CHEMICAL HERITAGE FOUNDATION

ERIK DE CLERCQ

Life Sciences Foundation

Transcript of an Interview
Conducted by

Mark Jones

San Francisco, California

on

13 May 2013

(With Subsequent Corrections and Additions)

CHEMICAL HERITAGE FOUNDATION
Center for Oral History
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INTERVIEWEE

Erik De Clercq was born in Dendermonde, Belgium in 1941. Some of his earliest memories as a child involve World War II and the festivities when Belgium was liberated. His mother was a tailor and his father worked as a chemist for a local fertilizer plant. He would often visit the plant with his father, which inspired him to pursue the sciences. De Clercq later attended the Catholic University of Leuven, where he decided to study medicine to combine his mother's aspiration that he become a doctor and his father's that he become a chemist. While studying, he balanced both his interest in chemistry and his burgeoning passion for internal medicine but ultimately decided to join the microbiology staff upon graduating in 1966. His mentor was Pieter De Somer, an entrepreneur who founded the antibiotic company Recherche Industrial Therapeutic. De Somer sent De Clercq to the United States to study interferons and with the encouragement of his wife, he settled on attending Stanford University. While at Stanford, De Clerq became interested in the university's biochemistry courses and began attending them despite being unable to enroll in their PhD program. He extended his stay at Stanford an extra year but eventually returned to the University of Leuven in 1972, where he would complete his PhD with a thesis on the induction of interferons.

In his research, De Clercq became interested in reverse transcriptase and ultimately discovered Suramin, which he thought could treat leukemia. After his tests failed to produce the results he was hoping for, he classified his discovery but later published them in the journal *Cancer Letters*. While he continued with his interferon work, he eventually stopped pursuing this line of research due to his burgeoning work in small molecules and De Somer's decreased interest in interferons. De Clercq began working with the chemist Antonín Holý on small molecules, particularly studying how anti-metabolites work against viruses. While Holý was initially hesitant, their eventual success with DHBA led them to publish their work in *Science* in 1978. In 1985, De Clercq's work with phosphonates led to research into their use for herpes, HIV, and hepatitis B treatment. While he published his findings in *Nature* in 1986, the toxicity of the treatment prevented it from being implemented. His work on phosphonates was in collaboration with Bristol Myers Squibb. De Clercq worked extensively with John Martin, the director of research at Bristol Myers Squibb. When Martin left his position to join Gilead Sciences, Bristol Myers Squibb returned the compounds to Holý and De Clercq, who then joined Gilead and continued with their work on phosphonates. While working with Gilead, De Clercq helped to develop products such as cidofovir, adefovir, tenofovir, Truvada, Atripla, Complera, and Stribild. De Clercq retired from the University of Leuven upon turning sixty-five, thought he continues to teach in the Czech Republic seasonally.

INTERVIEWER

Mark Jones holds a PhD in history, philosophy, and social studies of science from the University of California, San Diego. He is the former director of research at the Life Sciences Foundation and executive editor of LSF Magazine. He has served in numerous academic posts, and is completing the definitive account of the origins of the biotechnology industry, entitled Translating Life, for Harvard University Press.

