalgamation of data constitutes a theoretical construction. The aforementioned study did not isolate such a protein in any of the bodies, but, instead, inferred its existence on the basis of genetic data drawn from three different people.

According to Reid and others, the 1918 virus had initially invaded human beings sometime between 1900 and 1915. Since the HA gene was believed to have various mammalian – as opposed to avian – adaptations, and, therefore, was more human-like or swine-like --"depending on the method of analysis" -- the virus was placed within a mammalian clade.

More specifically, Reid and Taubenberger maintain that the purported 1918 virus sequence that had been constructed is most closely related to the oldest classical strain of swine influenza – namely, "A/sw/Iowa/30. Moreover, they note that the former viral sequence seems to be quite different from current avian influenzas but, also add that no one is certain about what avian influenza viruses might have looked like back in 1918.

How closely related the purported 1918 virus sequence is to the oldest classical strain of swine influenza is not specified. Furthermore, precisely what the considerable differences are that differentiate current avian influenzas from the alleged 1918 viral sequence that was constructed is also not spelled out in the CDC article.

Nonetheless, Reid and Taubenberger believe that the HA component of the virus originated from an avian viral source. However, they are uncertain about the extent to which the virus might have been undergoing changes within a mammalian evolutionary framework before it assumed the form that led to a pandemic.

There are a number of points to note with respect to the foregoing claims. First, one might highlight the acknowledgment by Reid and Taubenberger that whether a researcher considered the HA component to be swine-like or human-like depended on the nature of the method of analysis which was used, and, therefore, one needs to recognize that conclusions concerning the precise mammalian nature of the HA protein might be more a reflection of a given method of analysis than any intrinsic feature of the HA protein.

Secondly, because Taubenberger and Reid are uncertain about how long the HA component of the virus might have been undergoing evolutionary changes within a mammalian environment before emerging as something capable of bringing about a pandemic, they are not certain about how the virus came to possess its – alleged -- lethal qualities … or what the nature of such lethality actually involves. In fact, they can't even be certain if the virus is what was actually responsible for the deaths of so many people.

In addition, although they believe that the HA component of the virus ultimately came from an avian source, they have no data to demonstrate how the virus component might have been able to jump species. The alleged link between an avian source and a mammalian version of the virus is entirely speculative.

Finally, the so-called mammalian adaptations to which Reid and her associate authors allude are not necessarily expressions of evolutionary change. Those differences might be nothing more than artifacts of the computer program that is used to construct the theoretical version of the HA protein. In other words, as the computer programs that are used in such research is run a number of different times, the available base pairs and fragments that have been detected in a given culture are put together according to an underlying pre-fabricated template for – in this case – a given protein, but, nonetheless, differences will show up during each run as a function of the program and, therefore, one

cannot suppose that differences which show up in a constructed model of a protein are due to evolutionary changes over time rather than being expressions of the way the computer program constructs things on any given occasion.

Reid and her fellow authors also indicate that the alleged 1918 virus' HA1 protein exhibited four glycosylation sites. Virologists believe that glycosylation sites play a critical role in influenza viral functioning, but one should probably keep in mind that the foregoing belief is part of a theoretical framework in which the notion of "an influenza virus" is embedded rather than being an expression of experimentally observed performance involving those glycosylation sites.

Current HA proteins associated with human beings exhibit anywhere up to five additional glycosylation sites when compared with the alleged 1918 virus's HA1 protein. These extra sites are believed to be the result of a process of "antigenic drift" which constitute small changes that are introduced into a component – in this case a protein – that occur as a result of errors that occur during the process of being copied to form the next generation version of that component.

These instances of antigenic drift are believed to be adaptive in nature as a given kind of virus adjusts to its animal hosts. However, the foregoing perspective is somewhat presumptuous because one cannot automatically assume that any particular copying error that might occur will necessarily give rise to a functional adaptation.

Such instances of antigenic drift are cited as being one of the reasons why there is a new flu season every year or why someone might be able to become infected with an influenza virus on more than one occasion. Nonetheless, once again, this is like putting the cart before the horse because one cannot be certain that any given case of influenza that might occur in the future is necessarily infectious as a result of such changes.

