

**National Institute of Allergy and Infectious Diseases
Oral History Interview Project
Interview #2 with Dr. Robert Chanock
Conducted on February 1, 2001, by Peggy Dillon
at the National Institutes of Health, Bethesda, Maryland**

PD: Good morning, Dr. Chanock. I would like to continue the conversation about your career that we began several weeks ago. Previously, we focused on your background and early career leading up to 1968 when you became chief of the Laboratory of Infectious Diseases at NIAID. Today, I'd like to use that milestone of your promotion to lab chief as the starting point to our discussion, especially about the era of vaccine development in high gear. First, though, I just want to revisit one topic that we covered earlier, which was how you decided to pursue research instead of medicine. Could you briefly recap how that came about?

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PD: So, in other words, just to clarify, had you ever planned to become sort of a bedside physician?

RC: Well, I hadn't planned to be a physician at all. The decision was made by the army.

PD: Okay, so your decision . . .

RC: In medical school, I leaned very distinctly toward pediatrics because the Department of Pediatrics was most collegial and I had people I thought were really the most thoughtful, beneficent, caring physicians. Surgeons were really rough and brusque and so forth and my intent was to be a pediatrician. And I, I did my residency in pediatrics at the University of Chicago. And when I finished, I thought of additional clinical training in practice or possibly being a pediatrician in an academic setting. And the Chairman of Pediatrics at the University of Chicago, Francis Howell Wright, just a magnificent man. He was the sort of person that I wanted to be ultimately, wonderful man, respected by all both scientifically and as a person in terms of his morals, his ethics, his thoughtfulness, his sensitivity and so forth. And I said, "What do you think I should do?" And he said, "I think you need a little more discipline. I'm going to send you to work with Albert Sabin, who is an old friend of mine from Rockefeller Institute."

PD: So it was that interaction with him that steered you away from pediatrician to research?

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two years and then when the Korean War started, I was drafted into the army because all of the young doctors who had been sent to medical school by the army or the navy were called to duty first. They had been trained, supported, but they hadn't served. You see when the war ended, all of the trainees were just released. They became civilians.

PD: Okay.

RC: So, there I was and with a number of early successes and I said, "Gee, this is wonderful."

PD: But even preceding them, when you said you had originally planned to be a pediatrician, well, when you thought of being a pediatrician, why didn't you just go for it?

RC: Well, I followed the instructions of Francis Howell Wright, a man that I respected tremendously. And he said, "I think you might enjoy research. So do it and then you can make your decision and you will, it will be on an informed basis. I mean, you will know what you, the basis for your decision. If you don't know what research is about and you don't know what's involved and you don't know whether you're able to do it, you can't make that decision."

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RC: So, the decision was made in the laboratory and I had finished my academic training, but I had to wait two years before taking the examination for certification as a pediatrician, in other words, the boards, the American Board of Pediatrics certifies pediatricians two years after they finish their training, after an exhaustive set of examinations and all that sort of thing. And so in the last three months that I was in Cincinnati, I had planned to spend a lot of time reviewing pediatrics before I took the board examination. And Albert Sabin said to me when he found out that this was my intention, he said, "You know, I think you've got a real career in science and we have three or four papers together in three months, and I will teach you how to write papers," which is probably one of the most difficult things of all in science. So we worked on these papers and did nothing else. I'll give you a copy of the papers if, these were all first one, two, three, four, five papers were published in 1953, '54 with Dr. Sabin in the *Journal of Immunology*.

PD: You co-wrote with Dr. Sabin.

RC: Well, I did the first drafts. He never wrote the papers for me. He just told me what I had done wrong and what the proper procedure should be and I learned how to write papers. I learned how to analyze data and present it in a way that was used in a friendly, you know, to the reader and so forth. And it was a three-month intensive crash course in analyzing data, presenting it in a form suitable for publication and writing the paper and having it published and accepted by the *Journal* and so forth. So, between 1950 and 1952, I did work that resulted in five papers. Now, this was, you know, I was elated. I

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can do this and I enjoy it and it's more meaningful in one way and that is, if you are expert in diagnosing pneumonia and treating pneumonia, you can have a tremendous impact on the lives of maybe several hundred children. If you develop a method for preventing that disease, you will have an impact on hundreds of millions of children in time.

PD: So you were seeing the bigger picture and professional success in this.

RC: That's right.

PD: Thank you for clarifying that point. I wanted to move ahead then to 1968 when you became chief of the Laboratory of Infectious Diseases. During that year, this Institute underwent a major reorganization, which resulted, among other things, in the Laboratory of Infectious Diseases being split into the Laboratory of Viral Diseases and Infectious Diseases.

RC: Yes, it had to be split because there were over a hundred people in the laboratory.

PD: Yes, tell me how that reorganization occurred and why?

RC: Well, the reason it occurred was that Bob Huebner had done such a splendid job, had done so many important things in cancer research and had received so much money and

so much support from the Cancer Institute that the director of our Institute was embarrassed and really never presented what Bob had done in, during congressional hearings and so forth. The director was afraid that they would say, that he would be asked by the Congress, “Why is it that your foremost scientist is working on cancer? You have an Institute of Infectious Diseases. There is a Cancer Institute.” And by the time it was clear that Bob Huebner had to move to cancer, he was receiving about three times as much money from the Cancer Institute as from his own Institute.

PD: Okay.

RC: So he just moved his base of operations, but he didn’t change anything. He was able to work on a much larger scale now. So, he had a tremendous impact on the field of cancer research. I think I mentioned it in the earlier discussions. So Bob moved to Building 37, [which] was the new building devoted to cancer research that had just opened up. But we were still very close and we still saw each other an awful lot. And he helped me and he helped the laboratory. One of the things that I commented on before and that I think is very important is the varying styles of research. I was taught by a man who was a—let’s see, how can I say it—was an isolated, solitary, scientific giant. He had a very small staff. When I, when I went to Cincinnati, Albert Sabin and his technician were the only people rumbling around in this huge laboratory. He had lots of space and lots of, and I was the third person. And later that year, one or two other people came, never a large group, and Sabin did most of his work himself.

When we had his 80th birthday celebration here, I asked him, how many monkeys were used in the development of the polio vaccine, the live polio vaccine?” And he said, “Well, I counted up the number of monkeys about halfway through the project and it was ten thousand, which meant that he had used 20,000 monkeys and he inoculated every one of them himself, observed them everyday that they were alive for evidence of paralysis or a change in neurologic status of another sort and so forth. And, sometimes he would go up and make rounds, as you would in the hospital where the doctor looks at the patients and evaluates them in the hospital. He made rounds once or twice a day on all the monkeys that were in residence then, after he inoculated the animals. He didn’t trust anybody else to do them. He read the slides. Each monkey was autopsied and he did quite a few of the autopsies himself and then the central nervous system tissue was fixed and [formed] and many sections were taken. He read those sections. He had trained himself to be a neuropathologist. He wasn’t trained.

PD: So he was very much his own person.

RC: His own person, yes, and he really did most of his work himself. Now the project that I worked on was not polio at all. It was something quite different. It was arthropod borne encephalitis viruses, which we now call flaviviruses or alpha viruses. So there’s this isolated scientific giant. And then when I come here, Bob Huebner was probably the paradigm for an entrepreneurial scientist. He had a big laboratory, people worked

harmoniously. He designed very, you know, very grand scale, the protocols in such a way that there were checks and balances and controls that were included.

Certain things were done blind. There was a number given to a material and then it was tested and until the tests were over, nobody knew what number one was or number two or number three, So there were all sorts of controls. He had a hundred people in the laboratory when he left because he was a great entrepreneurial scientist. He was extraordinarily successful in interacting with other people, with energizing them, with, you know, stimulating them, but not directing them, you know, to, right down to the last level of control. He read the data and interpreted it. If there was something wrong, it was repeated, but he didn't do much himself.

PD: Okay.

RC: He was just, he had great, he was very daring, very courageous. He took huge leaps way beyond the distance that any other scientist I know, would ever, you know, attempt to attain. And he just made huge leaps and sometimes, many times, he fell flat on his face, but when he succeeded, it was spectacular, you see.

PD: So they were opposite in their approaches.

RC: They were as opposite as opposites can be.

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RC: Yes, or the avian viruses in Hong Kong, you know, that are struggling to gain a foothold in people. They've infected people, but the virus hasn't spread to other people, but a couple of mutations more and they may be able to and then we'd have a worldwide pandemic like 1918. But you could respond more rapidly with this reassortment strategy than you can by making an inactivated vaccine, because if you make, you'd have hundreds of doses or thousands of doses, you know, in a little tissue culture tube that you could use. But an activated vaccine takes a lot of a lot of eggs.

PD: Which brings me to my next question, which is how do you choose to look toward a live virus vaccine or attenuated?

RC: Well, you have to look at the, it's disease-specific. With hepatitis-B, we're never going to have that, or we're not going to have that for, in the first place, we can't grow the virus and in the second place, it would be too dangerous to use this technique for viruses that produce persistent infection. HIV is an example. In other words, use of an inactivated vaccine has sort of been ruled out of court because if you have a virus that's in the genome forever and mutation occurs at a high, with high frequency. You could actually change, and the attenuated virus can become virulent because it's there for life, you see, it's got a long time for. You can wait a long time for that right mutation to come out because its DNA is integrated into the wholesale genome. And hepatitis-B would be like that and C is also a chronic infection. It's even more chronic than hepatitis-B, probably won't have an attenuated vaccine, but we have an acute infection and very good

PD: And yet, you learned at the knee of both of them.

RC: Yes, well, there are times when you want to do it yourself and there are times when you want to have the whole group do it. So in the earlier studies, I did most of the work myself. But very soon, it wasn't possible to do this because we had so many things working well. So I had to learn to become entrepreneurial, too. But the lessons I learned with Albert weren't lost, you see.

PD: You just brought them here.

RC: Yes.

PD: So, go on more about the split, in 1968.

RC: Well, Wally Rowe was a section chief and I was a section chief. Wally Rowe was an extraordinarily fine scientist. He and Bob Huebner were here before I came, you see. And Wally and Bob discovered the adenoviruses and defined what they were, what they did, who was infected, and who was affected by them and what the consequences of the infection were, the epidemiologic patterns of spread and epidemics and so forth. And Wally also discovered the cytomegaloviruses and was just a, he was real giant. And so the lab was split into two parts because Wally wasn't into entrepreneurial science at all

and I was sort of halfway into entrepreneurial scientists at that time. But I was, the laboratory just kept moving along.

PD: So that was what the split was about. They simply needed to reassign things.

RC: Well, we had a hundred people. I mean to go from four or five people to a hundred people for me just wasn't possible.

PD: So you, you stepped into the shoes of Dr. Huebner.

RC: Well, into one of the shoes.

PD: That was a big shoe to fill.

RC: Oh, God, yes.

PD: How were you tapped?

RC: Well, the scientific director, John Seal, who was a navy captain, he was head of NMRI across the street, Naval Medical Research Institute at the Naval Medical Center and he was a navy captain. He was the founding commanding officer of the NMRU, that's Naval Medical Research Unit, in Egypt. And I think he was in charge of a much larger

had tests that would tell us whether people got infected and we could isolate it in certain types of media and auger and so forth. And we did epidemiologic studies and then we decided we would try to make a vaccine.

And one of the discoveries that was made here by a technician and the description of an award that was given to him for “growing mycoplasma pneumoniae on glass” was very critical to our efforts to develop a vaccine. In other words, we had huge bottles and he determined that if you cultivated the mycoplasma in these huge bottles, they were about this long and about this wide, under special conditions, the mycoplasma stuck to the glass and then all you had to do was wash the huge bottles many times and you had pure organisms on the glass and all you had to do was scrape them off and then you had something that could then be inactivated by formal and used as a vaccine. So a vaccine was developed and tested in the Marine Corps recruits and it was only 50 percent effective. And that’s not good enough.

It would be good enough for HIV, but since we could treat with tetracycline, we felt it wasn’t worth going ahead with an attempt to make a better vaccine, develop a better vaccine. So, we actually identified this, the agent of atypical pneumonia. We described how it behaves in different populations. It turns out that about, it’s the most important cause of pneumonia in older children and young adults. And, of course, recruits are young adults.

unit at Great Lakes. When he retired from the navy, he was tapped to become the scientific director and he was wonderful. And he made the choice.

PD: How did this splitting affect the laboratory?

RC: Well, Wally Rowe was interested in chronic infection and we were interested in acute infection so there wasn't any, I mean, we weren't competing in any area, but we, you know, cross-supported each other. So it went fine.

PD: Okay, it was an obvious way to deal with the growth of the work that was in here.

RC: Neither one of us was Bob Huebner. A hundred was quite, I mean, right now, we have about eighty people in the lab.

PD: It was bigger then.

RC: Well, it would have been a hundred and sixty if it had been doubled, you see.

PD: So tell me how you pursued this new mission as laboratory chief. Did you have latitude to determine the lab's future course? Was that predetermined?

