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EVE 0065
Grand Rounds, Dept. of Medicine, Mount Sinai School of Medicine
Invited Speaker Edwin D. Kilbourne, MD on Influenza
November 28, 1973

FENTON SCHAFFNER [ACTING CHAIRMAN OF MEDICINE]: We have been looking into the matter of conference rooms and so far have been unsuccessful. The move also to the Annenberg Building, as far as the Department of Medicine is concerned, is also going to be delayed, so that while we had hoped to be there in the spring, we probably will not be there at least until the summer. Now, maybe some of us will be fortunate enough to be on vacation at the time the move occurs, or something like that.

I also found out that one of the casualties of economy, and in order to make the space bank, one of the casualties was the major Department of Medicine conference room, so we will be the only department without a big conference room. [moans from audience] However, there is going to be a conference room, a building conference room, which will hold a hundred fifty people on the 20th floor. We will be on the 23rd floor, so that it's not too bad. Now, we will have a library—a small library/conference room type of thing. I'm not sure how many people it will hold. It may be enough for the group. We will have to find out as we try things. That will be on the 23rd floor.

UNIDENTIFIED MALE: There's a library conference room on the 24th floor, but it currently was designated to the space bank.

FS: Right. That's our—that was supposed to have been our big conference room.

UM: And we cannot find someplace else?

FS: No. We have—that is not our space. That space belongs to the School, and so we have no call on that space. We will still be working on trying to move out of here. We will, on December 12th, switch from this room to the Guggenheim Hall, in 5 East 98th Street, for the first [Alexander] Gutman Memorial lecture, and Dr. Wyngaarden [James B. Wyngaarden, MD] will be giving that lecture on gout. And that will be at two o'clock. Now we will, if we can get this room at two o'clock, from then on, all noon conferences will be—all grand rounds and such activities-- will be at two o'clock instead of noon, and we will move the Mor [Mortality and Morbidity?] conference probably to twelve-thirty. We should know by next week whether that move is a permanent one or not, depending on the availability of this place.

Anybody else have any items of interest that they want to bring up for conversation, discussion?

MALE AUDIENCE MEMBER: One of the problems was the two o'clock meeting, where a group of people who were tracked, for example, [unclear]. And they have raised the concern that two o'clock—that might make the two o'clock [unclear] sort of compromised. So it may be

important either to move that clinic earlier, so they can [attend], or move it later so it can start later.

FEMALE AUDIENCE MEMBER: [Statement unclear]

FS: Okay. Well, there was an alternative suggestion that Dr. Spilman [Edra Spilman, MD, in charge of space planning at Mount Sinai School of Medicine] made and that is we move the conference to three o'clock, in which case we could have the 13th floor Annenberg room. That takes care of the clinic, because then the clinic physicians can spend their hour in the clinic and leave. I have no really strong feeling about this. For the practicing physicians, three o'clock could obviously be better than two o'clock, and two o'clock is better than noon.

MAM: Well, almost everybody comes for two, depending on the rounds, but the rounds starts—

FS: Right. Well, they're only the ones that are on service at that time, but I think everybody would—

MAM: Two o'clock conferences are a great time for—

FS: I think it's a reasonable time. [Numerous unintelligible statements] So, is there any objection to three o'clock? [Unclear]

FAM: [Unclear] three o'clock. We cannot use the room [unclear].

UM: No, no, I'm not talking about for Dr. Wyngaarden's lectures.

MAM: Dr. Wyngaarden —

FS: That's fixed.

MA: That's fixed.

UM: Yeah, that's fixed. We're not going to change that. The notices are all out and everything, so that we're not going to change. No, this would be—

MAM: After that.

FS: After.

MAM: So Mor conference would still be at twelve-thirty?

FS: Yeah.

MAM: So then you could have like an hour of Attending rounds if you wanted to?

FS: We shouldn't overdo it. [Several unintelligible statements] Well, the way it is now, but they have Attending rounds after the]

Well, all right. Maybe we'll see. I'll look, and I'll talk to Dr. Spilman some more.