Perhaps, somewhat more importantly, Reid and the other authors of the aforementioned article did not come across any sequence changes for the HA protein that might account for why the 1918 influenza virus was, supposedly, so virulent. For example, unlike modern avian influenza A viruses involving H5 or H7 variants which exhibit "cleavage site" mutations that are associated with added virulence due, allegedly, to the way in which such sites supposedly permit a virus to grow in tissues outside of its usual host cells through the insertion of amino acids in the aforementioned cleavage sites, the 1918 virus did not contain any sequences that coded for amino acids which could become inserted into the cleavage sites in its HA proteins.

Because Dr. Reid and her associate researchers could not identify any biological markers associated with the HA protein that might have been capable of generating the sort of enhanced virulence that supposedly was exhibited by the 1918 influenza virus, the researchers maintained that there were probably an number of factors which might have synergistically interacted with one another to give expression to enhanced virulence, and, therefore, lethality during the 1918 pandemic. However, the foregoing claim concerning the multifaceted nature of virulence really amounts to little more than an admission that the researchers actually have no idea why the 1918 influenza was capable of doing the damage that it was perceived to have done, and whether, or not, that virus was even responsible for what took place in 1918.

The aforementioned research group wrote a second paper in June of 2000. This article focused on the neuraminidase gene which codes for a surface protein known as NA and was entitled: "Characterization of the 1918 'Spanish' Influenza Virus Neuraminidase Gene."

The NA protein is believed to enable a virus to escape from an infected cell, and, therefore, helps the virus to spread to other cells. According to immunologists, antibodies arise in conjunction with the NA surface proteins of viruses, and while such antibodies do not prevent infection, such antibodies are believed to help stem the tide of viral spread from taking place within human beings.

Unlike the genetic sequence for the hemagglutinin surface protein (HA) which needed to be pieced together using data from tissue samples that came from three different human bodies, the research group that was working with the tissue samples that had been sent to them by Hultin which had been obtained from excavated cadavers in Alaska, the researchers were able to work out a genetic sequence for the neuraminidase using tissue samples from just one body. Nonetheless, whether one is working with tissue samples from three bodies or one body, the process of generating a genetic sequence from such samples is pretty much the same and, consequently, such a process depends on using a computer program (set of algorithms) involving a theoretical template for whatever viral component in which one is interested in order to be able to make educated guesses about whether the RNA fragments that are present in a given tissue sample contain a sufficient number of the right kind of fragment sequences that might have underwritten the expression of a certain kind of surface protein … in this case, the neuraminidase protein.

In short, the hypothesized genetic sequence for the neuraminidase protein that many virologists believe to have been present in the 1918 influenza virus – along with the genetic sequence for the hemagglutinin (HA) viral surface protein -- is a theoretical construct. Neither the protein nor its purported genetic sequence was not found intact inside of a virus that had been properly isolated but was, instead, put together by running a variety of RNA fragments that were present in tissue samples through a computer program to see whether, or not, such fragments could be put together in a way that was capable of matching -- to varying degrees – the theoretical template being used in the underlying program.

This is like taking the scattered letters of an alphabet that are within a sample of some sort and, then, running those letters -- along with various fragmented, short combinations of those letters -- through a computer program containing templates of certain words – say hemagglutinin and neuraminidase – in order to see whether, or not, one might be able to come up with a set of possible alphabet sequences that were capable of matching up with the program templates. One's understanding is being filtered through the lenses of a theoretical framework, and, as a result, one might, or might not, be introducing some degree of obfuscation into the process of trying to understand whether such words were actually present in the sample or one merely had discovered a way to come up with such words using the alphabetic fragments that were available in a given sample.

To claim that such words actually were present in the original sample -- but simply had degraded over a period of time -- is a problematic contention. After all, such words were not actually found intact in the sample one was studying but, rather, those words had to be constructed as possibilities based on what is known about the presence of various kinds of exemplars from an alphabet that were found in a given sample that contained both single

instances of the alphabet along with various fragments of combined components of that alphabet.