ABOUT THIS TRANSCRIPT

Staff of the Life Sciences Foundation conducted this interview, which became a part of our collections upon the merger of the Chemical Heritage Foundation and the Life Sciences Foundation into the Science History Institute in 2018. The Center for Oral History at the Science History Institute edited and formatted this transcript to match our style guide, but, as noted, Science History Institute staff members did not conduct the interview. The Center for Oral History, Science History Institute, is committed both to preserving the recording of each oral history interview in our collection and to enhancing research use of the interviews by preparing carefully edited transcripts of those recordings. The preparation of interview transcripts begins with the creation of a verbatim typescript of the recording and proceeds through review and editing by staff of the Center; interviewees may also review the typescript and can request additions, deletions, or that sections be sealed for specified periods of time. The Center keeps track of all changes that staff, interviewers, and interviewees make to the original typescript. Please contact us if you would like additional information about these materials. We have established guidelines to help us maintain fidelity to the language and meaning of each recorded interview while making minor editorial adjustments for clarity and readability. The transcript also includes time stamps at five-minute intervals. We omit without noting most instances of verbal crutches and all instances of nonlexical utterances. We also make small grammatical corrections where necessary to communicate interview participants' meaning. Finally, staff of the Center create the abstract, chronology, and table of contents. With the availability of online full-text searching of our transcripts, the Center for Oral History opted to discontinue the practice of preparing a back-of-the-book index for each oral history transcript in 2020. **The Science History Institute is committed to the responsible presentation of the history of science by addressing evidence of inequality and oppression as well as the subsequent silences in our collections. To that end, we recognize there may be language in our oral history collection that is outdated, offensive, or harmful, such as, but not limited to, the following: racist, sexist, Eurocentric, ableist, and/or homophobic language or depictions.**

INTERVIEWEE: **Erik De Clercq**

INTERVIEWER: **Mark Jones**

LOCATION: **San Francisco, California**

DATE: **13 May 2013**

JONES: What we would like to do is, is record a professional biography and, you know, tell how all of this developed so maybe we could start at the beginning with some biographical background, maybe talk about your youth, your family, education, growing up? Where are you from originally?

DE CLERCQ: I'm actually from Belgium and the reason that I was surprised by Mendel because yesterday I gave here a kind of inauguration talk on the Holy symposium. And Tony Holy has been since thirty-vie years, actually since 1976 my coworker, and yesterday I called him one of the big Czech following [Gregor] Mendal, [Karoslav] Heyrovsky and [Otto] Wichterle the discoverer of the soft lens.

So that's why. [Laughter] Since I'm not a Czech but I'm not suddenly not from the progeny of a priest. [Laughter] But it's surprising, I saw here the picture of Mendel, yeah. So to explain a little about. . . well you probably have some of my biography, at least you have a picture. [Laughter]

JONES: I also have a very long CV [curriculum vitae] with I don't know many publications on it, and that's a little daunting, but maybe we could go through a little bit of that, how the science developed over time?

DE CLERCQ: That is actually— I'm not going to give you a review of all my publications [Laughter] but—

JONES: Maybe we can get a thorough summary of the work?

DE CLERCQ: The total number is something like two thousand five hundred. I mean peer reviewed, but you see I'm pretty old and I've had the opportunity to continue writing so. [Laughter] Actually to give a little bit about the biography. I do not know how far I have to go, I mean to go back.

JONES: Let's start at the beginning. Where were you born? What was your birthplace?

DE CLERCQ: The birthplace is in a place called Dendermonde, [Belguim,] which is in the province of East Flanders in Belgium. It is in the Flemish part of Belgium. As you probably know there are two parts—you have the Flemish part and you have the French part or the Waloon part. Then you have a small what I would say part that is the German part, which we inherited after the Second World War from Germany. I grew up in a rural place. I mean it's very far from what you could call any city. It's just incidental that—

JONES: And you're growing up maybe after the war, in the years—

DE CLERCQ: Actually the first years, I was born in 1941 so that means that the war ended in 1945, but I have no recollection of what happened during the war. Certainly not suffering or anything of that. What I still remember vaguely is a kind of festivities for the Liberation. So I was already four years old and that was perhaps the date that I could still remember. So I went to school in a very small village.

JONES: What did, what did your parents do? Were they. . .

DE CLERCQ: My father was a chemist but not the professor chemist. He was an employee chemist. And my mother was a tailor actually. She worked with the girls. I am an only son so that's. . . let's say, I've never had sisters or brothers but the girls that worked with my mother, they had a kind of sisters for me. [Laughter]

My father was an employee in the chemistry— in a plant of fertilizers. I used to always go with him on Sundays to the plant and that's probably where I got my indoctrination into chemistry. Because I smelt the sulfur, they used sulfuric acid for the fertilizing purposes, for making fertilizers. Perhaps that somehow determined my later— **<T: 05 min>** what I would say later inclination for chemistry.