MAM: We could ask the clinic who is set to start half an hour earlier, or three-quarters of an hour earlier for the Wednesday's group. I mean that's the combination that you in the medical clinic and the specialty clinics, and it wouldn't be a burden. As a matter of fact, it might improve the traffic flow so that they don't all jam up at the same time.

FS: Well, they're going to running by appointments anyway [the Internal Medicine clinic]. That whole thing is changing—hopefully changing to computer-oriented appointments or something.

MA: Are they going to be examining patients also by appointment? [laughter]

FS: I don't know. We may be in for a severe disaster over there when we move in. [Laughs] That remains to be seen. Anyway, I'll talk to Dr. Spilman about the feasibility of three o'clock in the 13th floor.

MAM: You know, the 13th floor, the elevators—there's only one elevator that runs up there [unclear]. They run on their own schedule most of the time, four runs an hour—fifteen minutes, like Long Island Railroad.

FS: They're not much better in this building.

MAM: Oh, no. I'm saying but every elevator at that time develops its personality.

FS: Well, we shall see. I also just heard that the AOA [Alpha Omega Alpha] lecture in January on the 24th is going to be Dr. Louie Weinstein. That, too, will probably be in Guggenheim Hall, I guess.

FAM: No, the Annenberg Building.

FS: That's the 12th floor Annenberg you got for that one. Okay. Who's talking next week?

FAM: Dr. Levin is talking next week.

FS: On?

FAM: On graphic [unclear] the neck bone. [chuckles]

FS: And are we going to have a meeting in Christmas week, between Christmas and New Year's?

MAM: Yeah, that'll be CPC [Clinical Pathological Conference]. It's on your desk.

FS: Okay.

MAM: With respect to Dr. Wyngaarden, he'll be here that Wednesday morning. We are trying to conduct some rounds with Dr. Wyngaarden, with the medical students and house staff,

throughout the morning. Can we get a schedule so that the house staff and medical students can know approximately when he will be around?

FAM: Yes, we'll work on that.

FS: Between Dr. Ribner and Dr. Briggs, you will have liaison. Also, we're trying to arrange for a departmental Christmas party. I don't know what the status is. Josie, do you know anything about the status of that?

JOSIE: No. We'll probably have it on the 20th or so.

[Several unintelligible statements, laughter]

FS: As far as I remember, the New Year's party was a Hospital function, and I think that's been given up. It wasn't—the last couple years it didn't exist, and I don't know of any plans to resurrect that thing. But this would be strictly a departmental cocktail party. [pause] Yeah, we're recording. All of this is coming down for posterity. [Pause in recording]

Dr. Kilbourne is going to talk to us, a little bit short of breath, on influenza. Dr. Kilbourne is a Professor and Chairman, Department of Microbiology.

EDWIN KILBOURNE: Thank you, and needless to say, a lot of apologies. When things don't get on my calendar, they don't get on my calendar, as you can see. I have it on for December fifth. I'll be glad to come back. [laughter] How much time do we have? Cut off at one o'clock?

FS: Until one o'clock, a few minutes after.

EK: Okay. Well, I have lots of things to say, and lots of slides, and practically no organization to my thoughts at the moment, so forgive me.

Influenza is a unique infection. It's the only infection that I know of, certainly of man, in which the infectious agent is capable of mutating so extensively that the virus can circumvent pre-existing immunity. The only possible exceptions to this is [unclear]somysis, where there's a little bit of evidence that there may be antigenic variation occurring during the course of illness which may lead to relapse. Some evidence with *Borrelia recurrentis*, a relapsing fever, that this may be the case, but the evidence is rather tenuous.

So you have basically a problem in molecular variation in genetic level, and what I'd like to try to do in the next few minutes is to try to tie this in with the nuances and the varieties of the disease as we see it. Now, this Round [conference] is very timely, because just this morning I had a call from the Bureau of Biologics, who are in control of flu-vaccine regulation, among other biologicals. And they wish to set up a meeting, actually a week after next, to consider the possibility of yet another change in vaccine formulae. Now, we can add this to the lamentable confusion of the present, about why you're giving two doses

and so forth, but in fact this represents information from the Far East that yet another strain change in the Hong Kong variant has occurred, which is of the same magnitude as the change which we found with the England 42, which occurred in 1972, compared to the original variant.