RC: Well, the course was really set by the successes we had before 1968. We had already discovered most of the important respiratory track viruses that caused disease, you know, in the lower respiratory tract that hadn't been known before 1950. In other words, the first half of the century, the only respiratory path pathogens were the influenza viruses. That's all there was. It was either influenza or nothing. And a lot of, as I mentioned earlier, there was a lot of disease that just couldn't be explained by influenza, a tremendous amount, so we filled in that big void, respiratory syncytial virus, the most important virus in early life, parainfluenza viruses, type 1, 2 and 3; crew bronchiolitis pneumonia; and then there was the mycoplasma pneumoniae, which everyone thought was a virus.

It was called the primary atypical pneumonia virus of Eaton, Monroe Eaton, but studies that we did in Marine Corps recruits at Paris Island indicated very clearly that the agent that caused that atypical pneumonia, it was atypical, it was called atypical because it wasn't pneumococcal pneumonia, where you have, you know, high temperature, sweats and either die or you recover in four or five days, you know. This is a pneumonia that goes along for along time and causes a tremendous amount of debility—weakness, fatigue, and so forth. But you don't die from it, you just drag yourself, your body around and you just can't function. And in the military, that's very bad. So, when we found that there were many, there was a very high incidence of Paris Island recruit training center for [greens], we went down, we set up a big study and we studied the epidemiology of the disease.

And, finally, we did a controlled study of tetracycline as a therapy in this disease. There had been anecdotal reports that tetracycline was beneficial and would terminate the disease manifestations and would terminate fever and x-ray changes and, in other words, fatigue, all the symptoms and signs of the disease resolved very quickly after tetracycline. And we, we studied maybe four or five hundred consecutive cases and it was clear that tetracycline was beneficial, very, very beneficial therapeutically. So it wasn't a virus because viruses don't respond to antibiotics. So we worked very hard and we were able to recover mycoplasma and it was called, we called it mycoplasma pneumoniae and we grew it. We were able to grow it in broth and artificial media, agar or broth, and we used the organism in, that we could grow artificially in serologic tests where we tested the serum from patients with atypical pneumonia very early after diagnosis and again, much later to see if there was a development to see if antibodies that were specific for the mycoplasma developed in convalescence and they did.

We were able to take the colonies of mycoplasma pneumoniae and transfer them to a slide and then add to one slide the acute phase serum and convalescent phase serum to another slide and then do immunofluorescence analysis where you determine whether the antibody, that is, the immunoglobulin sticks to the colony or is washed away when you wash the slides and it was just night and day. There was no antibody in the acute phase and the convalescent serum just lit up the colony. It was so bright you could hardly stand it, it was very difficult to look at them with the microscope. It was just like fireworks. So, we established that and then we really went to down and we had an organism and we

So, at that point, we said, “Well, if we have this very important mycoplasma that has been associated with disease, the lower respiratory tract of humans, there have to be others, there can’t just be one mycoplasma, so we spent a fair amount of time trying to find other, identify other virulent mycoplasmas that were important in human disease and we couldn’t find a single one. We discovered a lot of, a number of mycoplasmas that just sort of sit around in your mouth and various parts of your body, but they don’t cause any disease.

PD: Okay.

RC: So we stopped. So, by 1968, 1970, we were out of the mycoplasma business.

PD: But, as you said before, you had a definite path to follow based on the discoveries you had made since the 1960s.

RC: In 1962, ‘63, yes. And then with RS, of course, respiratory syncytial virus and parainfluenza and the adenoviruses, we spent a lot of time defining how they behaved in human populations. That was obviously a first step. You had to know how the viruses behaved if you wanted to develop a vaccine against them. You have to know who needs vaccine and what are the, what protects the host, following recovery from an infection. Which of the immunologic responses are most important in providing, you know, long-lasting

protection, resistance and so forth. And so we did a lot of viral immunology and we really

felt we knew the most important things that were required for intervention and then we started.

Well, the first intervention was the adenovirus vaccine. That was back in the '63, '64, we discovered that, well, the inact, there was an inactivated adenovirus vaccine that was developed by two separate pharmaceutical companies. And they were, these vaccines were used in the military and they were protective, but they had two contaminating viruses that couldn't be removed, because one of them was a virus that was required for the adenovirus, growth of the adenovirus in monkey kidney culture. The human adenoviruses don't grow in the cell substrate that was used at that time for vaccine production, if the cultures were contaminated with a virus called SV-40 that the adenoviruses would grow. So when it was discovered that SV-40 was in the cultures, the vaccine was stopped right away. So here we had these raging outbreaks of febrile respiratory disease in the military where a 20 percent of susceptible recruits and that would be about 50 percent of the recruits lacked antibody to the epidemic adenoviruses. So 50 percent of the recruits were vulnerable and 20 percent of the 50 percent ended up in the hospital.

PD: That's a lot of recruits.

RC: A lot of recruits and a lot of disease and a huge cost to the military and so forth. So, and vaccine was required, but you couldn't use the inactivated vaccine because the only substrate that was licensed then was monkey kidney and that was because monkey kidney was a cell substrate for the polio vaccine. So, we developed a live attenuated vaccine.

PD: Right.

RC: And I think I described that before.

PD: You did talk about that before.

RC: That's selective intestinal infection, a vaccine that produces a selective intestinal infection, but the adenovirus is entero coated. It goes through the stomach and is released in the intestines, grows there, doesn't produce symptoms, induces resistance and doesn't travel back to the respiratory tract which is there it houses disease ordinarily.

PD: You did talk about that before.

RC: Yes. So we were flush at that point. We said, "God, we can do this, we can make a vaccine to everything, so we tried every other virus and it only works for adenovirus.

PD: With the entero-coated capsule.

RC: Yes.

PD: Okay, so here you are, laboratory chief. How did you stay on focus with the lab's long-standing tradition of having people pursue long-term goals instead of saying, taking a more reductionist approach to opportunities that came along with these new technological advances, how did you . . .

RC: Well, respiratory virus was the foundation.

PD: Say that again.

RC: That was, we started mainly with that. And one of the things that happened along the way is that, to, to fill in the total picture of respiratory disease in adults, we had to explain what happened in wintertime because the rhinoviruses had already been discovered in the mid-fifties. And they cause common colds. So, common colds occur very commonly in the fall and in the spring.

There 's a lot of common cold illnesses in the winter, but they didn't yield adeno, very little, very few of those illnesses were cause by paraflu, RS, adenoviruses, rhinoviruses. So to look at this sort of completely, to look at this period of time when we couldn't explain the etiology of most of the respiratory, common cold-like illnesses, we used

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PD: But even preceding them, when you said you had originally planned to be a pediatrician, well, when you thought of being a pediatrician, why didn't you just go for it?

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PD: You co-wrote with Dr. Sabin.

RC: Well, I did the first drafts. He never wrote the papers for me. He just told me what I had done wrong and what the proper procedure should be and I learned how to write papers. I learned how to analyze data and present it in a way that was used in a friendly, you know, to the reader and so forth. And it was a three-month intensive crash course in analyzing data, presenting it in a form suitable for publication and writing the paper and having it published and accepted by the *Journal* and so forth. So, between 1950 and 1952, I did work that resulted in five papers. Now, this was, you know, I was elated. I

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can do this and I enjoy it and it's more meaningful in one way and that is, if you are expert in diagnosing pneumonia and treating pneumonia, you can have a tremendous impact on the lives of maybe several hundred children. If you develop a method for preventing that disease, you will have an impact on hundreds of millions of children in time.

PD: So you were seeing the bigger picture and professional success in this.

RC: That's right.

PD: Thank you for clarifying that point. I wanted to move ahead then to 1968 when you became chief of the Laboratory of Infectious Diseases. During that year, this Institute underwent a major reorganization, which resulted, among other things, in the Laboratory of Infectious Diseases being split into the Laboratory of Viral Diseases and Infectious Diseases.

RC: Yes, it had to be split because there were over a hundred people in the laboratory.

PD: Yes, tell me how that reorganization occurred and why?

RC: Well, the reason it occurred was that Bob Huebner had done such a splendid job, had done so many important things in cancer research and had received so much money and

so much support from the Cancer Institute that the director of our Institute was embarrassed and really never presented what Bob had done in, during congressional hearings and so forth. The director was afraid that they would say, that he would be asked by the Congress, “Why is it that your foremost scientist is working on cancer? You have an Institute of Infectious Diseases. There is a Cancer Institute.” And by the time it was clear that Bob Huebner had to move to cancer, he was receiving about three times as much money from the Cancer Institute as from his own Institute.

PD: Okay.

RC: So he just moved his base of operations, but he didn’t change anything. He was able to work on a much larger scale now. So, he had a tremendous impact on the field of cancer research. I think I mentioned it in the earlier discussions. So Bob moved to Building 37, [which] was the new building devoted to cancer research that had just opened up. But we were still very close and we still saw each other an awful lot. And he helped me and he helped the laboratory. One of the things that I commented on before and that I think is very important is the varying styles of research. I was taught by a man who was a—let’s see, how can I say it—was an isolated, solitary, scientific giant. He had a very small staff. When I, when I went to Cincinnati, Albert Sabin and his technician were the only people rumbling around in this huge laboratory. He had lots of space and lots of, and I was the third person. And later that year, one or two other people came, never a large group, and Sabin did most of his work himself.

When we had his 80th birthday celebration here, I asked him, how many monkeys were used in the development of the polio vaccine, the live polio vaccine?" And he said, "Well, I counted up the number of monkeys about halfway through the project and it was ten thousand, which meant that he had used 20,000 monkeys and he inoculated every one of them himself, observed them everyday that they were alive for evidence of paralysis or a change in neurologic status of another sort and so forth. And, sometimes he would go up and make rounds, as you would in the hospital where the doctor looks at the patients and evaluates them in the hospital. He made rounds once or twice a day on all the monkeys that were in residence then, after he inoculated the animals. He didn't trust anybody else to do them. He read the slides. Each monkey was autopsied and he did quite a few of the autopsies himself and then the central nervous system tissue was fixed and [formed] and many sections were taken. He read those sections. He had trained himself to be a neuropathologist. He wasn't trained.

PD: So he was very much his own person.

RC: His own person, yes, and he really did most of his work himself. Now the project that I worked on was not polio at all. It was something quite different. It was arthropod borne encephalitis viruses, which we now call flaviviruses or alpha viruses. So there's this isolated scientific giant. And then when I come here, Bob Huebner was probably the paradigm for an entrepreneurial scientist. He had a big laboratory, people worked

harmoniously. He designed very, you know, very grand scale, the protocols in such a way that there were checks and balances and controls that were included.

Certain things were done blind. There was a number given to a material and then it was tested and until the tests were over, nobody knew what number one was or number two or number three, So there were all sorts of controls. He had a hundred people in the laboratory when he left because he was a great entrepreneurial scientist. He was extraordinarily successful in interacting with other people, with energizing them, with, you know, stimulating them, but not directing them, you know, to, right down to the last level of control. He read the data and interpreted it. If there was something wrong, it was repeated, but he didn't do much himself.

PD: Okay.

RC: He was just, he had great, he was very daring, very courageous. He took huge leaps way beyond the distance that any other scientist I know, would ever, you know, attempt to attain. And he just made huge leaps and sometimes, many times, he fell flat on his face, but when he succeeded, it was spectacular, you see.

PD: So they were opposite in their approaches.

RC: They were as opposite as opposites can be.

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RC: Yes, or the avian viruses in Hong Kong, you know, that are struggling to gain a foothold in people. They've infected people, but the virus hasn't spread to other people, but a couple of mutations more and they may be able to and then we'd have a worldwide pandemic like 1918. But you could respond more rapidly with this reassortment strategy than you can by making an inactivated vaccine, because if you make, you'd have hundreds of doses or thousands of doses, you know, in a little tissue culture tube that you could use. But an activated vaccine takes a lot of a lot of eggs.

PD: Which brings me to my next question, which is how do you choose to look toward a live virus vaccine or attenuated?

RC: Well, you have to look at the, it's disease-specific. With hepatitis-B, we're never going to have that, or we're not going to have that for, in the first place, we can't grow the virus and in the second place, it would be too dangerous to use this technique for viruses that produce persistent infection. HIV is an example. In other words, use of an inactivated vaccine has sort of been ruled out of court because if you have a virus that's in the genome forever and mutation occurs at a high, with high frequency. You could actually change, and the attenuated virus can become virulent because it's there for life, you see, it's got a long time for. You can wait a long time for that right mutation to come out because its DNA is integrated into the wholesale genome. And hepatitis-B would be like that and C is also a chronic infection. It's even more chronic than hepatitis-B, probably won't have an attenuated vaccine, but we have an acute infection and very good

PD: And yet, you learned at the knee of both of them.

RC: Yes, well, there are times when you want to do it yourself and there are times when you want to have the whole group do it. So in the earlier studies, I did most of the work myself. But very soon, it wasn't possible to do this because we had so many things working well. So I had to learn to become entrepreneurial, too. But the lessons I learned with Albert weren't lost, you see.

PD: You just brought them here.

RC: Yes.

PD: So, go on more about the split, in 1968.