In any event, once again, just as was true in conjunction with the constructed hemagglutinin gene sequence in which Dr. Reid and her fellow researchers were not able to identify anything in that sequence which might have enabled the proposed 1918 flu virus to be especially virulent, so too, the researchers came to the conclusion that their constructed sequence of the neuraminidase gene did not exhibit any properties that might suggest, or were known to be associated with, a capacity for enhanced virulence or lethality that was assumed to exist in the 1918 influenza virus.

For instance, there is a certain amount of evidence to indicate that the loss of a glycosylation site in the neuraminidase gene at amino acid 146 is associated with an increase of virulence in certain current influenza viruses. However, nothing of this kind was detected in the gene sequence of the neuraminidase surface protein from the 1918 tissue samples from Alaska, and, in passing, one also might note that correlating certain features in gene sequence with enhanced virulence is not the same as demonstrating that such gene sequence features are the cause behind observed increases in virulence.

According to the phylogenetic analysis conducted by the aforementioned research group, the neuraminidase gene sequence from the 1918 tissue sample was classified as being intermediate between mammals and birds. What exactly is entailed by the notion of "intermediacy" is not spelled out, but such considerations notwithstanding, the researchers contend that the intermediary status of the neuraminidase viral protein indicates that the virus was, most probably, introduced into human beings at some point just prior to the 1918 pandemic and that the source of the change in virulence is most likely rooted in an avian source of some kind. Yet, the CDC article also goes on to note that the research group was not able to trace the precise nature of the pathway that led to increased virulence.

So, once again, one is talking about theories of virulence and phylogenetic transitions that are bereft of the sort of evidence which is necessary to be able to demonstrate that such a theory has credible empirical legs. Correlational possibilities and plausibilities are not the same thing as empirically demonstrated causality.

The CDC article proceeds to mention further facets of the 1918 influenza research project that led to the appearance of articles focusing on six more of the eight genes that are believed to be present in the 1918. Thus, in 2001, a paper published in the *Proceedings of the National Academy of Sciences* was authored by Christopher Basier and others which provided an account of a nonstructural gene (NS) that was believed to be present in the 1918 influenza virus, and this was followed, in 2002, by a paper from an Ann Reid led research group which appeared in the *Journal of Virology* and dealt with the matrix gene that was alleged to be present in that same virus.

In 2004, a further study was published in the *Journal of Virology* that put forth an account of the nucleoprotein – NP gene – which is believed to have been present in the 1918 influenza virus. Finally, a year later, Taubenberger et. al. wrote an article that was published in *Nature* and focused on different polymerase genes which are considered to have been a part of the 1918 influenza virus.

All eight of the genes that are believed to make up the genome of the 1918 influenza virus are theoretical constructs. None of those genes were actually discovered by examining the sequences of a genome that had been located within a virus that had been

isolated from all other aspects of the tissues and cultures that served as the basis for the research that was being carried out by Basier, Reid, Taubenberger and their associates … research that was being published in a variety of prestigious scientific journals.

Following the publication of the foregoing papers, a program was set in motion that was intended to create a live version of the 1918 virus. The first step in this process of going "live" involved the creation of plasmids, and this was done through the work of microbiologists Peter Palese and Adolfo Garcia-Sastre, both of whom worked at the Mount Sinai School of Medicine in New York City.

A plasmid consists of a tiny, circular strand of DNA. Such strands are capable of being amplified through means of laboratory controlled forms of replication.

The plasmids that were generated by Palese and Garcia-Sastre would be utilized in a process of reverse genetics that researchers hoped might enable them to study the possible relationships between viral structure and function. In turn, the foregoing sort of studies could help lay the basis for moving to the next phase of producing viable forms of viruses which will be discussed shortly.

