The Influenza Pandemic in Japan, 1918 1920 : The First World War between Humankind and a Virus

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図書名	The Influenza Pandemic in Japan, 1918 1920 : The First World War between Humankind and a Virus
その他の言語のタイトル	日本を襲ったスペイン・インフルエンザ
シリーズ	Nichibunken monograph series ; 18
URL	http://id.nii.ac.jp/1368/00006047/

Chapter 1

The 1918–1920 Pandemic Virus

First Girls' Higher School students commuting to school following the city's advice to wear facemasks. (*Tōkyō Asahi shinbun*, 11 January 1920)

The influenza epidemic now most commonly discussed in other parts of the world as the 1918–1919 influenza pandemic has long been called the *Supein kaze* ("Spanish cold") in Japan. Despite the medical distinction between the common cold and influenza (flu), at the time of the epidemic it was known colloquially by such other terms as *sekai kanbō* ("world cold"), *isei kanbō* ("alien cold"), and *waru kaze* ("virulent cold"). Influenza was, and still is, translated in Japanese as *ryūkōsei kanbō* ("epidemic cold"), hence the confusion in terms (although the loanword "infuruenza" is the most common today). There is no clear evidence connecting the 1918–1920 pandemic particularly with Spain, but I have used "Spanish influenza" in the Japanese edition; for this English edition for an international readership, and since—as I shall detail in Chapter 3, thousands of people continued to die in 1920—I will call the disease the 1918–1920 influenza.

Structure and Characteristics of the Virus

Influenza is caused by a virus that infects birds (migratory birds, water birds such as ducks and geese, chickens, etc., pigs and other mammals such as horses, ferrets, etc.), and humans. A virus has no cells so some specialists do not consider it a living organism. It invades and replicates itself within the cells of living animals, breaking down the walls of the cells and releasing multiple copies of itself. The toxicity of a virus, as distinct from the substances found in blowfish and some mushrooms and the elements of gases like sarin, is different from that of a poison, but results from this multiplication of the virus; particularly when it occurs in the cells of the respiratory system it can sometimes cause death. Not all viruses are virulent, but, some, like the influenza virus, can become extremely toxic because they can easily mutate.

Obviously invisible to the naked eye or even under an optical microscope, the influenza virus is around 100 nanometers (1nm = 1 millionth of a millimeter) in size. Examination of its structure only became possible after the invention of the electron microscope in the 1930s. It was found to consist of eight RNA segments packaged in a lipid lined with a substrate protein; the package is covered with protrusions formed of two kinds of proteins. Only in the 1990s, seventy years after the 1918–1920 pandemic, was the virus identified in tissue from the cadaver of a person who had been infected. At the time of the pandemic, therefore, or even for several decades following it, people did not have reliable knowledge about the nature of influenza virus, how to prevent its infection, or how to treat those afflicted.

Recent research on influenza viruses has determined that there are three types: A, B, and C, the type being determined by the substrate protein of which the particle is formed. The most virulent is the type-A virus that infects animals, including human beings. The influenza that spread in Japan in early 2005 was fortunately of type B, for which mortality is relatively low (type-B virus is less likely to mutate). Type-A viruses are

further classified by subtype. The two kinds of proteins forming the protrusions covering the surface of the virus are hemagglutinin (HA), of which there are 16 varieties (H1 to H16), and neuraminidase (NA), of which there are nine (N1 to N9). Each subtype is identified by the varieties of these two surface-covering proteins. In theory, 144 combinations of these proteins are possible. Ducks, it is confirmed, have been infected with all of them. The type-A virus is found mostly in ducks but also in other fowl, humans, pigs, horses, seals, whales, and other mammals and birds. The virus that struck in the 1918–1920 pandemic was H1N1, while that known as the "Asian flu" that spread in 1957 was the H2N2 virus, and the "Hong Kong flu" of 1968 was H3N2. The influenza virus of most recent concern to us today in its potential to spread among humans is H5N1, which changed to a new type influenza from the "bird flu."