RC: Well, Wally Rowe was a section chief and I was a section chief. Wally Rowe was an extraordinarily fine scientist. He and Bob Huebner were here before I came, you see. And Wally and Bob discovered the adenoviruses and defined what they were, what they did, who was infected, and who was affected by them and what the consequences of the infection were, the epidemiologic patterns of spread and epidemics and so forth. And Wally also discovered the cytomegaloviruses and was just a, he was real giant. And so the lab was split into two parts because Wally wasn't into entrepreneurial science at all

and I was sort of halfway into entrepreneurial scientists at that time. But I was, the laboratory just kept moving along.

PD: So that was what the split was about. They simply needed to reassign things.

RC: Well, we had a hundred people. I mean to go from four or five people to a hundred people for me just wasn't possible.

PD: So you, you stepped into the shoes of Dr. Huebner.

RC: Well, into one of the shoes.

PD: That was a big shoe to fill.

RC: Oh, God, yes.

PD: How were you tapped?

RC: Well, the scientific director, John Seal, who was a navy captain, he was head of NMRI across the street, Naval Medical Research Institute at the Naval Medical Center and he was a navy captain. He was the founding commanding officer of the NMRU, that's Naval Medical Research Unit, in Egypt. And I think he was in charge of a much larger

unit at Great Lakes. When he retired from the navy, he was tapped to become the scientific director and he was wonderful. And he made the choice.

PD: How did this splitting affect the laboratory?

RC: Well, Wally Rowe was interested in chronic infection and we were interested in acute infection so there wasn't any, I mean, we weren't competing in any area, but we, you know, cross-supported each other. So it went fine.

PD: Okay, it was an obvious way to deal with the growth of the work that was in here.

RC: Neither one of us was Bob Huebner. A hundred was quite, I mean, right now, we have about eighty people in the lab.

PD: It was bigger then.

RC: Well, it would have been a hundred and sixty if it had been doubled, you see.

PD: So tell me how you pursued this new mission as laboratory chief. Did you have latitude to determine the lab's future course? Was that predetermined?

RC: Well, the course was really set by the successes we had before 1968. We had already discovered most of the important respiratory track viruses that caused disease, you know, in the lower respiratory tract that hadn't been known before 1950. In other words, the first half of the century, the only respiratory path pathogens were the influenza viruses. That's all there was. It was either influenza or nothing. And a lot of, as I mentioned earlier, there was a lot of disease that just couldn't be explained by influenza, a tremendous amount, so we filled in that big void, respiratory syncytial virus, the most important virus in early life, parainfluenza viruses, type 1, 2 and 3; crew bronchiolitis pneumonia; and then there was the mycoplasma pneumoniae, which everyone thought was a virus.

It was called the primary atypical pneumonia virus of Eaton, Monroe Eaton, but studies that we did in Marine Corps recruits at Paris Island indicated very clearly that the agent that caused that atypical pneumonia, it was atypical, it was called atypical because it wasn't pneumococcal pneumonia, where you have, you know, high temperature, sweats and either die or you recover in four or five days, you know. This is a pneumonia that goes along for along time and causes a tremendous amount of debility—weakness, fatigue, and so forth. But you don't die from it, you just drag yourself, your body around and you just can't function. And in the military, that's very bad. So, when we found that there were many, there was a very high incidence of Paris Island recruit training center for [greens], we went down, we set up a big study and we studied the epidemiology of the disease.

And, finally, we did a controlled study of tetracycline as a therapy in this disease. There had been anecdotal reports that tetracycline was beneficial and would terminate the disease manifestations and would terminate fever and x-ray changes and, in other words, fatigue, all the symptoms and signs of the disease resolved very quickly after tetracycline. And we, we studied maybe four or five hundred consecutive cases and it was clear that tetracycline was beneficial, very, very beneficial therapeutically. So it wasn't a virus because viruses don't respond to antibiotics. So we worked very hard and we were able to recover mycoplasma and it was called, we called it mycoplasma pneumoniae and we grew it. We were able to grow it in broth and artificial media, agar or broth, and we used the organism in, that we could grow artificially in serologic tests where we tested the serum from patients with atypical pneumonia very early after diagnosis and again, much later to see if there was a development to see if antibodies that were specific for the mycoplasma developed in convalescence and they did.

We were able to take the colonies of mycoplasma pneumoniae and transfer them to a slide and then add to one slide the acute phase serum and convalescent phase serum to another slide and then do immunofluorescence analysis where you determine whether the antibody, that is, the immunoglobulin sticks to the colony or is washed away when you wash the slides and it was just night and day. There was no antibody in the acute phase and the convalescent serum just lit up the colony. It was so bright you could hardly stand it, it was very difficult to look at them with the microscope. It was just like fireworks. So, we established that and then we really went to down and we had an organism and we

had tests that would tell us whether people got infected and we could isolate it in certain types of media and auger and so forth. And we did epidemiologic studies and then we decided we would try to make a vaccine.

And one of the discoveries that was made here by a technician and the description of an award that was given to him for “growing mycoplasma pneumoniae on glass” was very critical to our efforts to develop a vaccine. In other words, we had huge bottles and he determined that if you cultivated the mycoplasma in these huge bottles, they were about this long and about this wide, under special conditions, the mycoplasma stuck to the glass and then all you had to do was wash the huge bottles many times and you had pure organisms on the glass and all you had to do was scrape them off and then you had something that could then be inactivated by formal and used as a vaccine. So a vaccine was developed and tested in the Marine Corps recruits and it was only 50 percent effective. And that’s not good enough.

It would be good enough for HIV, but since we could treat with tetracycline, we felt it wasn’t worth going ahead with an attempt to make a better vaccine, develop a better vaccine. So, we actually identified this, the agent of atypical pneumonia. We described how it behaves in different populations. It turns out that about, it’s the most important cause of pneumonia in older children and young adults. And, of course, recruits are young adults.

So, at that point, we said, “Well, if we have this very important mycoplasma that has been associated with disease, the lower respiratory tract of humans, there have to be others, there can’t just be one mycoplasma, so we spent a fair amount of time trying to find other, identify other virulent mycoplasmas that were important in human disease and we couldn’t find a single one. We discovered a lot of, a number of mycoplasmas that just sort of sit around in your mouth and various parts of your body, but they don’t cause any disease.

PD: Okay.

RC: So we stopped. So, by 1968, 1970, we were out of the mycoplasma business.

PD: But, as you said before, you had a definite path to follow based on the discoveries you had made since the 1960s.

RC: In 1962, ‘63, yes. And then with RS, of course, respiratory syncytial virus and parainfluenza and the adenoviruses, we spent a lot of time defining how they behaved in human populations. That was obviously a first step. You had to know how the viruses behaved if you wanted to develop a vaccine against them. You have to know who needs vaccine and what are the, what protects the host, following recovery from an infection. Which of the immunologic responses are most important in providing, you know, long-lasting

protection, resistance and so forth. And so we did a lot of viral immunology and we really

felt we knew the most important things that were required for intervention and then we started.

Well, the first intervention was the adenovirus vaccine. That was back in the '63, '64, we discovered that, well, the inact, there was an inactivated adenovirus vaccine that was developed by two separate pharmaceutical companies. And they were, these vaccines were used in the military and they were protective, but they had two contaminating viruses that couldn't be removed, because one of them was a virus that was required for the adenovirus, growth of the adenovirus in monkey kidney culture. The human adenoviruses don't grow in the cell substrate that was used at that time for vaccine production, if the cultures were contaminated with a virus called SV-40 that the adenoviruses would grow. So when it was discovered that SV-40 was in the cultures, the vaccine was stopped right away. So here we had these raging outbreaks of febrile respiratory disease in the military where a 20 percent of susceptible recruits and that would be about 50 percent of the recruits lacked antibody to the epidemic adenoviruses. So 50 percent of the recruits were vulnerable and 20 percent of the 50 percent ended up in the hospital.

PD: That's a lot of recruits.

RC: A lot of recruits and a lot of disease and a huge cost to the military and so forth. So, and vaccine was required, but you couldn't use the inactivated vaccine because the only substrate that was licensed then was monkey kidney and that was because monkey kidney was a cell substrate for the polio vaccine. So, we developed a live attenuated vaccine.

PD: Right.

RC: And I think I described that before.

PD: You did talk about that before.

RC: That's selective intestinal infection, a vaccine that produces a selective intestinal infection, but the adenovirus is entero coated. It goes through the stomach and is released in the intestines, grows there, doesn't produce symptoms, induces resistance and doesn't travel back to the respiratory tract which is there it houses disease ordinarily.

PD: You did talk about that before.

RC: Yes. So we were flush at that point. We said, "God, we can do this, we can make a vaccine to everything, so we tried every other virus and it only works for adenovirus.

PD: With the entero-coated capsule.

RC: Yes.

PD: Okay, so here you are, laboratory chief. How did you stay on focus with the lab's long-standing tradition of having people pursue long-term goals instead of saying, taking a more reductionist approach to opportunities that came along with these new technological advances, how did you . . .

RC: Well, respiratory virus was the foundation.

PD: Say that again.

RC: That was, we started mainly with that. And one of the things that happened along the way is that, to, to fill in the total picture of respiratory disease in adults, we had to explain what happened in wintertime because the rhinoviruses had already been discovered in the mid-fifties. And they cause common colds. So, common colds occur very commonly in the fall and in the spring.

There 's a lot of common cold illnesses in the winter, but they didn't yield adeno, very little, very few of those illnesses were cause by paraflu, RS, adenoviruses, rhinoviruses. So to look at this sort of completely, to look at this period of time when we couldn't explain the etiology of most of the respiratory, common cold-like illnesses, we used

organ culture to search for these agents. And this had been done successfully in England.

One virus had been recovered. And organ culture is a slice of tissue that is maintained in its normal, structural configuration and a tissue which functions exactly the way it does in the body in culture was used.

Now it was very simple. We took tracheas and just cut them and then we had a circular ring and in the center were the epithelials. In the center, you had the lumen of the trachea and there were cells that were ciliated, had little hairs and these little hairs were moving all the time. So all you had to do was look for ciliary in motion and if you put a material, if you inoculated a material into a culture where the cilia were beating and after a couple of days they stopped beating, this suggested there was something there that could be a virus.

So using this sort of an approach, we were able to recover several new viruses. And they were, they turned out to be corona viruses. It's another group of agents that, at that time, were known to be very important in diseases of animals, but not in people. The British group had isolated one corona virus. They had determined that their virus was a corona virus. We had three or four here that were corona viruses and then at the University of Chicago, Dorothy Hamre isolated another one, directly in, in normal type of tissue cultures, so we had three different groups and it really turned out that ours, our viruses and the British viruses were the same so there were really two subgroups of corona viruses, extraordinarily difficult to recover. But once you have a virus like that, you try

organ culture to search for these agents. And this had been done successfully in England.

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to tease it into, you try to fit it into or you try to make it grow in the usual types of culture that you use in the laboratory.

So the corona viruses here, we isolated here, were adapted to cultural ultimately. It took a couple of years and then we were able to do serologic tests and, yes, indeed, corona viruses are very important in the winter period, the period between fall rhinovirus excess and then the spring period where, interval there where rhinoviruses are of major importance. So we filled in this void collectively, the British group, the University of Chicago, Dorothy Hamre, and the work we did here.

PD: Dorothy Hamre? H-A ?

RC: H-A-M-R-E.

PD: Okay. Yes. And then the British group was at Salisbury, England. This was the Common Cold Research Unit in Salisbury. Now, following that success, there were two possible routes to travel. No one had ever isolated a hepatitis virus in the laboratory and, second, no one had ever isolated a virus that caused gastroenteritis.

RC: So we set up cultures of an intestine. Now the intestine is mobile, instead of having cilia-beading in the center? See, it's something like this. This is a cross-section of a trachea and then these cilia-beading.

PD: Right, it's like a ring with little hairs on the inside of that don't . . .

RC: That's right.

PD: Yes.

RC: So, with the intestinal organ cultures, you can't do that, so what you do is you look for mobility.

PD: And when was this when you studied?

RC: Well, this was back in the late sixties. So, in order test organ cultures, you had to have materials that came from or were recovered from patients and had a very high probability of containing an agent. And in some cases, you could verify that the material that you were going to test in organ cultures contained an agent was to do volunteer studies. So, this approach then, was, consisted of two parts. With gastroenteritis, we looked for evidence of a filterable agent that caused acute gastroenteritis. The hepatitis group program started with Bob Purcell.

When it was very clear that there was an awful lot of hepatitis around, and studies that Saul Krugman had done, the man, you know, Albert Sabin's cousin, indicated that there

were at least two different hepatitis viruses because hepatitis was rampant in the institution for children who were mentally compromised, Willowbrook, an institution in New York, and children who came. Every child developed hepatitis when they came in because they were throwing feces around, you know, and these were children who were really compromised so a child would come in, develop hepatitis and, six months later, another case of hepatitis.

And so it was very clear that there were two agents that were circulating. One had a very short incubation period of 30 days and the other a longer incubation period, about 90 days. So, what sparked my interest was the fact that, well, was the fact that there was a very high frequency of post-surgical, cardiac surgery hepatitis in the clinical center. Patients who were operated on received a lot of blood at the time of operation, 22 units in some instances, so their heart valves were replaced and all this sort of thing. They get well, and then 90 days, 100 days later, they'd come down with hepatitis. And it was very, very frequent.