Once the foregoing plasmids had been created, they were shipped to the CDC. Because researchers at the CDC were going to use those plasmids during the process of generating live versions of the 1918 influenza virus, the CDC instituted what it considered to be rigorous protocols for ensuring that such research would take place within an environment that exhibited the necessary qualities of biosecurity and biosafety … and these enhanced set of protocols turned out to constitute what is known as BSL-3, one level lower than the maximum conditions for biosecurity and biosafety that have been established in conjunction with BSL-4.

Dr. Julie Gerberding -- who is now the executive vice-president for strategic communications, global public policy & population health, as well as the chief patent officer, for Merck & Co., Inc. but at the time of the proposed 1918 influenza reconstruction project was the Director of the CDC -- appointed a microbiologist, Terrence Tumpey, to be the individual who would be solely responsible for working within the BSL-3 containment facility in conjunction with the attempt to recreate a live viral version of the alleged cause of the 1918 influenza pandemic. The foregoing proposal also had been approved by the National Institute of Allergy and Infectious Disease under the authority of Anthony Fauci.

The project actually got under way in the summer of 2005. The plasmids which had been sent to the CDC -- and, previously, had been constructed by Dr. Palese for each of the eight genes that were theorized to constitute the *1*918 Influenza virus and -- were introduced into human kidney cells by Terrance Tumpey. Once inserted into the kidney cells, the plasmids induced those cells to generate what the members of the reconstruction project believed were a complete set of RNA sequences for the 1918 virus.

There is some question, however, as to whether, or not, the RNA sequences that are being alluded to in the foregoing claim actually captured the structural and functional properties that might have been present in the alleged agent of the 1918 pandemic. After all, Taubenberger and Reid -- together with their associate researchers who had been involved with the various studies that produced the 8 genes that, supposedly, made up the composition of the 1918 influenza virus -- had acknowledged, as noted earlier, that they saw nothing in the 8 genes that might be considered to be a possible causal source of the virulence that was thought to be present in the 1918 influenza virus.

If the reconstructed edition of the 1918 influenza virus had no obvious capacity for inducing infectious lethality in its hosts, then perhaps, something is missing from the reconstructed, alleged version of the 1918 influenza. Indeed, one should keep in mind that each of the 8 genes that had been created by Taubenberger, Reid and others were, actually, all constructs that were based on various kinds of computer programs, algorithms, templates and the like in order to produce what was presumed -- on the basis of an array of theoretical considerations, assumptions, and calculations – to be an accurate re-creation of the 1918 influenza virus. However, absent the presence of a causal mechanism for infectious lethality in such a model, then, perhaps, the researchers should have exercised some degree of scientific caution concerning precisely what it is that had been created and whether, or not, such a creation has anything to do with the agent that supposedly led to a pandemic in 1918.

An article, entitled: "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus" appeared in the October 7, 2005 edition of *Science*. Following the publication of the foregoing article, the researchers undertook a series of experiments which was conducted in order to assess the pathogenicity of the reconstructed entity.

In other words, the researchers wanted to evaluate the capacity of their creation to infect and disrupt the healthy functioning of organisms into which their reconstructed agent was going to be introduced. This process of evaluation involved conducting a number of experiments involving mice.

The CDC article proceeds to give an overview of the experimental procedures that were used and, in the process, indicates that one set of mice were infected with the reconstructed agent, while other sets of mice were exposed to various combinations of the eight genes that constituted the reconstructed agent that had been combined with various strains of influenza A viruses (H1N1) that affect human beings on a seasonal basis. These latter concoctions are referred to as "recombinant viruses."

There might, or might not, be problems surrounding the character of the foregoing experimental setup. For example, nothing is specifically mentioned in the CDC article about how the different sets of mice were infected or just what it was that constituted the vector that was being introduced into those mice.

To begin with, living organisms come into contact with potentially infectious agents by interacting with the surrounding environment. Therefore, unless the various experimental sets of mice were being exposed to a possible infectious agent via air, water, food, or through their physical interaction with the environment, then, one is using a mode of vector introduction into the test subjects which is of questionable scientific value.