Let me begin at the beginning of my story with the first slide, please. Well, the first point I'd like to make is that influenza as a term has two meanings. One is the strict scientific meaning, in which it defines a very specific disease caused by a specific virus or group of viruses. And in the broader generic sense, in clinical practice it comes to refer to any combination of symptoms of a febrile illness and respiratory tract involvement. And for this reason, the disease is not reportable, despite its enormous importance, economically and otherwise. May I have the next slide, please?

Well, really, the whole story of influenza is on this one slide. The basic problem is this: that in recent years and about every decade, there has been a major mutation of the virus with respect to the energetic nature of its external protein, the protein of which has been counted as the environment, and the environment being man's respiratory tract and antibody. And when this variation occurs and this energetically novel virus is introduced, as a kind of Andromeda strain, in a universe where you have susceptible population, it differs from measles or polio, because regardless of whether one is fifty or one is five, one will have little or no antibodies to it. But in this situation a pandemic occurs, and in present day modern life, this is the only infectious agent that causes pandemics, an essentially global saturation of the world population with the infectious agent within a couple of years, and consequently an enormous impact in terms of high morbidity in a brief period of time. So the impact of influenza is double. The impact economically is—in terms of the high morbidity. The secondary impact, which is the one we're most concerned of in vaccination, is the impact on mortality. The secondary bacterial pneumonia is the usual cause.

Now after this period of saturation, which takes a couple of years, usually—this represents one year of this pandemic exhibition of the virus—there is a briefly endemic persistence of the virus in the population, and then there are cycles, which are roughly biennial in occurrence, during the rest of the decade. And during this time we see a progressive decline in the extensiveness of the epidemic, and to some extent in the clinical severity of the individual case, although this is less evident than the epidemiologic suppression of the disease. And coincident with this, we can tell by serologic examination of the population, an increase in specific antibodies to this new agent.

At the end of roughly a decade—the intervals recently have been 1957-1968—we are now in sort of the middle period of a decade, we see a situation where the population antibody level is high against the agent, and when the agent is less easy to detect in patients, or in the population, either on the basis of evidences of serologic conversion, looking for the virus as it occurs in pneumonia patients, or in terms of the clinical exhibition of the disease.

It is at this point, where apparently there's some kind of a vacuum established—an ecologic niche, if you will—when in the immediate past there has been the introduction of yet another agent, which we could call A3, or A4, or whatever, which again will be very different in its co-proteins from the original infecting virus. Now the reasons for this are complicated, and we'll get back to those in a minute. But this is essentially the problem.

Now the point I would also stress is that during this period of a decade, the virus has not been holding still, but in fact the strain recovered, let's say, three years after the introduction, can be shown to be antigenically somewhat different than the original strain. So we've got two kinds of antigenic variations in the preceding. The first kind is a kind of step-wise, progressive point mutation that we associate with drug resistance to bacterial drugs, or bacteria, and this is of relatively minor degree.

And I might say, parenthetically, that the necessity for frequent vaccine change during this period of, say, the prevalence of the Hong Kong type, is open to question. That is, these differences can be shown, but their actual significance in terms of compromising immunity is quite borderline. But then at the end of the decade, the kind of antigenic change that occurs is a profound one, and as one would expect, as shown by the lack of population immunity. And this obviously requires, in prophylactic terms, the creation of then a new vaccine which will match the new strain. Next slide, please.

Now a look at the recent past history of influenza, in terms of this present century anyway, suggests that we have had pandemics in 1918, with the introduction of an antigenically new strain somewhere in this period, probably about 1929. And then the other recognized pandemics after 1918 were 1947, '57 and 1968. These are the periods of the introduction of an antigenically novel virus which has swept the globe.

Now, I've also tried to introduce here in this slide, which is a little complicated, the newer nomenclature of the viruses, which recognizes the fact that there's not one surface protein, but two, that vary independently and are antigenically different. These are the hemagglutinin and neuraminidase androgens, respectively. We'll say a little bit more about these later. And consequently, this terminology has arisen.