At that point, my next-door neighbor, our neighbors across the street, were the Braunwald's, Gene Braunwald and Nina Braunwald. We were very good friends and they lived right across the street from us. And Gene was the Clinical Director at the Heart Institute, and Nina was the Deputy Cardiac Surgeon. She was the first female cardiac surgeon certified anywhere in the world. So Nina did the surgery and Gene Braunwald did a number of, was involved in a number of research projects, brilliant

fellow, absolutely brilliant. Subsequently while they were, we were sort of across the street from each other for about seven or eight years and then he went to, he and Nina went to San Diego and he was the Founding Chairman of the Department of Medicine at the new University of California Medical School at San Diego, UCSF, no, no, UC?

PD: UCSD.

RC: SD? University of California at San Diego, yes. And after about seven or eight years, he was tapped to be the leading professor of medicine at Harvard and he was the Chairman of Medicine at Brigham, Peter Bent Brigham.

PD: Peter Bent Brigham, up in Boston?

RC: Yes. And Nina was in the surgery department. And he became, his book on, *The Textbook of Cardiology* is THE book. He retired from the Brigham and he's now in charge of what's called "The Partners," the Brigham and Mass General, you know, the two crowns in the jewel of the Harvard Medical School, probably in the United States. These are the two leading hospitals, the Brigham and Mass General. They've come together and he's head of "The Partners," these two schools.

PD: Wow! So you were talking about the link between the cardiac surgery and the hepatitis.

RC: Yes, I wanted you to understand what a fantastic fellow Gene Braunwald was, and his wife as well. So, Nina, we used to swim together in the summer at a community pool. And every Sunday, we would spend an hour or two in the water. We'd swim and then we'd talk a lot. And Nina kept saying, "I'm so frustrated. We operate on individuals, we put in new aortic valves and everything is great and then they come down with hepatitis." And I said, "Well, that's interesting. Would it be possible to set up a surveillance? Bleed these patients before they're, before they're operated on and then bleed them later in a prospective manner so we had serum before surgery and then after surgery, you know?"

PD: Hold that thought. I'm going to turn the tape.

[End Tape 1, Side A]

[Begin Tape 1, Side B]

PD: Okay, so you're talking about . . .

RC: So now we have a systematic collection of serum from patients who were operated on by the cardiac surgeons, was initiated, the program was initiated. And we had, we assigned one of our epidemiology nurses to just drive anywhere within a hundred miles and collect

the appropriate specimens. These patients were bled every month or two over the period of about a year.

PD: And, again, when was this, around?

RC: This would be probably in, in the late sixties.

PD: Okay.

RC: So, we had material, but, the only test that could be done at the time was hepatitis-B the Australia antigen. So the early specimens were tested for hepatitis-B and that was all that was available. And then when it was recognized that these, that this test detected hepatitis-B infection, the blood supply became, was then cleared of, the threat of hepatitis-B was removed because all of the units of blood that were given at surgery were first tested for evidence of hepatitis-B and only those that lacked hepatitis-B antigen were used, so hepatitis-B was eliminated as a source of hepatitis in post-surgical times. But, when hepatitis-B was removed, there was still an awful lot of hepatitis left, see.

PD: And this was what you were trying to find out more about.

RC: That's right, and we succeeded. But now I'm going to go back to gastroenteritis. At that point, Bob Purcell switched from mycoplasma, he was working on mycoplasmas from about 1963 to about 1967 or '68. Now, with gastroenteritis, the situation was different.

There's a condition known as non-acute, non-bacterial gastroenteritis, gastroenteritis which does not yield a cultivatable pathogen—cholera. We don't have cholera around here. You know, shechylosis, all of the bacterial pathogens are used to, have been used extensively to try to identify the etiology of acute, non-bacterial gastroenteritis. Usually, it's epidemic. The setting in which this disease occurs is very simple. Water-borne, we know it's water-borne because outbreaks occur in camps, in various swimming pools. They occur when groups get together. They are often food-borne. If you have 500 people and you go to a banquet and half of them come down, and you say, "Did you have this, this and this?" And you can actually localize it to a specific food, you see. So, food-borne, water-borne, mollusk, . . .

PD: Really!

RC: Mollusk-borne, clams, oysters.

PD: Okay.

RC: So, in a monograph called "Illness in the Family,"—I don't think I've got it here right now, that came from Western Reserve Medical School. This is long-term surveillance of about 500 families, the most common cause for seeking medical help, acute respiratory tract disease, which is what you'd expect. But 15 percent of all visits to a physician are because of acute non-bacterial gastroenteritis. It goes through the family. It goes

through, you know, institutions and so forth. And so, we said, people don't die of this and they get awfully sick. And the incubation period is about one to two days at the most. The disease lasts for about two to three days. And when it hits, you feel like you're going to die, you're so sick. You must have had this.

PD: Probably. I've blocked it out.

RC: It's very, well, if you've had it, you remember it. On the first day of illness, you think you're going to die. On the second day of illness, you wish you would die, you're so sick and then the third day, you're recovered. So we obtained materials from various outbreaks from CDC and there was one outbreak that was particularly enticing. This was an outbreak of acute nonbacterial gastroenteritis in a school population, Norwalk, Ohio—not Connecticut, Norwalk, Ohio. Fifty percent of the children were hit. The epidemic curve was like this, wwhett!.

PD: Fifty percent.

RC: But 50 percent of the teachers also came down and 50 percent of the parents of those living in the home. This was multiple, this was really very, very exciting. So, we obtained materials, stool filtrates, no fecal swabs from that outbreak that had been collected. We put them through a filter so that there was no, bacteria couldn't pass and we did extensive safety tests looking for any virus that could be detected at that time. And we couldn't, there were no viruses. We had excluded bacteria. We then fed this to

volunteers and two of the first three volunteers developed acute bacterial gastroenteritis, so we had something that had the infectious virus in it and we used this stool then, we could pass this from volunteer to volunteer. It was a transmissible agent. And the first, the first three volunteers came from a college, Kuhka College from Upper New York.

PD: Kuhka?

RC: Kuhka. And there, the students have to do community service and many times, the students came down and volunteered to be subjects in the clinical research protocol. So we . . . this was done in the Clinical Center on the eleventh floor. Walked into the room on the second day and there were three students, three ladies lined up in three beds. But the room had really, had been built to handle two beds, but there were three beds in parallel. And we gave, we had a big volumetric cylinder, which is something like this, that would hold about two liters, because when you vomit, sometimes you vomit a tremendous volume, so and we walked in the room and it was very clear what had happened, the first bed and the third bed, the volumetric cylinder had a lot of fluid in it. In the middle, there was nothing. So we walked in and the two students who had gotten sick were beaming. They had succeeded and the young woman who was in the center was crying because nothing happened. She failed. We hired her as a technician subsequently. She was in our lab for about eight years. She was terrific.

PD: Wow!

RC: And that was the beginning, you see, now we know, we knew we had the virus. Now we have to develop a system to detect it. So, we did other studies very quickly. We took the stools from the positive, from the two students who became ill and we then went through the same regime, we emulsified and made a filtrate and then safety tested it to be sure there was nothing that you could detect, no bacteria and all that sort of thing. And we could pass it, you know, from one volunteer to another. And the illness was the same illness that occurred in the Norwalk School outbreak. So now we had an agent of nonbacterial gastroenteritis. We couldn't see it. We couldn't cultivate it. We did the organ cultures. It didn't work. But, what did work was electron microscopy. Oh, gosh.

PD: Which was recently?

RC: Oh, this was 1972.

PD: Okay. And so, how long had that technology been around?

RC: Well, it had just been developed. I wish I had a . . . I'm going to have to get in here.

PD: Okay, do you want me to pause for a minute?

RC: Yes. Sure. It was *Field's Virology*.

PD: *Field's Virology*, Third Edition.

RC: Yes.

PD: And there's a chapter in here . . .

RC: On the Norwalk group of viruses.

PD: Okay.

RC: They got the name from the fact that the first of the group came from Norwalk outbreak.

PD: In Ohio.

RC: In Ohio, yes. So here it is and here's what happened. Dr. Kapikian looked very hard and very long in an attempt to identify an agent in the stool. It didn't, the filtrates didn't grow, it didn't prove a demonstrable effect on any of the cultures that were available, organ cultures, regular cultures, you know, couldn't grow. It still hasn't been grown.

But the way it was discovered was the stool, the stool filtrates were used in the search for the agent using the technique of immune electron microscopy, which means that you have a, you don't have a virus that you can identify straight out just by looking at the

filtrate, but you add to the filtrate, serum collected in the acute phase of illness or before illness and then serum collected later where you would expect to have an antibody for the agent. And that's exactly what happened. It took him six months to visualize this by immune electronic microscopy. For example, well, there are a lot of pictures in here. Let's see, and everything we know, everything we knew about this for many years really came from studies with immune electron microscopy. It was a back breaker.

PD: How did it transform the field?

RC: Well, it identified the agent.

PD: Okay.

RC: So here's a clump of Norwalk virus particles that were held together by small, by antibody. You can see that.

PD: That's what's linking them?

RC: Yes.

PD: They almost look like snowflakes.

RC: Clump, clump, well, these are the particles and, you see, between them, there's a little strand and that's the antibody that links the two viruses together.

PD: Okay.

RC: So, with this technique then, two things were possible. One was you could identify the agent in stools of volunteers who had been infected and become ill or in patients who were involved in an outbreak. So it, the amount of virus is not very large so it takes a long time to look through a stool to be certain that the particles aren't there. If you have the particle and if you know what the particle looks like and you have serum that defines its existence, serum from an individual before infection, no antibody, serum after, lots of antibodies. And the antibody actually sort of concentrates the virus into clumps like this, you see.

And if you have a clump, you have antibody, but you also have the virus. So if you use antibodies from other patients who were known to have been infected, you can then look at specimens that have just been received to see if the virus is there. So, you have a way of identifying the virus and you also have a way of detecting an antibody response. So, using IEM, which is a back breaker, as I mentioned before, it was possible to identify three or four different groups of Norwalk-like agents and to link them to the outbreak from which they came. And it was possible to do some very simple biophysical tests where the in-point was always IEM. Later, it was possible to use materials from stools

that represented antigens that had moved, that had come from virus, in other words, degradation products and so forth in the serologic test, like and ELISA test.

PD: Liza test?

RC: E-L-I-S-A.

PD: Okay.

RC: And that's a specific serologic test. So ELISA tests were developed and so forth. And it was possible then to sort of get a pretty quick idea of what the epidemiology of this was, what proportion of individuals had antibody, what, how, how did antibody develop? What was the development of antibody? The pattern of the development of antibody in different populations, and so forth? So, this is, here are the two, the first two volunteers.

PD: Right. That chart is showing their . . .

RC: Their symptoms, yes. Now, this virus can cause vomiting, it can cause diarrhea or both.

PD: Okay.

RC: So, this patient had mostly vomiting here and this patient had mostly diarrhea, see. Eight stools, vomited 20 stools, had 8 liquid stools.

PD: In how long a period?

RC: Just in the second and third day.

PD: Oh, my.

RC: So, now, this is an aggregate with the volunteers, pre-challenged serum. See, the particles are separate. Here are particles that are just covered with antibodies. See that halo around?

PD: Yes.

RC: Those are antibody molecules. So, now, finally, after many years, it was possible for two groups to clone parts of the virus. There's so little of it, it was very hard to find enough R&A in the specimen. But a group at Baylor and a group at Stanford were able to clone parts of the virus and, finally, the total sequence was known and then it was clear that this was a calicivirus.

PD: Calici.

RC: Caliciviruses were only known as animal viruses at that time. San Miguel, Sea Lion, there are a whole series of animal diseases that are caused by calicivirus, but this was the

first human calicivirus, the Norwalk. There are now about eight or ten different serotypes. And when all of these viruses, now, you see, once you have the DNA sequence, you can express the various antigens so the serologic tests now are just, you know, falling off a log. Do you understand?

PD: Yes.

RC: You have the DNA. You express the protein that's on the cover, that represents the covering of the virus and you use that in the serologic test and ELISA test and whatever else. And you just whiz through an outbreak. And when you want all the outbreaks of gastroenteritis, that is, outbreaks in which bacteria were not implicated, 95 percent are caliciviruses.

PD: Stunning.

RC: Yes, but they still have not been cultivated. This is since 1972. Still working hard. We've never been able to grow it in a tissue culture.

PD: What are the . . . ?

RC: We don't know.

PD: Okay.

RC: So, there you go. Now, . . .

PD: You're going to link this with the hepatitis?

RC: Yes.

PD: Okay, great.

PD: It's a very direct link. Now, you come to hepatitis. Here we have hepatitis-B defined by the Australia antigen test. That's the surface-like covering, the protein that covers the hepatitis virus is called the Australia antigen. It was discovered serendipitously, nobody knew what it was. They thought it was a genetic marker of some sort. It was a protein that was present in serum. And it's the coating of the virus that comes together and it sort of makes a little particle of its own and that was the Australia antigen. So you use that in a complement fixation test and an ELISA test and you can determine whether a person has had hepatitis-B.