Secondly, there are a number of questions that should be raised in conjunction with the nature of the precise contents of the potential infectious agent to which the test animals were being exposed. For instance, since the CDC reconstruction project supposedly had succeeded in generating the RNA sequences for the complete genome of the purported 1918 virus, then shouldn't they have been able to produce completely isolated versions of the entities to which such RNA sequences give expression … versions that would be uncontaminated or unadulterated by the presence of any other components such as would happen if one were to embed the reconstructed virus in some sort of culture which, supposedly contains said agents but, in addition, also often tend to involve a number of other components, as well, that are considered by researchers to be necessary to maintain a viable culture.

The term “viable” in the foregoing means something that serves the purposes of a group of researchers rather than something that necessarily reflects what is likely to happen outside of a laboratory. If the potentially infectious vector which is being introduced to experimental groups of mice consists of anything except a purified compilation of the reconstructed virus, or anything but a purified amalgamation of various kinds of recombinant viruses in control groups, then whatever other components are being mixed in with the reconstructed virus or mixed in with recombinant viruses that are being used as control groups might have the capacity to obfuscate the character of the biological dynamics that are taking place within organisms in conjunction with the possibly infectious agents to which they are being exposed?

According to the account provided by the CDC article concerning the foregoing experiments, there was a marked difference between the impact of the reconstructed version of the 1918 influenza virus on mice and the nature of the impact which the recombinant viruses had when they were introduced to various control groups of mice. For instance, mice that had been given the reconstructed version of the 1918 influenza virus contained quantities of the replicated virus that were 39,000 times higher than were produced through one of the recombinant viruses.

One question that might be asked in conjunction with the aforementioned claim in the CDC article is the following possibility. Given the claim that mice which, somehow, had been exposed to the reconstructed version of the 1918 influenza contained 39,000 times the amount of that reconstructed version than mice which were not exposed to the reconstructed version, how does one know that all the entities which are being claimed to be exemplars of the reconstructed version (some 39,000 times some given amount) are what they are said to be? In other words, have samples from the set of entities that arose in conjunction with the fully reconstructed edition of the 1918 influenza virus been properly isolated, opened up, and shown to contain an intact RNA genome that is the same as the reconstructed version from which the large quantity of replicated entities supposedly arose and which also can be shown, when re-introduced to other mice, to produce the same kind of patterns of replication?

According to the CDC report concerning the reconstruction project for the 1918 influenza virus, another indicator of the virulence of their reconstructed agent -- beside the degree of replication that is observed -- concerned the possible lethality of that agent. More specifically, the reconstructed edition of the 1918 influenza virus was said to be 100 times more lethal than “one of the other recombinant viruses tested.”

Does the foregoing claim mean that the recombinant viruses were also lethal but 100 times less so than the fully reconstructed edition of the 1918 influenza virus, and, if this is the case, then why would such a recombinant virus be lethal? Furthermore, one might entertain various questions in relation to the extent of the lethality to which the article seems to be alluding in conjunction with the recombinant viruses which are not specified, as well have questions about the nature of the mechanism of lethal pathogenicity that might be involved in those deaths.

In other words, if one accepts the premise that the fully reconstructed edition of the 1918 virus was 100 times more lethal than “one of the other recombinant viruses tested,” then just how lethal was the latter recombinant virus? How many mice in this group died, and what was the cause of death?

Moreover, there is a certain amount of ambiguity present in the CDC article with respect to experiments involving the reconstructed virus when the article indicates that the fully reconstructed version was 100 times more lethal than "one of the other recombinant viruses tested". In other words, does the foregoing claim in the CDC article mean that other versions of the recombinant viruses were associated with higher degrees of lethality than the one recombinant virus, in particular, that was tested and which, apparently is being referenced in the quoted statement. Or, alternatively, were the other recombinant viruses found to be more lethal than one of the recombinant viruses that was tested but were, to varying degrees, less lethal than the reconstructed edition of the 1918 influenza virus, and, if the latter is the case, then, once again, what is the extent to which such recombinant viruses are associated with dead mice and why do such deaths occur at all?