I think the significance, I might point out to you of it, is that if one examines these older strains with a newer technique, one can show that whereas the hemagglutinin antigen, H, was subject to considerable variation during the time after 1918, the neuraminidase antigen—as the minor antigen of the virus—was subject to less variation, and hence the common designation of N1. So the H2N2 refers to the hemagglutinin, the neuraminidase of what we used to call the Asian strain, which is prevalent in the 1957-'68 period. We're now in the period of H3N2, or Hong Kong subtype prevalence. Anything you hear about England strain, or 42, or whatever, is simply another Hong Kong variant. We are in the Hong Kong decade right now. Next slide, please.

Now, this is a highly schematic representation of the virus, and it does illustrate some of the newer information that we have, which is important. But of course, it is an

envelope virus, meaning that it is formed by budding directly from the plasma membrane of the cell. And like all viruses, including the myxoviruses, of which this is an example, or the recently christened togaviruses—used to be called arboviruses—these are, as you would expect, they are disrupted by organic solvents, which interact with the lipid covering which is acquired from the host. So that the outside of the particle would be represented on the very exterior by two virus-coated proteins, where I've sort of cartoon-ized the way they look, but the hemagglutinin spikes are apparently represented to a greater extent on the surface of the virii.

The mushroom-shaped things are the neuraminidase spikes. The hemagglutinin protein is the protein which is responsible for the binding of the virus to the cell. It is also responsible for raising the antibody, which will be neutralizing to the particle. The neuraminidase is an interesting protein. Neuraminidase is, of course, widely distributed in nature, including the mammalian cells and in many bacterial species. The neuraminidase here is specific for the virus—is a virus-coated antigen under the control of the viral genome, and is a primary antigen that is probably important in releasing the virus from the cell as the particle buds off from the plasma membrane.

Now, recent knowledge shows that within—just inside these two proteins is a lipid bilayer which is derived from the host. This is not coded for indirectly by the virus genome, but represents host material. And there's also a carbohydrate polysaccharide [unclear] in here, not shown, which is antigenic, but again is post-deterrent. And within this is the major protein of the virus, which delimits the core. This is known as the internal membrane matrix or M protein. This is a small moleculate protein, about twenty-five thousand.

The heart of the virus, of course, represents its genetic material, which is distributed actually in a segmented form. The RNA, which is the genetic material, occurs in five to seven discrete segments. We're not quite sure whether these are linked in any fashion within the virus itself. This has considerable importance with reference to the possibility of genetic interaction between strains that we found in Asia, because these seven nuclear protein fragments can be apparently randomly reassorted within the cell that is doubly infected with the virus. This provides a uniquely high recombination rate, which makes it possible to do some unusual things genetically with the virus, and also makes the virus able to do these things in nature quite readily. So, so much for the basic particle. You really cannot understand influenza without understanding the nature of its genome, and the nature of its external proteins. The next slide, please.

In gorgeous Technicolor, we have a representation of the various subtypes that have prevailed. The point that I emphasized inadequately with the first slide is the fact that not only is influenza remarkable in the appearance of a brand new strain from time to time, but when this happens it completely supercedes the preexisting strain, which apparently disappears from the face of the earth.

So the remarkable thing to me is not so much that the virus—that something new appears, but that the old one is completely gone. So that we have these to examine only because we have deep freezers, and although we had the prototypes then of 1957 and even 1918, in terms of the Swine virus, these are things which are just in the laboratory at the present time. And I've tried to show that there's an independent variation of the hemagglutinin and the mushroom-shaped neuraminidase molecules with time. There apparently are different selective forces operating against them.

Now the main thing I wish to show you here, which has been the source of some confusion in the literature and probably still is, is the fact that what happened between 1957 and 1968 was a complete change in the hemagglutinin, which is rather badly represented here as being green, as opposed to blue, whereas there was no change in the neuraminidase. So this represented, then, a complete change in one protein, with little if any change in the other. And it tells us that pandemics can occur with the mutation of only one of these two proteins.

And for this reason, I believe, although I can't substantiate this completely, the impact of '68 was milder than what we'd seen in 1957, because the population had raised antibody to the neuraminidase, although it could not deal with the virus that has completely changed hemagglutinin. So I think that the epidemic of 1968—or the pandemic—was damped by the pre-existence of anti-neuraminidase antibody. Next slide, please.