PD: Okay.

RC: So it detects antibody and if you detect the particle in their serum, that means that they're infected. Now, when hepatitis-B was eliminated from the blood supply, there was still a lot of hepatitis in this cardiac study. So, at that point, everybody said, "Well, that's

hepatitis-A, that's the short incubation hepatitis, you know, that Saul Krugman had established at Willowbrook. So there was B and there was A. Nobody knew what A was. They just knew that it was a short incubation. So Kapikian and Purcell looked at specimens from volunteers who had been studied during World War II and had been given the short incubation hepatitis, which has essentially no mortality associated with it. It's an acute disease, just knocks the hell out of you and you're debilitated for a month or so.

PD: A month?

RC: Up to a month, . . . really, you just can't do what you would like to do. So, but nobody knew what this virus was. It was a clinical insight that had caused . . . It was a short incubation period and it generally was involved in food, could be food-borne or water-borne, based on epidemiologic studies. So Al Kapikian and Bob Purcell and Steve Feinstone looked at specimens from volunteers and it was very fortunate that the specimens were collected, you know, prospectively, every day and they looked for a virus using pre-infection serum and post-infection serum. And they found it. It looks just like the virus of Norwalk, but it's a picornavirus.

PD: A picornavirus?

RC: That's the class of viruses that polio and the enteroviruses and the Coxsackieviruses belong to. So, now here we suddenly have hepatitis-A and IEM, you detect the virus, IEM, you detect an antibody response.

PD: So this is in the 1970s, by now?

RC: '72.

PD: Okay.

RC: Yes. Oh, Norwalk is '72. This would be '73. Now, let's look here. Hepatitis-A, so it was discovered by IEM. Having this virus, everybody thought, all we have to do is take those B-negative cases and study them for A. Not one of the cases that wasn't B turned out to be A. And that's where the designation, Non-A, non-B hepatitis, it's not B and using the early IEM or later test based on ELISA and so forth, there was not a single case in the post-surgical hepatitis that was A. Oh, we don't have any good picture. The picture of A and IEM are exactly the same as the Norwalk, but it's a picornavirus and Norwalk is a calicivirus, but they look the same under the scope. So this meant that the hepatitis that remained after you removed B from the blood supply was not A. A third virus, that's hepatitis-C. That's how non-A, non-B was discovered, by testing for the post-transfusion hepatitis that was not B, because B had been removed and it was certified to have been removed. Of course, none of these individuals had a B response,

so now we have A, we have non-A, non-B, C. And that was cloned by the people at Kyron.

PD: Kyron?

RC: Yes, about '79 or so.

PD: Okay.

RC: And then once you have the DNA, then you can express the DNA, you can express the antigens and then develop a serologic test and all that sort of thing. So, very, very sensitive tests that were developed so you could then look at, and tests were done for A, obviously, and then A was then cultivated in tissue culture. And very, it grows very slowly, a very fastidious virus. Okay, so now we have A. We've seen it, recovered it in culture; B has not been recovered in culture, but there's tons of it in patients who were chronically infected and it's also cloned and the DNA is expressed, you know, so you have purified antigen, which is the vaccine. Now, you've got C and most of the leftover hepatitis is C, non-A, non-B.

And that's been very, there is no vaccine yet. It's a very tough virus. It has not been grown yet. B has not been grown yet. A has been grown, but not B or C, but the vaccine for B works. It's beautiful. It's the surface antigen expressed in yeast. In other words,

the DNA of the surface antigen is introduced into yeast and as yeast grows, it produces this antigen. So, what's exciting is that hepatitis B vaccine has almost eliminated liver cancer in the Far East. Worldwide, the two most important cancers are cancer of the liver and cancer of the cervix, which is caused by a papilloma virus.

PD: Right.

RC: Now, the, an effective vaccine for B has, at least in Taiwan, eliminated liver cancer and I think cervical cancer will be eliminated by immunization, but in the United States, pap smears sort of handle that. But these tests are not done in developing countries.

PD: Not regularly, the way they are here?

RC: Oh, no. No. So, a vaccine for the papilloma viruses is going to take care of that. So, when you come down to it, the two most important cancers are caused by virus, but not in the way that people thought in the beginning.

PD: When they were originally trying to link viruses with cancer?

RC: Yes, the DNA viruses that came from rodents and so forth, see, that paradigm is not the paradigm. The paradigm here is hepatitis B causes a chronic infection and from that, something happens and you have cancer. And the same for papilloma. So, now, being

able to grow it in suitable cell substrate meant that it was possible to develop a hepatitis-A vaccine and there are two vaccines that have been developed. The first one licensed was the one that came from this lab, Bob Purcell and Sue Emerson and Smith, Kline and French, Smith Kline Beecham in Belgium. So it's an inactivated vaccine and it works. So you can, you now have a vaccine for A, you have one for B. You don't have one for C unfortunately, yet. Now, there's D and that was discovered here also by Bob Purcell and a visiting scientist from Italy, let's see, he ought to be in here. D is a virus that, it's a defective virus.

In Italy, there was a pathologist, whose name I'm trying to come up with here. I can't understand why it's not in. Hepatitis-Delta, okay, 2-8. Hepatitis-D was called the, it was originally called the Delta antigen. It was discovered in the livers of patients who had hepatitis B and these were often individuals who had much more severe hepatitis than usual. Mario Rizzetto was the gastroenterologist who recognized a nuclear antigen in the liver cells of patients who had chronic hepatitis-B, but who were sicker than individuals who didn't have this antigen. And nobody knew what the antigen was. So, Mario came and spent a couple of years here working with Bob Purcell and by using quantitative, methods of quantitative virology, they were able to show that hepatitis-D was a defective virus that would only grow in the liver of an individual who was infected with hepatitis-B. In other words, this virus was not a complete virus. It lacked something and that something was supplied by the hepatitis-B. So only patients with hepatitis-B virus support the replication of this defective virus.

PD: Okay.

RC: Now, what's interesting is that this virus is extraordinarily small and it's more like a plant virus group. The group is, the viruses in that group are called viroids. They don't have a large enough genome to be self-sustaining. They have to infect something, a tissue that has another virus that will provide what is lacking in that virus. So, by studies in chimps, during studies in chimps, they were able to show that when they diluted the serum of a chimpanzee that had hepatitis-B and D, they diluted it and diluted it to the point where there wasn't anymore hepatitis in the recipient animals. In other words, they would take a, they would dilute it to one to ten, one to a hundred, one to a thousand. And the recipient chimps would develop hepatitis. But then, if they went beyond that, there wasn't any hepatitis. That's because there wasn't any B. The B had been diluted out, but when they took the higher dilutions, now, that did produce hepatitis and inoculate them into a chronically-infected hepatitis-B chimp, D developed, see. So just by quantitative virology, it was possible to show that this was a defective virus that required D for its growth.

PD: Brilliant.

RC: And that's where D is and D, when D occurs in a B patient, the disease is more severe. You don't need a vaccine for this because if you prevent B, there's no D. D can't occur,

see. So we now have vaccines that are effective for A, B, and, of course, with the B vaccine, you prevent D.

PD: Right.

RC: You need B for D.

PD: So you have them for all but C so far.

RC: C so far. Now, the next virus group, so you see how all of this sort of came out of studies initially looking for previously unrecognized respiratory viruses, the recognition of Norwalk by IEM and then the application of IEM to the search for hepatitis-A and so forth. Now, the latest virus that's come along is hepatitis-E and this, there have been really tremendous outbreaks of hepatitis in Asia that are associated, that occur after a monsoon when the river beds, river bed is diverted, rivers are diverted into new river beds and so forth, and the water that's supposed to come out of the water purification plant is replaced by sewage because, in other words, the water supply is just totally contaminated. It's water borne and they, these large outbreaks, hundreds of thousands of people. Everybody said, "Well, it's hepatitis-A." Wrong. It isn't. And Bob Purcell sent Doris Wong, who you met out here, over to India and she collected a number of materials there from these outbreaks which had been studied epidemiologically, but not

successfully etiologically, brought them back here and none of them were A so they were E.

PD: Because it was something you hadn't seen?

RC: Hadn't seen it before. So a Russian scientist actually studied this and he gave himself a filtrate and he got sick, very sick and then he saw the particles. Now, Bob Purcell and Sue Emerson have studied E by developing an animal model. There are certain monkeys who develop hepatitis when they receive E and they have used recombinant DNA to express a surface antigen of E and they were able to protect against hepatitis-E. So hepatitis-E vaccine is in the works and it has been tested in monkeys and chimpanzees and it prevents hepatitis. It's being tested in people now. And when you go to the Middle East or if you go to Africa, you're at risk. It hasn't caused epidemics in the United States, but it's here. And it turns out that it's in small animals and in pigs.

PD: So all of these discoveries have happened over roughly a 30-year period in hepatitis.

RC: Yes.

PD: I was wondering if we could go back a little bit to a philosophy of this lab even before you became chief.

RC: But you see, Bob Purcell has worked on hepatitis for more than 30 years. Al Kapikian came in the door to building 7 the same day I did, July 1st, 1957. And he's been working, he's been working on gastroenteritis viruses since about 1968. So what does that give us, 32 years.

PD: Right.

RC: And the rotavirus project came out of the Norwalk project because then the question is are the serious diarrheas that lead to hospitalization of infants in Washington, DC caused by Norwalk viruses? Not so. But then he saw the rotavirus, which is a much bigger virus, which has a characteristic structure and is present in just millions and millions of particles, you know, in a small specimens, aliquot of a specimen. He, looking for Norwalk, he found rotavirus. Now, rotavirus was described just about six months before that in Australia. There were autopsy material or biopsy material from children with very serious life-threatening diarrhea studied by electron microscopy and there were these 70 nanometer particles. Hepatitis-A and Norwalk are 27 nanometer particles. So if you look at them, this would be Norwalk and Norwalk would look like this and this would be the rotavirus. You can just tell them apart.

PD: The rotavirus is much bigger.

RC: Much, much bigger. Yes, and there's tons of it in the stool, tons of it. So, the rotavirus program started and it led to the development of a very successful vaccine which was licensed and then was terminated by CDC, inappropriately.

PD: In 1998.

RC: Yes, and we are convinced that they are wrong because we have done other studies that show what they predicted would happen did not happen and there are no excess cases in this [acceptation] and we're in a big fight with them now.

PD: Do you want to talk about the history of that process and the discovery?

RC: Well, Dr. Kapikian will describe and why they're wrong.

PD: You're all set?

RC: Yes. So these things sort of flow one from the other and that's what I've given you, the flow.

PD: So they're not separate entities.

RC: They're not little discrete things. They represent, the project is the viruses that cause hepatitis in people. What are they? How do they do it? And how do we keep it from happening? And the same for the gastroenteric pathogens. Now, rotaviruses are the most common cause of serious diarrhea, not the two or three-day diarrhea, but serious diarrhea that has a high mortality in developing countries. About a million infants die every year in developing countries from rotavirus. A hundred thousand alone in India, one hundred thousand infants die every year.

PD: Every year?

RC: In India, yes, big time. In this country, it's about 50 to a hundred thousand hospitalizations and very few deaths.

PD: And so you were talking about how these were all linked.

RC: Yes.

PD: And how, wasn't there . . .

RC: We've never had to sit down and say, "God, what are we going to do now." I mean, it's clear what you have to do and one of the things is to know when to start something and when to stop it.

PD: Is there an intellectual and/or intuitive process by which you make those decisions?

RC: No, I think it's your, you have to be able, it's your ability to perceive when it's time to, you have to recognize when you stop and when you start. For example, we started mycoplasma after we showed that it was a very important cause of a, a very important type of pneumonia. We killed ourselves to look, to find other mycoplasmas and after about six or eight years, we couldn't, we stopped. I mean, we could, Bob Purcell could have done mycoplasma nomenclature, antigenic relationships, characterization for the rest of his life if he had a mind to.

And there are a lot of people who just do that. They just dig in. But our interest was in the agents that cause disease and we didn't want to study a lot of benign mycoplasmas, he didn't want to study a lot of benign mycoplasmas.

PD: So you take it to a point where you conclude that that is, in fact, what you would be doing if you continued and then you stop.

RC: Yes.

PD: Well, this speaks indirectly to a question that I wanted to get back to, which was this lab's long-standing practice of letting a scientist pursue a project from start to finish. And it was this way before you became chief.

RC: Oh, absolutely.

PD: And it's been that way ever since. Tell me about this process. Is it unique to this lab or to NIH?

RC: Well, I think it's a process that's very difficult to consider in an academic setting because in academia, you apply for grants and you're reviewed every year or every two years and you can't say, "Well, we haven't done anything in the last 10 years, but this is something very important and we have to stay with it because of its public health importance."

PD: But you have.

RC: And we've been allowed to do it, you see. And this is the way this laboratory has operated, you know, for 60 years.

PD: Since it's very beginning.

RC: Armstrong, yes.

PD: Dr. Armstrong.

RC: Charles Armstrong.

PD: Let me just put in a new tape and we'll continue talking about this.

[End Tape 1, Side B]

[Begin Tape 2, Side A]

RC: [Joking] And I would like to warn the listener that we don't project that this will end until 02, early in 02 [2002], early in January 02.