The CDC article does indicate that the HA or hemagglutinin gene from the fully reconstructed edition of the purported 1918 flu virus seems to play a critical role in rendering the virus to be lethal. The evidence for such a claim rests with an experiment in which the gene from the fully reconstructed edition of the 1918 gene was removed, while the seven other genes from the reconstructed virus were combined with a seasonal influenza virus labeled as: "A/Texas/36/91" or in more abbreviated form: "Tx/91."

The latter recombinant virus did not result in the death of any mice. Furthermore, such mice did not undergo any sort of weight loss, whereas many mice exposed to the supposedly fully reconstructed rendition of the 1918 virus not only died but, as well, some number of the latter group of mice lost up to 13% of body weight within two days of being exposed.

The foregoing experiment involving "TX/91" is described in a somewhat ambiguous manner. Presumably, the only difference between, on the one hand, the recombinant virus that combined seven genes from the fully reconstructed version of the 1918 virus with the "Tx/91" control virus would have centered around the absence of the HA gene. However, since nothing was said in the CDC article about the number or kinds of genes that might have been present in the "TX/91" to which the seven genes from the fully reconstructed version were being added, one is not really certain if the only difference between the fully reconstructed virus and the recombinant "Tx/91" virus is the presence or absence of the HA gene, or whether there are other differences in genomic structure as well.

Furthermore, the phrase: "lost up to 13% of body weight" which appears in the CDC article sounds like a lot of television advertisements which indicate that if one buys a certain product, then, one can save up to "x" amount, or if one uses a certain product, then one's condition can improve by "x" amount, but, in reality, the amount which can be saved, or the benefit that actually accrues, turns out, in most instances, to be substantially less than whatever the indicated "x" amount might be, and, yet, the original statement would not constitute a lie because there were some cases in which "x" amount was saved or "x" benefit accrued. Consequently, to say that some mice "lost up to 13% of body weight" doesn't necessarily provide one with much information or provide any insight into what the nature of the dynamic that might have caused such a loss in body weight.

One would like to know how many experimental mice exhibited the foregoing loss in body weight. One also would like to know how many mice in the experimental group exhibited little, if no, weight loss, as well as how many mice in the control group exhibited some degree of weight loss, even if not substantial.

Aside from the issue of numbers involving various kinds of weight loss, one might also like to know something about the causal issues underlying such weight loss. Why did some mice experience more weight loss than others, and what factors might have affected how much weight, if any, was lost?

Apparently, according to the CDC account of the reconstruction project, the presence or absence of the HA gene had a marked effect on the symptoms that arise. However, exactly what role the HA gene plays in the nature of the symptoms that arise, or do not arise, is not actually spelled out.

The CDC article describing the experiments involving the fully reconstructed gene version of the purported 1918 influenza virus also indicates that within four days of being exposed to the aforementioned reconstructed edition, mice displayed various forms of inflammation in their lungs that were reminiscent of, or similar to, the sorts of lung tissue inflammation that had been observed in conjunction with many human beings during the alleged 1918 pandemic. In other words, apparently, the lungs of the exposed mice filled up with fluids, or exhibited signs of pneumonia, or had some other kind of lung inflammation.

However, the term "similar" that appears in the CDC article is somewhat open-ended. As a result, one remains unsure as to the extent or degree of similarity between the sorts of lung complications that emerged in conjunction with the mice that were exposed to the fully reconstructed version of the purported 1918 virus and the kind of lung complications that were fairly common among the human beings who were said to be infected with the 1918 virus.

The CDC article also describes a set of experiments that were run using a human lung cell line referred to as "Calu-3 cells". More specifically, measurements were taken at 12 hours, 16 hours, and 24 hours following exposure of those cells to the alleged fully reconstructed edition of the 1918 virus, and, then, these measurements were compared with measurements that were made following the exposure of the human lung cell line to various forms of recombinant viruses involving different arrangements of certain genes from the fully reconstructed form and various kinds of seasonal flu viruses that supposedly affect human beings.