Well, this is really more of the same, in which I've indicated that if one can judge pandemic severity clearly, that we can rank things the same that…. We, of course, have no information about the antecedent virus in 1918, so we don't know the extent of the change in that situation. We can guess that it was considerable. And in the intervening time there will be mutational changes and the absence of a pandemic at this point—although our records are not terribly good from that period. The worst pandemic of modern times is the one that we saw in 1957, which has considerable associated mortality, as many of you know. And that was associated with change in both antigens. As I've said, I believe that the rather moderate nature of the '68 pandemic was predicated on change in only one protein. Next slide, please.

And the other point I'd like to make is that the kind of variation that we're talking about—at least that we can prove and recognize—is a variation in antigenicity. This is not to be equated with variation in the intrinsic virulence of the virus, because I am unable to find any good evidence in the literature that would satisfy me that the virus, even of 1918, was intrinsically more virulent in man than the viruses that have come along subsequently. Now, it's not easy to prove virulence because it's always reciprocal of host susceptibility, but if we look at the uncomplicated picture of influenza—this happens to have been in 1957—as a brief, usually three-day fever, this picture is perfectly typical and characteristic from 1889 to 1918, 1968—all the way through. Flu now is what flu always has been, as far

as the clinical records will say. But on the other hand, the case fatality rate is a variable and is an important variable, and we can go into reasons for that. The next slide, please.

In patients that have underlying cardiopulmonary disease, specifically rheumatic heart disease, and still more specifically mitral stenosis, influenza is a notorious killer, and this is, I think, most dramatically brought out in the period of modern study in 1957. And so this actually represents what must be the same virus that we've seen on the previous slide causing a three-day illness, operating in a patient with underlying cardiac disease that died, and died in this instance of a primary influenza virus pneumonia, uncomplicated by secondary bacterial pneumonia. [Pause in recording] —ones that we recognize have to do with the antigenicity. Next slide, please.

Well, I was making the point, again, that if you line up the symptomatology, and make a clinical profile of 1947 to 1957, this being a relatively mild year and this being a severe, that the average case looks really no different. Next slide, please.

Well, this goes back to the point I was trying to make on one of the initial slides, and that is, what is happening during the period of prevalence of a given subtype. And I've simply tried to show that the selection that goes on is the reciprocal of the antibody that the host raises, that when the new agent is introduced into the population in a pandemic introduction, that it creates—I'm afraid it doesn't show too well here; this is supposed to be pink. But the pink people here represent those who had the experience with this pink virus here, that for the virus to survive, because it's an intimate, obligate parasite of man and has no other place to go, except as I shall qualify later, [it] must mutate.

Now it's constantly mutating, but it must be selected for, so that then, during this inter-pandemic period, we have a series of sequestral changes which will effect the external proteins of the virus, particularly hemagglutinin, and similarly we will have a changing phenotype of the population, in terms of the antibody that it's carrying around. With every burst of disease, an epidemic, during this period, we're going to have the raising of a new crop of qualitatively different antibodies to these changing antigenic determinants. Next slide, please.

Now, these are peptide maps, tryptic digests of the isolated hemagglutinin of influenza virus. What is their significance? I think their significance is profound. These are not our data, but those of Graeme Laver in Australia. And what he has done, and I think you can see it easily from the back row, he has examined the Asian strain or A2 strain, and the Hong Kong strain with respect to the mapping, and hence indirectly the amino acid sequencing of the hemagglutinin proteins, the changeable proteins.

Now, these are two A2 strains. These would represent the pink and the red and the white variants within the period I just showed you on the previous slide—minor antigenic changes. With these minor antigenic changes, the maps look virtually identical. If you look terribly closely you can find a peptide here or there which—which has changed in this map distribution. I think you'd all agree that this and this are two quite different proteins, and

it's very difficult to see how, with even one or two sequential mutations, you would go from this to this. So this is sort of a reaffirmation of the immunologic evidence of strain difference, which is quite important in terms of our considering whence come the new strains. Certainly it seems most unlikely that they can come by a series of mutational steps from one year to the next, to arrive at such different proteins. Next slide, please.