PD: Caveat noted. We were talking about this laboratory's long-standing tradition of having a scientist pursue a project from start to finish and I was wondering if that is unique to this lab or NIAID.

RC: It's not the common practice and the reason that this has evolved is it was very clear to Armstrong that there had to be long-term efforts, particularly involving public health, major public health problems that couldn't be solved, probably would not be solved over a short period of time. You know, there had to be continued efforts and using all of the newer technologies and newer insights that had developed in other laboratories as well as in LID. And as I mentioned before, this is the sort of thing that is almost impossible in academia. One, one example of, of a long-term project that did last quite awhile is the Illness in the Family study that was carried out at Western Reserve, families that were

studied prospectively over a long period of time and so forth. This was, actually, that study was, I think, funded by the United States Army . . .

PD: Oh!

RC: . . . because it involved respiratory disease and diarrheal disease and things that were very important in the military. But ordinarily, there was no way you could do this in a university setting. And this decision, I mean, this insight, actually, comes from Charles Armstrong and he set, he sort of set the compass, he and Bob Huebner.

PD: And was that in recognition of the fact that these kinds of intractable public health problems were going to be elusive for a long time? They could see that they would require long-term study?

RC: Yes, that's right. Yes. That's right. It couldn't be on a yearly basis or a two-year basis on a subject. You had to just go in and slosh in the trenches. And then, you slosh for a long time and nothing happens, but then, if you weren't there, when it did happen, you would feel very unhappy, very upset. So we take a, we sort of have a parochial view of the projects that, we feel that this is our virus. We discovered it and we want to stay with it, that sort of thing.

PD: So it must attract a certain kind of researcher.

RC: Well, what you have to do is give up the idea of quick gratification. I mean, if you want to have gratification, you know, on a daily basis, you work in an ER where you can bring people back to life, you know, by giving somebody in hypoglycemic shock, you give them some glucose intravenously and they sit up, you know, that sort of thing. But, you just have to delay and, the possibility of gratification. Gratification comes, maybe, after a very long period of time, but when it comes, it's like a thunderclap.

PD: And that's happened on quite a number of occasions here.

RC: Yes. But even if it hadn't, we would still be slogging along.

PD: So you have had quite a number of the scientists stay here for 10, 20, 30 years?

RC: Yes.

PD: Is there an average length of time?

RC: No, there is, many of the scientists that we would have liked to have stayed went off to academia and they're sort of superstars in medical schools and schools of public health and this sort of thing. But the people who are on-board now, most of them have been here a long time.

PD: They include yourself.

RC: Kapikian, Purcell, Murphy. I think Brian is a 30-year man now. Al is a 44-year man, like I am.

PD: He started the same day you did.

RC: The same day and he came in right out of an internship. And he wore a tie, a shirt and a tie, and he had a stethoscope, he had a lab coat with a stethoscope. Very shortly after he arrived, Bob Huebner saw him on the elevator and he said, "Al, what are you going to use that stethoscope for? Are you going to try to listen to the tissue cultures growing and so forth?" And then Al never carried a stethoscope. There was no reason to have a stethoscope in this laboratory. We work with the, with materials from patients with disease. We don't see patients directly, except when we had volunteer studies going on in the Clinical Center on the 11th floor. I wouldn't have missed the opening scene of the Norwalk story for anything in the world, walking in the room and seeing this lovely young lady crying flanked by two people who had vomited about two liters of fluid beaming. That's gratification.

PD: And a high experience?

RC: Yes, we knew we were, we knew we had it then, see.

PD: Could you describe for me a typical day in the lab here shortly after you arrived?

RC: Well, Bob Huebner often slept over because he lived 40 miles away and he would come into the lab and look, try to bum a cigarette from somebody else, take some coffee. He would do it often in his shorts. It was a very, things were very casual and very loose.

PD: Were they long days?

RC: Oh, yes.

PD: Like, so you would arrive at?

RC: Seven-thirty, eight o'clock and then leave at six or seven or something like that.

PD: Did you come in on the weekends?

RC: Yes.

PD: Do you still?

RC: Well, I work at home now. Part of, most of my job is serving as an English teacher. I correct papers. No, I edit manuscripts and chapters and all of them. That takes a lot of time, so my wife always tells her friends that I'm an English teacher.

PD: But the, the typical day as you would get here? I mean, was it all at the bench or?

RC: Well, it just varies from time to time. We spent a lot of time on the problem of the inappropriate termination of the recommendation for use of the rotavirus vaccine. Al and I are just, you know, e-mailing all over the place, telephone conferences and trying to get this thing back and the prospects look better everyday, but we just have to keep at it because the people at CDC just want to bury us. They don't want this to be discussed. They don't want anybody to know what we're doing. And it's just been a very noncollegial sort of an experience.

PD: At the Centers for Disease Control?

RC: Only, now, this is not generic, now. This is the vaccine program people, people who are evaluating vaccines for efficacy and safety and so forth. I don't want to say anything more for attribution at this point, . . .

PD: Then you don't want to discuss, . . .

RC: . . . but I think you've got the idea.

PD: Well, there's been quite a bit written about that. Do you want to talk about your participation in trying to get that, the virus back, that vaccine back on the market.

RC: Well, the problem is that they have, they don't want us to speak in public and they control the meetings and the timing of the meetings and the place of the meetings and the list of people who are invited to meetings and so forth. So we have a manuscript that is being considered now by *Lancet*. We've sent a manuscript with our new data, which we think really just turns the thing all the way around.

PD: Okay.

RC: And the other point is, you know, there are people down there who say, "Well, Dr. Kapikian, you don't understand epidemiology." Bull feathers. He was President of the Epidemiology Society, the highest honor in epidemiology. My, God, it's unbelievable. And as if we had never done anything here, they talk about this kind of thing. We did those studies 30 years ago. We defined, we actually originated a number of the technologies. They drive us crazy, well, not crazy, crazier. Okay, I don't think I want to, I should.

PD: You don't want to go on the record anymore about that?

RC: No, I think that's enough.

PD: Well, going back to the late '60s, early '70s, there were a number of technological breakthroughs that were happening and you talked about IEM. Were there others that were happening around then that were transforming the kind of work you do?

RC: Well, cultivation, a number of viruses were cultivated for the first time. We had the, well, the innovations, I mean, you know, the major changes came with the recombinant DNA revolution where, we were able to study viruses at the nucleotide level and express proteins of viruses that we couldn't cultivate in culture, hepatitis-B is probably the most important because of the fact that that is a very successful vaccine, very successful. It will, in time, eliminate liver cancer, number one cancer, worldwide.

PD: Really?

RC: Yes.

PD: What has it, what has been its impact to date?

RC: Well, it's so important that many people recommend that vaccination be universal starting very early in life. The vaccine is more immunogenic, that it's more effective when given early in life than later in life. As you age, you become refractory to it. So, I mean, that's a tremendous achievement. And I think what Bob and Sue Emerson have achieved with hepatitis-E is important because in developing countries, this is a very important problem. Hepatitis-E is like hepatitis-A. It's a short incubation period. People don't die ordinarily, but there's an exception. Pregnant women have a 20 percent mortality if they're infected.

PD: That's a lot.

RC: That's terrible!

PD: Yes.

RC: And the outbreaks are hundreds of thousands of people. So it's important. And it, it's a, you know, if you're going on an around-the-world trip and you end up in India, you could be there at the wrong time.

PD: Okay, so going back to technological breakthroughs, what were the other major advancements that were moving you along in the early seventies.

RC: Well, we defined viruses originally by just what they, how they grew in culture and what they did in animals and developing animal models for, you know, as surrogates for study of the human, infection and human disease. But when we were able to sequence, clone and sequence viral genomes, we were able to do an awful lot more and now, in the last couple of years, it's been possible to rescue infectious virus from a DNA copy of the genome. If it happens to be an RNA virus, you make a DNA copy and if you manipulate that copy appropriately and you have the right sequence, the proper sequences in that copy, you can now derive a virus that's infectious. Once you have that, you have DNA now that you can play with and manipulate.

PD: So when did you become able to clone and sequence those viral genomes?

RC: Well, this would be back in the late eighties, but the rescue occurred much later. For example, the respiratory syncytial virus, our favorite, one of our favorite viruses, one of the most important viruses. A 15-year project took ten years to do it. And now, we've had five years in which we've been able to manipulate the genome of RS virus. We can make it do things of our design, not of its design.

In other words, or before you, if you wanted to study mutants, you had to just, you know, do all kinds of things, very gross things and you'd be able to achieve, you'd be able to force, you know, mutation, but you couldn't make, you couldn't determine beforehand what that change was going to be. You'd have the whole virus area, and, well, I'll take a

little bit of this out, see what happens. Take a little bit of this out, let's see what happens, take a little bit of this out, see what happens. You can take different parts of different viruses and put them together into a new virus. That's what's called making a chimera, you know, a chimera's a hybrid. So we have, we have chimeric viruses now.

PD: And what are the implications of them?

RC: The implications, we're moving faster and more effectively. Rotavirus is an example. Rotavirus has 11 gene segments, individual pieces of double-stranded RNA. In terms of vaccinations, there are only two of these RNA segments that are important. There are two separate proteins on the surface of the cell. The genes that code for those are the genes that you want to have in a vaccine. So what we did was we established, this was the work that AI has done. We established that rotaviruses of animal origin are attenuated and specifically, we identified the rhesus rotavirus as a rotavirus from a rhesus monkey was attenuated in adults and in infants. Then, what we, what we did was we then substituted the gene for the most important protective protein into this rhesus rotavirus so that it, it behaved like a rhesus rotavirus. It was attenuated, but the protein that was expressed at the surface was human. So we have one human rotavirus gene and ten rhesus rotavirus genes. And we've done that with the bovine strains as well. So, in other words, we now are in the age of designer vaccines.

PD: And are they on the market or are they still in process?

RC: Well, the rhesus rotavirus is, would be the first one to be licensed. We also have chimeric dengue viruses and chimeric tick-borne encephalitis viruses. Tick-borne encephalitis virus occurs infrequently in this country, but in Europe and Asia, it's very common and it's a Class 4 agent, very high mortality. So what we've been able to do is to make a chimeric virus which has the protective protein of the tick-borne encephalitis virus and all the rest of the genome is dengue. And putting, when you make a chimeric virus, you also slow the virus down. What sort of car do you drive?

PD: I drive a Volkswagen Beetle.

RC: Okay, Volkswagen Beetle. You're on a lonely road and you have a breakdown and you get towed to some little gas station. And so, he says, "Ah, I know exactly what the problem is. It's this piece here. It's got to be replaced." You say, "Fine, do it." "Well, I don't have any Volkswagen parts, but I can put a Dodge part in there." And you do it and he does it, and the car chugs along, but it doesn't go very fast, mixing parts. The parts of viruses have been selected over eons to be able to work together and you put another part in there that doesn't belong there, you can chug along—which is what you want to do in a vaccine—but you don't go fast. Do you understand?

PD: You want the perfect part.

RC: Or if somebody wants to keep you from reaching your destination, they put a Chrysler part in there. Do you understand?

PD: Yes.

RC: Or let's say you have a family member who drives too fast and you want to slow him down, you put in a, you know, Chrysler part into your Volkswagen and they can't go more than 40 miles an hour. Okay?

So, I mean, that's what chimerization is about in a way, so you put two viruses together, you take parts of one and you take parts of the other and you make this chimera and you've got things that will work together, but not too well and this is the recipe for a successful vaccine.

PD: And it's proven to be very effective?

RC: Well, the rotavirus vaccine was wonderful. It still is and, hopefully, we'll get others saying this with us. But the chimerization, for example, of this tick-borne encephalitis virus, which is, you know, 30 percent mortality in Asia and Europe, from Scandinavia to Vladivostok, ocean to ocean, this tick-borne virus group is very, very important. We made a chimera of this TBE, just the coating . . .

PD: TBE?

RC: Tick-borne encephalitis, . . .

PD: Yes.

RC: You know, the surface proteins and everything else was dengue and it just knocked the hell out of it. It made it completely benign so that it was impossible to detect any evidence of virulence in this virus. And our system is so sensitive that we can, we can measure differences of several billion-fold between the most virulent and the most non-virulent virus. Yes. So chimerization is wonderful. It's a wonderful thing because it's, it's very stable. I mean, you've got these genes that are, you know, very, very large in terms of the number of nucleotides. And it's going to take a lot of mutations to reverse the effect of chimerization.

PD: And this technique began?

RC: Well, it wasn't possible to do this before. Now you can do it with DNA recombinant DNA, you see.

PD: So, again, in the late eighties?

RC: Yes. Well, chimerization, I think the rotavirus chimeras were somewhere around '85, '86, we started working with them. But the dengue, TB was '91. And now we have chimeras of the paraflu viruses, of RS virus, and so forth, putting animal counterpart genes into human RS or putting human RS protective genes into an animal relative and that sort of thing. So there's a whole new, there's a whole new science now of bacterization by chimerization.

PD: I'd like to go back a little bit to the '70s and use, maybe, flu vaccine research as a template for long-term projects.