According to the CDC article, the reconstructed version replicated rapidly within the human lung cell line into which they had been introduced. In fact, the reconstructed virus produced "as much as 50 times" the amount of virus as various forms of the recombinant viruses did.

Once again, the notion that one virus produces "as much as 50 times more" of that virus than does another kind of virus doesn't really explain how frequently this maximum of 50 times greater production actually occurred. Rather, the statement only indicates that there were some cases in which this sort of rate of multiplication was observed, but there also were other instances in which this kind of differential in production was not observed, but no details are given concerning the latter sorts of cases.

The CDC article goes on to state that one of the conclusions drawn from the aforementioned sorts of experiments is that the polymerase genes that were present in the reconstructed viral form also appeared to play a significant role in the pathogenicity (i.e., virulence and capacity for infectivity) that was observed when human lung tissue was exposed to the fully reconstructed edition of the alleged 1918 virus. Nonetheless, what the nature of that enhanced role might be is not really spelled out.

In addition, what takes place in a laboratory Petri dish is not necessarily an accurate reflection of what takes place in the much more complex environment of a living organism. Do the dynamics occurring within a laboratory point to certain possibilities in conjunction with life? Possibly … however, there is a potential for many a slip twixt experimental cup and living lip.

As noted earlier, Taubenberger and Reid were of the opinion that the 1918 influenza virus might have derived certain gain of function properties from an avian source … properties that were theorized to have made a species jump at some point prior to the onset of the pandemic. The researchers had reached the foregoing point of view because they felt that the reconstructed influenza virus had segments in its genetic sequence that seemed to be much closer to avian influenza A viruses (H1N1) than they were to various kinds of H1N1 mammalian influenza viruses, but what precisely was entailed by the notion of appearing to be "closer" to avian influenza A H1N1 viruses than to H1N1 mammalian editions of such viruses was not really specified or explained.

In order to test the foregoing thesis concerning the possible origins of the alleged 1918 influenza virus, 10-day old fertilized chicken eggs were exposed to the CDC reconstructed virus and, then, compared with results from experiments that exposed the same kind of eggs to various editions of a modern human influenza A virus that contained different combinations of the two, five, and seven gene recombinant viruses that had been created by Dr. Tumpey during earlier stages of the series of experiments that were being run through the CDC concerning the alleged 1918 influenza.

According to the CDC article, the fertilized chicken egg experiments indicted that the reconstructed version of what was assumed to be the virus at the heart of the 1918 pandemic had a much more lethal effect upon the chicken egg embryos than did any of the recombinant versions of the human influenza virus. In fact, none of the recombinant viruses seemed to have the same degree of lethality in conjunction with the fertilized egg embryos as the fully reconstructed version did, but the CDC article is unclear about whether, or not, the presence of any of the recombinant viruses led to symptoms of one kind or another in the fertilized chicken embryos.

Furthermore, the pathogenicity of the fully reconstructed edition of the 1918 influenza virus in relation to fertilized chicken eggs was said to be "similar" to the kind of pathogenicity that was observed when fertilized chicken eggs were exposed to various kinds of current H1N1 editions of avian flu viruses. However, the nature of the alleged 'similarity' between, on the one hand, the fully reconstructed edition of the putative 1918 virus and, on the other hand, contemporary versions of avian flu viruses was not specified, nor was there any discussion in the CDC article concerning whether, or not, similar sorts of pathogenetic outcomes might have been produced in more than one way. Yet, if there were multiple possible paths to similar sorts of effects in the chicken embryos, then, one couldn't necessarily conclude that the reason for such similar outcomes is necessarily due to the role that avian flu viruses might have played in the theorized gain of function that supposedly showed up in the virus that is alleged to have caused the 1918 pandemic.

In addition, although the researchers believe that the foregoing experiments with chicken egg embryos showed – as the researchers also had concluded with respect to the human lung cell line experiments – that both the HA, or hemagglutinin gene, as well as the polymerase genes of the reconstructed influenza virus played significant roles in enhancing the virulence of the alleged 1918 influenza virus, once again there was an absence of details

in the CDC article concerning just what the nature of those roles might have been, or how such capabilities actually came into being (rather than theoretically might have come into being in such a fashion), and why such features would have generated the kind of pathogenicity that had been observed in 1918.