In addition to its anthropozoonoic (transmittable from animals to humans) character and the numerous subtypes that have been found, a further feature of the influenza virus is the speed with which it can develop mutant types. This is because influenza virus genes are composed of RNA, which by comparison with DNA, is less stable and more prone to mutation. Since the influenza virus has multiple (eight) segments of genetic information, it sometimes undergoes genetic crossing. When two types of influenza viruses infect a cell, theoretically genetic recombination can happen in 144 different ways. Also notable is the tremendous speed with which the virus replicates itself. One virus particle can replicate itself one million times in a single day. Because of this trait, it is thought that a virus achieves as much genetic change in one year as took place in a mammal over a span of a million years.

Variation in influenza viruses is of two types: continuous and discontinuous. As an example of the former, the seasonal influenza that spreads each year is slightly different from the type that spread the previous year, but since the virus's capacity to induce immune response in the body (antigenicity) shifts only slightly each time there is an outbreak, the defenses of the body's immune system work to some extent. In other words, the virus has undergone what we might call—if we were referring to automobiles—a "minor model change."

In the case of discontinuous variation, the antigenicity of the virus has changed so greatly that even someone who had previously survived infection by a type-A influenza virus would be newly infected and suffer serious symptoms again. In other words, the virus has undergone a "major model change." The grave danger latent in a new influenza virus is that such a major model change might take place, and, since no one will have immunity, the disease could spread rapidly throughout the world, the symptoms could be very serious, and the toll tremendous.

Mechanism of a Novel Influenza Virus

How did "bird flu" evolve into a novel influenza virus? Infection by the influenza virus begins when the virus adheres to the surface of a cell. It depends upon the congeniality of the receptors for the virus's HA protein and the virus receptors on the surface of the host cell. The receptors differ depending on the molecular structure of the virus in question; the HA proteins of the bird influenza virus, for example, are of a form that readily connects with the cell surface receptors of birds, but ordinarily is less likely to connect with receptors on the cells of humans.

The real threat lies in the fact that for the influenza virus, the lines between different kinds of hosts are not all that strictly drawn. The nature of the virus is such that, if it "accidentally" succeeds in infecting human cells often enough, it can readily change. So, the avian flu virus that happens to infect a human can become a new-type influenza virus that has acquired the ability to make humans its host. It is also confirmed that pigs are easily infected with viruses from both birds and humans. Genetic crossing in pigs between both of the viruses can presumably lead to the emergence of a new influenza virus. The possible pathways by which a new influenza virus could arise from avian flu are as follows: (1) the crossing of an avian flu virus in the body of pigs with a seasonal virus in humans; (2) the crossing in the human body of an avian flu virus and a human seasonal virus; or (3) the change within the human body of an avian flu virus into a human-type virus.

Discovery of the Pandemic Virus

The influenza pandemic that occurred between 1918 and 1920, spreading all around the world, was such a novel-type influenza. Its toll in lives rose to between 20 and 45 million, greater than for any other epidemic in recorded history. For a very long time, it was taken for granted that the pandemic was caused by the same pathogen, but in the strict sense, that was an assumption based on circumstantial evidence. That was confirmed by scientific means only in the 1990s.

In order to scientifically confirm what pathogen struck down so many people in 1918–1920 in different parts of the world, it was necessary to find genetic material of the virus in the bodies of victims for each area. Although not for the entire world, but in Alaska, other parts of the United States, and Britain, it was ascertained in the latter half of the 1990s, that the same virus, at least at the genetic level, had been responsible for the pandemic in those parts of the world. Recent research has confirmed that the 1918–1920 pandemic was caused by a bird virus that had mutated, changing so that it could infect and replicate itself in humans, and was the cause of the new-type of influenza that raged around the world.

Scientists' efforts to identify the 1918–1920 pandemic virus had a long history. At the Armed Forces Institute of Pathology (AFIP) in the United States, where millions of pathological autopsy specimens have been kept since 1862, Jeffrey K. Taubenberger and others extracted gene fragments from the lungs of victims of the pandemic and in 1995 they discovered for the first time the genetic material that is at the core of the "Spanish influenza" virus.[1] The decisive factor was that this research team had worked out a method for extracting genetic fragments of the virus from old tissue samples.