RC: Oh, well, we're talking chimerization there, too.

PD: Okay, but it started out with you and Dr. Murphy coming up with the . . .

RC: Well, it actually started before that. We made temperature-sensitive mutants of flu and we did it just by exposing flu to a chemical mutagen and certain mutations that were produced and we could score for them in the laboratory and the easiest one to score for is a TS-mutation, temperature-sensitive. Viruses grow within a certain temperature range and usually the top of the range would be 38, 39, 40. And we looked for mutants that didn't grow at 37 or 36, so that would mean that if they got into the very internal part of the body, they wouldn't grow, but they would grow in the nose, which has a temperature of about 30 to 32. So we looked for temperature-sensitive mutants and they worked

beautifully. We were able to produce a large number of them and in animals and in people, we showed that they were attenuated.

However, they were unstable because there was only a single, you know, TS mutation. And actually, Brian tried three or four mutations in a single gene and it still escaped because the virus, the [irony] virus that we worked with have a spontaneous frequency of mutation of about 10^{-4} or 10^{-5} , because they're RNA viruses and they don't have DNA polymerase correction mechanism built in. In other words, DNA viruses have two strands and if something happens to this one and this is the template, but when this strand is copied, you get the right sequence. Or, or there's a mechanism which will take out errors and then replace the sequence with a, with a proper sequence. So the recurrence of DNA, spontaneous DNA mutations is much, much lower than it is for the RNA viruses, which is where most of our work is.

So, what happens is you have a virus that has a temperature-sensitive mutation and it can't grow well, but if it is going to grow well, it can't, it will be able to if a temperature-sensitive, if a correction mutation occurs at the site of the original TS mutation. So the virus is struggling to be healthy again. The only way it can be healthy is to develop another mutation that will correct this TS mutation. And it's more complicated. That's what's called reversion. You're going back to the virulent virus. You have an attenuated virus and then it can revert. Now, very often the, the reversion is not a restoration of the

original sequence. A mutation can occur at another site somewhere and correct the phenotype, that is the property of the virus, so it will grow at high temperature again.

Because, you know, there are only a few proteins in the virus and they have to work together and if you have something that's like this, let's say, this would be the normal configuration and if you push it up here like this, if you had something that would, at another place, do this, and then the two come together and give you the right configuration, you have a virulent virus, so that's what's called a suppressor mutation, a mutation which suppresses another mutation, you see. So, anyway, with the, with our DNA recombinant-derived vaccines, now, we can put in mutations which are very stable and the best mutations, the most stable mutations are the deletion mutations where you don't fiddle around with the sequence, you just chop out a block. And you can do that.

PD: You can?

RC: Oh, yes. You can take out a whole gene, which I didn't think possible, but RS virus has ten genes and five of them individually, five of the genes can be taken out and the virus still grows, but in four of those instances, the virus is weakened. And it can't be restored because you have to have that whole block of sequences.

PD: So that's it and you've permanently disabled it.

RC: That's right, yes. Yes, you've amputated something.

PD: Okay.

RC: So these are the strategies we use. We use chimerization. We use, you know, we produce mutations that are, you know, just single mutations, but a lot of them, or alternatively we can produce, we can delete sequence. Now if someone had told me this five years ago, I'd say, "You're out of your mind." But that's the way it is. So now we're in the position of being able to delete or bring together genes or genetic genomes that never ever would get together in nature, you see, like these chimeras.

PD: They're completely lab created.

RC: Yes.

PD: They don't, they would never occur on their own.

RC: That's right. Yes. But they're stable as the devil because what you've, it is, it won't be possible as far as we can see for that, for a chimera to ever correct itself because they're got to be so many changes to go back to the, you know, the virulent configuration. So, those are the sorts of things we're doing. We're doing this with the paraflu viruses now, with the RS viruses. And Bob Purcell is doing some work like that, of that type with

hepatitis viruses. One of the ways of producing attenuated hepatitis-A virus, the current vaccine is inactivated vaccine, but if it's to be completely effective in the world, throughout the world, a live, attenuated vaccine is preferable.

PD: Why is that?

RC: Because a needle and syringe costs a lot of money.

PD: I see.

RC: Plus the fact that the vaccine has to be given by a health care provider. Oral vaccine, plup, you know, like the Sabin vaccine, you know, just drop it in the mouth.

PD: Well, and on the subject of the flu virus, . . .

RC: Yes. Well, we went from producing TS mutations into chimerization and Brian had a project, which was excellent and that was to use the genes of avian influenza viruses that is, viruses that come from, . . .

PD: Birds.

RC: . . . flu viruses that come from birds and mix them with human influenza genes, specifically, the protective protein, outer coat proteins would come from the human virus and the others from the avian virus and it worked beautifully. We were able to show that attenuation was achieved in animals and was tested in people, but, we couldn't, we really found we couldn't depend on that to consistently produce a, what, what is appropriately called a reassortant virus. It's a chimeric virus, but it's a reassortant virus in that you re-sort genes. You take two genes from the human virus and six genes from the avian virus. So you're resorting genes. It's a chimera, strictly speaking, but more specifically, it's done by gene reassortment. You put the two viruses into a cell. You co-infect and then you select out for the viruses that have the mixed parentage. That's gene reassortment.

And you can do that if there is a segmented genome. In other words, if each of the genes is packaged separately, you can go into a cell with both viruses. All the genes are produced and then they're randomly resorted into virus. Each virus has eight genes. In some cases, there will be one of this and one, but if you have ways of selecting for the reassortant genotype that you're interested in and we have been able to do this. You do this and then you end up with two human flu genes and then six from the avian. But, there were probably four or five attempts to use this as new antigenic variance of flu came along, the reassortants were produced and tested and the last time we did it, it didn't attenuate because it's the interaction of these various things. We don't know why.

PD: It's interesting.

RC: It wasn't, see, you have to show that the strategy works every time. And it did work and then it didn't work . . .

PD: Then it didn't work.

RC: . . . the last time. So, at the same time, John Maassab's virus, which M-A-A-S-S-A-B, at the University of Michigan, which was a cold-adapted virus. It was adapted to grow at suboptimal temperature. And that attenuated it and its six internal genes, you see, if you have a flu virus that has eight genes and two of them are coating for the outer proteins, all the other genes are called internal genes, . . .

PD: Okay.

RC: . . . except for the, for proteins that are inside the virus. So the internal genes of John Maassab's virus and the avian virus, itself, actually, and the avian viruses that we studied, it's a six/two ratio, six from the attenuated parent and two from the human and they code for the antigens that are protected, that induce protected immunity. So this vaccine, this donor consistently produces reassortants that are attenuated in animals and in people. And it took a long time for this to finally surface. I don't know why it took so long, but Brian was the one who did the critical studies that showed that the cold-adapted donor could continually produce attenuated reassortants. And two years ago, there was a,

the technology and the strategy was licensed to Wyeth and they gave it up after a year or two. They didn't know what they were doing, obviously.

PD: Didn't you and he come up with a nasal spray?

RC: Well, all the respiratories go nasal.

PD: But the particular vaccine was given.

RC: No, just dropped in the nose. But, I mean, they're looking at delivery systems now, but we dropped it in the nose. Just very simply.

PD: Was that a novel way of approaching vaccine?

RC: No, if you're doing a live respiratory vaccine, you drop it in the nose.

PD: Okay.

RC: So, a small company called Aviron licensed this and they did a big field trial and, god, it was successful, in every way.

PD: In the nineties.

RC: Yes, in the late nineties. Now, Brian's studies were successful, too, in groups of infants studied at Hopkins. We had a contract with Hopkins for clinical trials and it worked, but nobody picked it up. Well, anyway, Aviron, then did this big study and the head of this study was Bob Belshe. He came from this lab. He was a research associate here who worked on respiratory syncytial virus, and then went back to academia. He did the field trials, extraordinarily successful. It not only protected, I think it was 95 percent protective, it prevented otitis media, . . .

PD: Otitis media? Middle ear?

RC: Otitis media, caused by flu, yes, middle ear disease. In other words, otitis media is mainly initiated by a virus and others superinfection with bacteria. If you don't have the virus, you don't develop otitis media. RS is one of the major causes also, paraflu, and so forth. Well, anyway, this vaccine is, should be licensed very soon. And it's called FluMist.

PD: Now, then, and it wasn't marketed then in '98? It didn't come out on the market?

RC: It hasn't been licensed yet.

PD: Okay.

RC: They had a problem last year in terms of complying with the FDA requirements, you know, for a manufacture. But there's no question about it, this will be an important vaccine. And we're close to having our, to having a final RS vaccine by first using the old crude methods of, you know, . . .

PD: Jennerian methods?

RC: No, this is just hitting RS virus with mutagens.

PD: Mutagens.

RC: Growing them, but at low temperature and chemical mutagens. And now, it's possible to tweak it—taking out something here, adding something, you know, that sort of thing. So we're very, very optimistic about RS and also paraflu. Bob Belshe developed a cold adapted para-3 strain which looks like it's going to go the whole distance?

PD: Any time soon or do you not put deadlines on these things?

RC: Oh, probably three or four or five years, it'll be ready, but we'll be able to protect against paraflu 1, 2 and 3, RS and flu and adenovirus, that takes the cake. I mean, there's very little left.

PD: Wow! You will have achieved success in the majority of areas that you've been working all this time.

RC: Well, it isn't we, it's going to be awhile. But we will achieve Nirvana. This is what we're after.

PD: Isn't the ill a particularly difficult illness to treat because the virus mutates more than others?

RC: Well, it mutates and then it, there's antigenic variation based immunologic pressure where the person's immunity filters out the, suppresses the, the virus that the person has had experience with previously, but the only way the virus can grow, in effect, is to mutate. The mutants have the advantage and if the host doesn't have immunity, the virus that you had before, you're immune to, but if that virus undergoes a change, an antigenic change, you're susceptible again. So you can keep ahead of flu, by being able to very quickly making these reassortants that are appropriate for the strain that represents the threat. That's true for epidemic change which is, you know, gradual, or pandemic change, with a whole new virus, you know, set of virus, protective proteins emerge.

PD: Like the kind that emerged in 1918.

RC: Yes, or the avian viruses in Hong Kong, you know, that are struggling to gain a foothold in people. They've infected people, but the virus hasn't spread to other people, but a couple of mutations more and they may be able to and then we'd have a worldwide pandemic like 1918. But you could respond more rapidly with this reassortment strategy than you can by making an inactivated vaccine, because if you make, you'd have hundreds of doses or thousands of doses, you know, in a little tissue culture tube that you could use. But an activated vaccine takes a lot of a lot of eggs.

PD: Which brings me to my next question, which is how do you choose to look toward a live virus vaccine or attenuated?

RC: Well, you have to look at the, it's disease-specific. With hepatitis-B, we're never going to have that, or we're not going to have that for, in the first place, we can't grow the virus and in the second place, it would be too dangerous to use this technique for viruses that produce persistent infection. HIV is an example. In other words, use of an inactivated vaccine has sort of been ruled out of court because if you have a virus that's in the genome forever and mutation occurs at a high, with high frequency. You could actually change, and the attenuated virus can become virulent because it's there for life, you see, it's got a long time for. You can wait a long time for that right mutation to come out because its DNA is integrated into the wholesale genome. And hepatitis-B would be like that and C is also a chronic infection. It's even more chronic than hepatitis-B, probably won't have an attenuated vaccine, but we have an acute infection and very good

immunity developing. And flu, RS, paraflu, hopefully Norwalk some day, if we can ever grow it, things like that.

PD: What other notable breakthroughs during the seventies occurred that we haven't touched upon yet?

RC: Gee, I can't think of any.

PD: We've covered a lot of ground.

RC: We've covered a lot of ground, yes. I'm sure when you talk with Al Kapikian and Bob Purcell and Brian, you'll pick up a lot of those things.

PD: Well, I'm going to talk with them about subjects that I should bring up with you, and for now, but I may interview them down the road.

RC: Oh, you should, though. You should.

PD: Okay. Well, let me just flip the tape since we're almost over on this side.

[End Tape 2, Side A]

[Begin Tape 2, Side B]

PD: . . . talked about your work with the antibodies.

RC: Yes, I'm revising my estimate to 03 now.

PD: I see.

RC: It's been going so slowly.

PD: For the completion of this project.

RC: Now, there's been a lot of about discussion what is important in protection against virus infection. And we, the historical data is very clear. It's antibodies that protect, for the most part. And the evidence comes from the following: With hepatitis-A, it was known before the virus was ever discovered by Al Kapikian and Bob Purcell and Steve Feinstone. It was known that gamma globulin, which is pooled, immunoglobulin-G derived from a large collection of plasma units, when given to individuals who were traveling in regions of the world where hepatitis-A was, you know, occurring with high frequency, that the use of gamma globulin, inoculation of gamma globulin protected against hepatitis-A for about six months.

These were studies that were done in the military during the Korean War and even before that back in the late '40s. Gamma globulin is the total immune experience of the individuals who contributed to the pool of plasma units. It's everything you've seen before, you see. The antibodies are there, but they're not just the antibodies that you're interested in. They're all the antibodies that you own are pooled together and if you pool antibodies, units from enough people, you'll have antibodies that will see an awful lot of viruses. And it was clear that hepatitis-A, or short incubation hepatitis, could be protected against by a very small amount of IGG and this effect would last for, or not IGG, it's called gamma globulin.