Well, this is simply—these are gel electropherograms of the RNA of the virus to show that the RNAs are different molecular weights and are separate. Next slide.

Okay, now we get to consideration of perhaps how some of these changes occur. It is very easy in the laboratory to take two very different strains of influenza virus and to doubly infect a cell system, and to come out with progeny genomes which differ from either or both parents. And schematically represented is the fact that we're introducing two segmented viral genomes, which apparently can randomly reassort—not completely randomly, but reassort within the cell - so that you get the following redistribution of the parental genes.

Now, there is some confusion, considerable confusion, and some of it was reiterated in the provocative article in *Science* of a couple weeks ago, about how we shouldn't mess around with influenza recombination because we'll create the virus in 1918, is a misunderstanding about the potential of this. This kind of reassortment does not create new antigens, because if the hemagglutinin and antigen is coded for by, we'll say, this fourth green RNA [sound of writing on chalkboard], and these are reassorted allelically within the cell, what you come out with is certainly different viruses. These are recombinant hybrid viruses which are different, but one has not changed - it is not possible; we've tried to change the character of the antigenic determinants in this fashion.

What one can do, perhaps, with this—go on, please—next slide. What one can do very readily is to segregate out the genes for these various proteins, and this has proved to be enormously useful in segregating, we'll say, the neuraminidase and hemagglutinin antigens so that one can raise specific antibody to one or the other of these two proteins. You can appreciate that having segregated the antigens out in this fashion, that antiserum, then, raised against this recombinant would turn out to be specific for this neuraminidase, and specific for this hemagglutinin. This has been a considerable advance. Next slide, please.

I wonder if time is going to permit me to get into this. Let me just briefly make this point: the nature of the two antigens is an interesting one, in terms of immunologic response to them, and the implications for the disease. What we see here are plaques of influenza virus unneutralized by specific antibody. What we see here is the same system, but in the presence of antibodies specific for the hemagglutinin, or major protein antigen on the external coating—complete neutralization of the virus.

Here we see a phenomenon apparently unique for a neuraminidase containing viruses, as far as we can see, and probably for influenza viruses. And that is, in the

presence of anti-neuraminidase antiserum, we get not neutralization of virus in the classical sense, but rather we get a suppression of the evolution of the size of a plaque. Now, the importance of this goes beyond tissue culture because we have since shown that the same thing happens in mice; the same thing happens in man. The anti-neuraminidase antibody does not prevent infection but will suppress it, so that one can achieve an immunizing effect of this partially restricted infection, and let the definitive immunization be carried out by the infecting challenge virus. Next slide, please.

The presumed structural basis for this different kind of reactivity is—is only presumed. It could be on the basis of, if bivalent antibody binding is necessary for the neutralization to occur, the spheric representation of the proteins on a [unclear] surface might be, and there's some indication that they are, a close separate in terms of neuraminidase antigen, that an antibody molecule cannot make this bivalent linkage for that particular protein. It could, however, aggregate particles by extending between virus particles. Or indeed, it could influence the enzymatic activity directly, and inhibit release from—from cells. Let's see the next slide.

Now I think we'll have the lights, because I really don't have time to go into all of that. In closing, I could just say that we've speculated about the origin of pandemics, and I can give you the speculation verbally a little more readily that I can by showing the remaining slides. If the slides will help, we can come back to them, if time permits.

But, in essence, the theory has been that since recombination occurs readily in the laboratory, that perhaps it can occur readily in nature, and that if it does, it could provide a mechanism by which the human strains might, as a rare event, enter the lower animals which also have Influenza A viruses, and these include specifically swine, horse and numerous domestic birds. That in that setting, there could be a recombination, which would perhaps combine those genes necessary for the replication of the virus in man, and picking up the "new" antigens—new in quotes—present in the animal species, and translocate them into man at a time when you had this ecologic niche, after his own virus was at the end of the disappearance curve at the end of the decade.

That's a very hurried, capsulized summary of the idea. I'm sure you want me to say something about the practicalities of immunization and so forth, and I'd be happy to do so, if time permits that.