Although much speculation within the CDC article, as well as elsewhere, has been focused on the possible mechanisms of pathogenicity to be found in conjunction with any given form of influenza virus, one should keep in mind that not all mice died in the CDC experiments when they were exposed to such viruses, nor did all mice lose 13 % of their body weight within a couple of days following that exposure. Consequently, one must also take into consideration the characteristics of the organisms that are being exposed to a putative virus in order to try to account for the differential outcomes that occurred in such experiments despite being exposed to precisely the same reconstructed virus.

Death, like life, involves a dance between environment and organism. Why, despite being exposed to the same set of environmental features, some organisms die, while other organisms live, is an issue that cannot be reduced down to only questions of pathogenicity concerning a given virus, but, as well, one must take into consideration the degree of vulnerability, if any, that exists in various organisms and just what is entailed by such vulnerability. In short, one can't talk about the lethality of a viral agent or entity without simultaneously exploring the susceptibility of an organism to certain kinds of difficulties that might arise when engaged in various ways by various elements within a given environment.

In fact, given the foregoing considerations, one might ask: Is the pathogenicity that is observed in such circumstances a function of the virus or is it a function of the organism? Where is the locus of causality to be set?

If an organism is immune to the presence of a certain entity (say, some sort of viral agent), then, in reality, the latter entity has absolutely no pathogenicity relative to such an organism. So, if another organism of the same kind displays various kinds of biological difficulties when exposed to the same sort of environmental agent, can one really say that it is the entity's pathogenicity that causes such difficulties or is the causal dynamic much more complex than assigning pathogenicity to a entity such as a virus?

Perhaps, the reason why researchers have had such difficulty in delineating the causal process with respect to the 1918 pandemic is because their analysis should have been looking for something beyond the idea of an agent or entity that has some sort of capacity for generating pathogenicity in an organism. In other words, perhaps, they should have been looking into the complexities of how organisms interact with the environment and what both sides of the dynamic bring to the life, death, and well-being equation.

Finally, the research conducted by Taubenberger, Reid, Tumpey, and others that is, to a degree, delineated in the CDC article and which has been the focus of the present essay, hasn't actually demonstrated that the reconstructed genome that arose through their efforts was the same as the viral agent that supposedly played such a devastating role in the events of 1918. Although they believe they have demonstrated that their reconstructed version is correlated with certain kinds of results in various sorts of experimental contexts, nonetheless, by their own admission, they acknowledge that their reconstructed genome does not seem to display any features which have been empirically demonstrated to be capable of generating the sort of virulence or pathogenicity that is believed to have been characteristic of whatever transpired in 1918.

They talk about a possible mechanism for entry into a cell (e.g., hemagglutinin – HA gene) as well as a possible means of being able to exit from cells (e.g., neuraminidase – NA gene). In addition, they allude to the possible role that various polymerase genes in their reconstructed entity might have had in conjunction with the process of successful replication as well as possibly enhancing, in some way, the virulence of the alleged 1918 virus, but the capacity to enter, exit, and replicate do not necessarily give expression to a causal account of how such a virus generates its lethality within a human host

Consequently, the foregoing lacks causal concreteness. They cite experiments that were conducted at the CDC concerning the potential pathogenicity of their reconstructed creation, but none of those experiments demonstrate that their re-created entity is identical to what supposedly was at the heart of events in 1918, and, in fact, only indicate that in some fashion their reconstructed genome can be correlated with certain kinds of experimental results without being able to spell out what the precise causal dynamics were which underlay those experimental results.

Once can agree with the authors of the CDC article when she, he, or they conclude: "… that more work needs to be done." Whether the future work to which the article is alluding will be able to demonstrate that researchers will be able to causally prove that their constructions constitute accurate recreations of the agent that, supposedly, was responsible for the public health crisis that occurred in 1918 remains to be seen.