PD: IGG is immuno . . .

RC: It's immunoglobulin-G.

PD: Okay.

RC: So we had that experience. And then measles has provided us with this same answer.

When I was a resident in pediatrics, it was very clear that an infant or child who had been exposed to measles could be protected up to four days after exposure by the inoculation of gamma globulin, which meant very small amounts of measles antibody would protect against disease, see. And it was known from the studies of Bill Hammon, who was one of the six people who went to Russia in 1961. . . .

PD: Okay.

RC: He did a fantastic study involving 55,000 children in the West, western states, studied over two years who received either a gelatin placebo or gamma globulin, that recipients of the gamma globulin were protected from poliomyelitis. The efficacy of the gamma globulin was 85 percent, which meant that they hadn't really reached the 100 percent level or there wasn't enough antibody to protect everybody, but they were very close to having a, you know, complete protection. And this study was done over two years, 55,000 children and gamma globulin protected against polio. Gamma globulin had lots of antibodies to polio because polio was rampant in those days, see. This was a signal that if you could stimulate antibody with a vaccine, it would protect and that's why the vaccine was then put on the front burner, either inactivated or . . . so here we have examples of virus infections were antibodies protect.

And what you do is add something to the patient. You don't take something away. You don't inoculate them. You just provide them with more antibodies. And, and notably, the antibodies that will protect against the disease that you're concerned about. And, so, I mean, this was such a clear signal that I can't understand why so many people continue to seek strategies, or to develop strategies that would induce T-cells to be activated and so forth. They can be activated and they are important in resolving infection, but they don't provide you with resistance to infection. They resolve the infection that you've

acquired. So we actually did studies with RS virus where we tested antibody in, the effect of antibody in an experimental animal model, the cotton rat, which is the best small model.

PD: The cotton rat?

RC: Cotton rat, yes. So, what we did was we inoculated, well, we infected cotton rats with the virus and collected a large pool of the serum during convalescence. These were animals that were infected. They developed antibody and then we bled them. And we pooled all the bleedings together. So this was what you called a pool of convalescent sera.

PD: Convalescent?

RC: Convalescent, convalescing from infection. Yes.

PD: Oh, okay.

RC: So we had convalescent serum and we tested it in cotton rats by inoculating different dilutions of this pooled serum and then infecting, and then the next day, dropping RS virus into the nose of these animals and determining. No, the experiment was as follows: We inoculated varying amounts of this convalescent serum pool and then the next day we

bled the animals and stored the serum so that we could determine the level of antibody that had been achieved in their circulation and then we challenged the animal. And we found that if we inoculated a large amount of serum, an amount large enough to achieve a level of neutralizing antibody of about one to 300. That meant that the serum of the recipient animal could be diluted three hundred fold and it would still neutralize the virus. But the animals were protected if we, if they, we achieved a tighter, they would be protected for the most part, but if we went to one to 400 or 500, it was total protection, we couldn't recover virus from the animals four days after they were challenged. If we, if we achieved a much lower level of antibody, virus grew without restriction in the lungs. So what we achieved is what we were able to identify as the protective level of serum neutralizing antibodies, the level of antibody that's required in serum to protect against RS infection in cotton rats. It was one to 300, one to 400. Well, that was the basis for the antibody preparation that was developed by Medimmune.

PD: Medimmune?

RC: You don't know Medimmune? Oh, my god. Okay. This is the . . . well, I'll get something on the computer of it. This is the most successful product of a fledgling biotechnology company. They first developed a polyvalent preparation that was called RespigamTM, pooled plasma units of donors who had the highest level of antibody in their serum, pooled together and made into gamma globulin. And when this was inoculated

into, when infants and children who had high risk of developing serious RS disease, these are children who are born early, preemies, too early, you know, preemies.

Their mothers, most of the antibodies that the mother transfers to the infant occurs, the transfer occurs in the last four weeks of pregnancies. If a child is born six weeks early, he has little, very little antibody from the mother. So RS being a fairly devastating disease, if the young infant acquires it without having any protection from mother's antibody, bad news. If the child was born early and has what's called bronchopulmonary dysplasia, which is the, which is a sort of a chronic lung disease that occurs when a child is born too early. Their lungs are not ready for prime time.

So infants who were born early, infants who had chronic pulmonary dysplasia, children who had congenital heart diseases and then infants who were immunodeficient or who were treated for cancer early with, you know, cancer chemotherapy that knocks down their immune defenses, and so forth—and these are the infants who are most likely to die when they are infected with RS early in life. Bronchopulmonary dysplasia, their lungs are just not developed properly. They're not mature. Immunodeficients, immunodeficiency based on genetic disease or treatment with chemotherapy and all that sort of, so there are about 300,000 infants every year who qualify to be in one of these groups, you see. And they tested this preparation of human gamma globulin now, selected where the units were selected for high titer of virus antibody. The first year they did the study, they didn't, they weren't successful. They only achieved about one to 200

level. And then the next year, they achieved one to 300, 400 and it worked and it was licensed. It was exactly the level that we had predicted, you see.

PD: When was this?

RC: This would be '97, '96. No, it was more like '93, '94. And RespigamTM was, yes, and the SynagisTM now is a monoclonal antibody that's directed against the RS virus, F-glycoprotein, which is the major protective protein. And this is based on a monoclonal that we developed in this lab. It was a mouse monoclonal antibody. And what, what Medimmune did was to humanize it. You see, you know what an antibody, a molecule of, antibody molecule looks like?

PD: Describe it to me. I've probably seen it, but, I'm going to take this. . . .

RC: I'll just try to find a book here.

PD: Okay.

RC: So what they did was they took the mirroring monoclonal and used it as, they retained it. See. This is a combining site here. They grafted this onto a human monoclonal.

PD: It's like a tree with branches off of it.

RC: Yes. This is FC and this is the FAB. This is where the business is done. This part here attaches to cells.

PD: The bottom part.

RC: The bottom part, the FC fragment. Now, what they did was they used the FAB fraction up here, the antibody combining site of the murine antibody and they linked it to a human, a human FC. And then they tweaked it and made it more human, more human, but they always, but they retained the combining sites here that were combined, that were directed specifically to the F-glycoprotein. So it, it's functionally an RS F-glycoprotein antibody. But now it's, it's humanized so that 95 percent of the sequence is human. And what you want to do, you have to do this because if the whole molecule were murine, the children inoculated with it would develop antibodies against it and reject it after awhile. You couldn't use it over and over again.

And what they did was they, they inoculated this, well, the, the pooled gamma globulin was inoculated intravenously and it was a, like 750 milligrams per kilo. That's three-quarters of a gram per kilo. That's a lot of protein. It took three to four hours to inoculate this intravenously in hospital. Now, RS just travels through a hospital like wildfire. In the RS season, RS is all over the hospital. Kids who come into surgery become infected with RS. It's one of the major problems. It causes nosocomial infection.

That's hospital-acquired infection. The last thing you want to do with a child at risk is to have the child in the hospital.

PD: Right.

RC: You don't want that. So, what happens if you, well, having a monoclonal antibody means that you're giving only the antibody that's, that is going to produce a protected effect. You don't have all these other antibodies. They're not necessary. You want, you give a lot of antibody, just to give a small amount of RS antibody. So, with a monoclonal antibody, you would achieve about a 100 to 200 fold reduction in the amount of protein that you have to give, you see because this means about one two-hundredth of all your antibodies are RS, you see. So if you just give those alone, which you can do if you have a monoclonal antibody. Then, instead of giving, you know, a tremendous volume of material, you give a very small volume and it can be given intermuscularly with a needle. It can be given at home by the parents. It can be given by a visiting nurse.

PD: And then you work around the entire nosocomial problem.

RC: That's right.

PD: Okay.

RC: So, the other thing, these kids are in the hospital for three to four hours, you know, receiving this. If they just came in and you went, phwet, like that and they ran out, that would be better than being three to four hours in hospital. Okay. So this monoclonal antibody, this monoclonal antibody now achieves a level, at the dose given, achieves a level of one to 300, one to 400 neutralizing antibody activity. That means the serum of the recipient can be diluted one to 300, one to 400 times and still neutralize RS. Fifty-five percent reduction in severe hospitalizable disease in high-risk infants is achieved, was achieved by the RespigamTM, which is the polyclonal gamma globulin, or in the same efficacy that was seen with a monoclonal antibody. Now this monoclonal antibody is dynamite. It is, it is the first year that it was, after it was licensed, they sold, the sales were, I think a hundred and twenty-one million dollars. The next year it was 240 million. This year, it's 427 million and they expect about 800 million next year. It's a block buster.

PD: It's just taken off.

RC: Yes, and the situation with RS is the same all, worldwide, but in the United States, it's estimated that between 200 and about 4,500 infants die of RS. But in the old days, it was, the mortality was much higher, but now we can support very sick infants, you know, with ventilators and all sorts of things. But, in developing countries, that doesn't happen and RS is like rotavirus, there's probably a million deaths a year in infants. Now, the problem is the cost of this monoclonal antibody is about \$5,000 for the season. It has to

be given every month because the antibody has a half-life of about 21 days so if you give something, it'll be about half as much in another three weeks. So you give a little more than the amount that would give you, one to 300, one to 400 for three weeks. So that at the trough, which is the next month, just before the next month of inoculation, you'll still have one to 300, one to 400—\$5,000. Now, if you have a child with bronchopulmonary dysplasia and the child, the infant is premature, you will pay that.

PD: A small price to pay.

RC: Oh, yes, because, for example, the hospitalization of these infants is \$10,000-plus right straight out, but the point is, it's the life of the child. They are very compromised.

PD: And you give it up front and it transforms their life or it saves their life.

RC: Yes. So, anyway, that's, we are really very proud of this because we actually provided the foundation for it and the, and the antibody as well, the antibody that was used to fashion this humanized, humanized murine antibody.

PD: We, being yourself and?

RC: Brian.

PD: You are coming closer to your goal.

RC: That's right.

PD: Any idea when you will perfect the vaccine?

RC: March 32nd, 04. [joking]

PD: Okay, I'll write that down.

RC: No, it's going to be another three or four years before there'll be a product, but we can see it, we can feel it, we can almost touch it. That's the point.

PD: When did you start research on that?

RC: Well, we recovered the first human strains in '56.

PD: '56.

RC: I was at Hopkins that year and then I brought them here.

PD: Right.

RC: You know.

PD: Almost half a century.

RC: Well, it's 44 years, 45 years, actually, so that's long-term dedication.

PD: As laboratory chief, you decided to extend the research here beyond respiratory disease to include hepatitis or how did that come about?

RC: Well, it evolved.

PD: Okay, so it wasn't a conscious decision.

RC: No, we didn't sit down and say, "Well, what are you going to add to our menu?" The decision was made when we did the organ culture studies with gastroenteritis virus. You know, we couldn't find the agents. We then were able to do it by IEM and what did this do? It was, the natural extension was to do it with hepatitis-A and that opened it up for hepatitis-C. So each of these sort of evolves out of something that went before.

PD: Talk to me more about Doctors Purcell and Murphy and Kapikian. I mean are there any high points to their careers that you'd like to tell me about.

RC: No, I gave them to you.

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PD: We, being yourself and?

RC: Brian.

PD: Brian Murphy?

RC: Brian Murphy, yes.

PD: You've been talking a lot about RSV. What is the status of your work there? I mean.

RC: Well, we've identified a candidate vaccine strain that does everything that we would ever hope that a vaccine candidate would do. But it isn't completely, we're not completely satisfied, because it's not completely attenuated. The only thing that it does that is undesirable is that it produces stuffiness in the nose. We're talking about virus placed in the nose of a one-month-old infant. And I'll explain why we have to immunize at one month. And stuffiness is not a problem for you or me or most people, but infants don't breathe through their mouth. And if they're, if they're stuffed up here, they don't breathe, they don't feed. They can live, but they can't feed.

PD: That's right because they'll suffocate while they're feeding.

RC: Yes. So, the last vestige of virulence is now being taken out by the tweaking process.

PD: So you're moving right along.

RC: Yes.

PD: You are coming closer to your goal.

RC: That's right.

PD: Any idea when you will perfect the vaccine?

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PD: Talk to me more about Doctors Purcell and Murphy and Kapikian. I mean are there any high points to their careers that you'd like to tell me about.

RC: No, I gave them to you.

PD: Okay.

RC: Essentially all of the hepatitis viruses except B were discovered upstairs. And the agents of nonbacterial gastroenteritis discovered by Al Kapikian. Vaccine developed, you know, effective vaccine, an effective vaccine for hepatitis-A, the discover of hepatitis-D, the crazy little virus that nobody could ever even imagine, you know, it's a whole new scenario. It's so unheard of, unknown. Nobody would have ever predicted that.

PD: Okay. I'm going to put the pause button on for a minute. Alright, well, that concludes today's interview and, again, thank you for your time and we'll meet again to discuss the third installation of this topic.

RC: Okay.

RC: Right.

[End of Interview]