UM: Ed, would you also say a word about Influenza B, because apparently there's been some kind of mutation in that thing through the years.

EK: Yeah. The ABC's of influenza: we have Influenza A, Influenza B, and Influenza C [writing on chalkboard]. Now these are in contradistinction -- everything I've said so far has been about Influenza A. This is a major pathogen. It's the only one that's been involved in pandemics. It's the only one that infects animal species or is carried in animal species. This is presently what we're talking about.

Now in addition to that, and completely antigenically discrete, with no crossover whatsoever, but with the same biological characteristics in producing the same kind of clinical picture, is Influenza B. Influenza C is a sometime thing, which is probably important mainly in children as a rather minor respiratory infection, and you can really kind of preclude that in classical consideration right now. B has importance, because although it's mainly a disease of high school students, apparently, or older children, it can infect older people. It can induce pneumonia. It can, indeed, kill people, on rare occasions.

It is not subject to the frequency of antigenic variation that one see with Influenza A. Consequently, we do not recognize any subtypes, as we do here. We recognize here the subtypes I indicated: H1N1, H2N2, and H3N2. These are all the variants I've been talking about. Note, there have been differences observed, but not sufficient to justify different subtype designations. This year—or this past year, has been an exception for something called B Hong Kong 572. Now, this reared its head in the Far East. The same little man who's making viruses in an alley in Hong Kong apparently is making B strains, too, and releasing them.

So the confusing thing here is that this Hong Kong designation has nothing whatsoever to do with what we've been talking about over here. The strain designation simply reflects the site that happened to be isolated and reflects where laboratories are, so you'll see a lot of England strains because the WHO reference center is there. You'll see lots of New York strains because of work done here, and so forth. So it's—it's misleading. [Unclear]

Now the point about it is, however, that it does seem to be radically different from the B strain now represented in the bivalent vaccine, which as you know has both A and B. Why the two injections? Well, this is the practicalities of life. In a meeting at the Bureau of Biologics last spring, we learned that many of the pharmaceutical manufacturers would be unable to incorporate this new B variant into the bivalent, readily available, commercial vaccine. They had already made their batch lots, and pooled the A and B—the obsolete B. So, the exigencies of life being what they are, the recommendation was still necessary for the immunization of high risk groups, and so forth.

So the recommendation which was made, which has been unfortunately terribly confusing, is that the bivalent dose should be given because it contains the A that you want. But in order to get the B that you really want, maybe, because it hasn't appeared yet, one would have to get a supplemental injection of this separate strain. So this is what all the hoo-rah is about. And I think I would strongly urge anyone who has cardiac or pulmonary cases under their care to give the two injections, because there is always a possibility that this may create disease. The reading at the present time is that this winter, this strain seems to have taken over in England, and that the only B that they have seen there has been of this so-called Hong Kong 5 type.

Now to confuse things a little more—and I don't want to—there was a period where some transitional strains, which are intermediate between this strain and the old B

strains, were found in England and Western Europe. And it wasn't really clear which way the cat was going to jump for a while, and this is one reason, I think, for the tardy recommendations about what strain was incorporated in the vaccine. But we have this terrible problem of mutability, which is unique. For the polio virus vaccine, you can get a good vaccine, and then you turn it over to industry and they make it and that's it.

But the other point, of course, is the vaccine has a bad name, and it has a bad name for many reasons. It has been grown in chick embryos that had been heavily contaminated with bacterial endotoxins in the past, and a lot of the reactogenicity is clearly on that basis, although the virus has some intrinsic toxicity. In addition to that, the antigenic potency has been low. There's a period when the standards for potency were not—were not high. And coupled with that, if you give the wrong vaccine in the presence of the right epidemic, you're not going to get substantial protection.

So for all these reasons, the vaccine has come to have a bad name. It is actually a highly effective vaccine, even in its present form, except for the brevity of the immunity. It's somewhat like 75 to 90 percent protection will be given by the current doses of vaccine. And the current preparations are purified by either zonal centrifugation or by different chromatographic procedures. So they represent relatively pure preparations, and you may have noticed less reactogenicity in recent years.

FS: Anybody else have any questions? If not, thank you very much for this. [Applause]

[End of Recording]