As early as 1949 in Alaska, Johan Hultin, a young Swedish scientist, had exhumed corpses of Inuits who died from the influenza and had been buried in permafrost, believing he would find the virus, but the method for extracting the virus from old tissue was not known at the time, and he was not successful. In 1997, the retired Hultin learned that the AFIP had gained the capability to analyze the genetic structures of old tissue, so he again exhumed the corpses. This time he took samples and sent them to the AFIP, where the scientists were able to identify the genetic material of the 1918 influenza in the samples.

In the United Kingdom, members of the staff of the AFIP collaborating with British researchers at the Royal London Hospital identified the influenza virus in autopsy tissue of victims of the 1918 influenza preserved at the hospital. In all three cases, death had been confirmed as due to influenza, not from complications of other medical conditions or other illness. The findings of these three cases confirmed that the victims had died of the same virus. They demonstrated scientifically for the first time that it had been the same virus that had spread around the globe.

At the time of the pandemic, this was not known, and because so little was understood about the virus, each country was helpless in the face of the disease. All that could be done was to quarantine the patients and treat complications from the influenza, such as pneumonia and bronchitis.

Today, not only has the influenza virus been identified, but scientists have succeeded in artificially recreating the H1N1 virus.[2]

Limitations of Vaccines and Tamiflu

Today it is possible to be vaccinated against influenza and diagnosis kits are available that can determine in less than an hour whether a patient has an influenza virus. Quite recently various medicines to counteract the viruses have been developed. Yet if we were

1 See Davies 2000. This book describes how the discovery was made after digging up cadavers of influenza victims that had been frozen in the ground and the searching among several hundreds of thousands of specimens of the intestines of victims of disease kept at the Institute. Since the present work deals mainly with the events prior to the discovery, I refer the interested reader to the book for details.

2 "Special Report: The 1918 Flu Virus Is Resurrected," *Nature* 437 (6 October 2005), pp. 794–95.

to think that we have been freed from the threat of the influenza virus through vaccination, diagnosis, and medication, we would be wrong.

One reason relates to prophylactic vaccines. Each year in February, the World Health Organization, considering the previous year's influenza conditions around the world and in the southern hemisphere and other factors, announces which influenza viruses are expected to spread that year and calls on each country to produce vaccines, say, for two influenza viruses H1N1 and H3N2 and influenza B. Vaccines are made using chicken eggs, and since it is not possible to mass-produce the vaccine, production just barely meets the demand for the vaccination period in November and December in Japan, for example. Moreover, vaccination is voluntary in Japan. If the entire population were to be inoculated, even mobilizing all the country's pharmaceutical companies, they would hardly be up to the task.

Should influenza of a strain different from that for which the vaccine was made begin to spread, moreover, the vaccine would be completely useless. Even if everyone were vaccinated against the strains cited by WHO for the year, should a new strain, say H3N8, spread, the vaccinations program would have no effect. And of course starting to make a vaccine against a new strain once it has already begun to spread would not be in time to prevent an epidemic.

The second reason has to do with anti-influenza medications. When the virus invades a cell and replicates itself, the substances that play the important role are hemagglutianin (HA) and neuraminidase (NA). Anti-influenza drugs are devised to take the offensive against these proteins while they are still weak. The propagation of the virus begins when the virus attaches itself to a cell and penetrates it, the genetic material of the virus (RNA segments) breaking out of the virus package and reproducing within the cell. The neuraminidase is the protein that enables the virus to be released from the host cell. Tamiflu, for example, is a drug developed to inhibit the workings of neuraminidase, preventing the replicated virus from bursting out of the host cells.[3] The idea is to close the door on the virus, preventing cells from releasing the new genetic material produced. Still, this drug is by no means a panacea. The critical factor in use of Tamiflu is that it must be given to the patient within 48 hours of the time the virus was first contracted. Once the virus has already begun to multiply in large numbers, it has little effect. Prescribing Tamiflu thus depends upon when the patient contracted the virus, but how can we know exactly when we are first affected? This is very difficult to determine.

Tamiflu as currently developed is, in contrast to earlier drugs, a medication taken orally, and is effective against both type-A and type-B influenza strains. The timing,

3 At one point a drug called Rilenza was believed to be effective, but it had to be applied by spraying into the nasal cavity or the oral cavity for absorption by the tissue of the respiratory system. Later, the Swiss company La Roche began producing and selling "Tamiflu," and buyers scramble for this product around the world today.

however, is crucial: if taken too early, it has little effect, and if taken too late the virus may have propagated to the extent that the drug cannot cope with the speed of its spread. Since the timing is so important, the judgment of a doctor is inevitably important.

The third problem is side effects. Recently, patients on Tamiflu have been reported to show signs of abnormal behavior such as jumping or falling from balconies or even suicides. The response of Japan's Ministry of Health, Labor, and Welfare regarding these cases has been that such behavior is the result of the influenza virus affecting the patient's brain, rather than deriving from the effects of Tamiflu, but is this response adequate? No scientific cause-and-effect explanation is yet available regarding these cases, but we should keep in mind that many cases of such side effects have been reported in Japan where Tamiflu is in fairly wide use.

Japan is said to be the only country in Asia that takes concerted measures to defend against the spread of influenza.[4] Nevertheless, even these measures consist mainly of attention to availability of drugs and vaccines, and adequate networks have not been built concerning the administering or prescription of medicines. Even if effective drugs are made available, without informed doctors able to prescribe their timely use, it would not be possible to prevent influenza from spreading. Networks within the medical profession, as have been developed in Canada, need be constructed throughout the world.

Humans may be attacked by a new strain of influenza virus at any time. We are no longer at the "if" stage, only the "when." Like the much-threatened massive earthquakes predicted to imminently occur in the Tōkai and Tōnankai regions of Pacific-coast Japan, even directly under the Tokyo megalopolis, an influenza virus epidemic might break out any time. Like an earthquake, it is a natural disaster that humankind cannot prevent from happening. All we can do is to reduce the damage that might result by preparing as well as possible both in material and informational ways.

Although this is not limited to the influenza virus, the genetic material of the virus is of the unstable RNA type that does not possess the DNA of bacteria and higher forms of life, and yet it is capable of mutating like any living creature with a will of its own, attacking defenseless humans, birds, or pigs, invading their tissue, replicating with fearsome speed and killing its host. The virus does not, however, completely annihilate its prey, since to do so would destroy the very means by which it exists. Rather, it moves to a different animal host and may remain dormant, quietly out of sight for decades before once more making its appearance in some host with lowered resistance.

The 1918–1920 influenza, H1N1, too, emerged out of nowhere that is known, mutated to greater virulence, spread rapidly, and then faded away. As I shall recount in the pages below, where it began, how it mutated, and why it vanished remain shrouded

4 Walsh 2004, p. 64. The photograph which appears on the title page of this chapter, incidentally, is one of Japanese girls commuting to school wearing facemasks at the time of the "Spanish influenza" epidemic in 1918–1920.

in mystery. It is all the more unnerving that its appearance seemed to coincide uncannily with the end of World War I, ravaging soldiers as they struggled in bleak battlefields. It even looked as if the virus had been deliberately lying in wait for humans at a time when their movements were most active. One cannot help recalling how the SARS virus, too, began to spread in a remote corner of Southeast Asia just as the world's attention was riveted by the question whether the United States would declare war on the Saddam Hussein regime in Iraq in March 2003.

Both epidemics appeared with a timing that seemed to mock the battles humans visit upon their fellow men. Particularly in 1918, the H1N1 influenza went on to take between 20 and 45 million lives—an accurate tally is not available—which was several times the toll of the some ten million people who died in World War I. That was the greatest human calamity of the twentieth century, probably the greatest toll in human lives from one cause since the "Black Death" of the fourteenth century in Europe. The battles between humans and viruses are "close encounters of the third kind"—struggles that could end with far more horrible results than wars between human beings. Some idea of how the killing fields created by human beings pale by comparison to the wrath of nature could be seen in the devastation left in the wake of the 2004 Indian Ocean earthquake off the coast of Sumatra Island and the massive tsunami that followed, and by the Great Eastern Japan Earthquake and Tsunami of 2011. There is a possibility that the 1918–1920 influenza epidemic had something to do with the ending of World War I, taking as it did several tens of millions of lives.

Nevertheless, that 1918–1920 pandemic has been virtually forgotten not only in Japan but elsewhere in the world, as Alfred W. Crosby has recounted in his 1989 book mentioned in the preface. How could the "worst epidemic in history" be so easily forgotten? I hope to provide the reader with the answer at the end of this book.