JONES: Did you discuss chemistry with your father?

DE CLERCQ: No, no, no, I was interested in chemistry but I never did, like some other people that are real chemists, have done experiments when I was young. No. [Laughter] I never done it, but I mean, I was interested in chemistry that's for sure. But I was from a very simple, let's say, household. Where my parents lived in, let's say, a very simple neighborhood and but that's incidental. I'm going to be an honorary citizen of that village within just a few weeks. [Laughter]

JONES: Wonderful.

DE CLERCQ: Then I will speak my local dialect so because of course English is not my mother language. My mother couldn't even speak any English. My father could speak better French but also no English, so I didn't speak English at all until—but no, I'm jumping already a little bit ahead—until I came to the US [United States] in 1968. Now I'm jumping a little ahead because I spent part of my time during that period at Stanford [University]. So you see.

JONES: So you know the area?

DE CLERCQ: I know the area very well but it changed. I remember Embarcadero, [California,] a little from the old days. We must have been here and gone to Fisherman's Wharf and once we went even to Alcatraz sightseeing. [Laughter] That is now jumping ahead though.

JONES: When you go back to your village for the homecoming, do you still have friends there? Will you see people that you know?

DE CLERCQ: Oh, yes, sure, yeah, yeah, yeah. Certainly in the neighborhood. I mean the neighbors. I still have the old home of my parents. I so far have not been able to separate from it. [Laughter] I still keep that old home but it's really now due for renovation, that's for sure. But so I went there to the local— What do you call that?— junior class. No, not junior.

JONES: The primary grades?

DE CLERCQ: The primary grades.

JONES: Middle school, high school.

DE CLERCQ: And then at the age of twelve I changed to Dendermonde where I was born, to the high school. That was a high school based on what they call Greek Latin, humanities. So I had to learn Greek and Latin and at that time I have no idea what I would like to become. It's so I had all the options at that moment. Actually Greek and Latin was some kind of prerequisite to start the studies for priests, but I did not have the inclination for it. [Laughter] Then what

determined my further career was a lot of things. I liked algebra so that means I could do mathematics, I could do physics, I could do even what we call German philology and—

JONES: German philology, that's not algebra? You don't need—

DE CLERCQ: No.

JONES: Yeah.

DE CLERCQ: [Laughter] No, no, and algebra, I was not very well integrated to do that. I like the algebra but it was too weak my education then to start. My father, of course, he liked me to become a chemist and my mother wanted me to become a doctor because we call that a dokter—that had a lot of prestige.

JONES: Yeah, so they had some ambition for you?

DE CLERCQ: Well because I was a good student so I had several options. What that determined when I went to go to the universities, so from there on I went to the University of Leuven [now Katholiek Universiteit Leuven] which you call Leuven, [Belguim,] **<T: 10 min>** in native language. When I went over there I was still not sure what direction but then I was looking to the program and to start medicine. They had a lot of courses of chemistry and that was for me an ideal excuse to combine my mother's and father's aspirations. My mother wanted me to become a medical doctor and my father liked to see me as a chemist.

JONES: So this was conscious in your mind?

DE CLERCQ: When I was eighteen then I started medicine because I had so much chemistry, and I never regretted it. What is strange that now so many years now, we are talking about sixty years down the road or fifty years down the road, I still kept my love for chemistry although I have become a medical doctor.

JONES: Jumping ahead a little bit, I'm curious, do you find that your training in medicine helped you at all doing the pharmacological chemistry, maybe the understanding of physiology?

DE CLERCQ: Yes, yes, I would say because I saw then later on the chemistry is a service to the medical problems and the fact that I got a background in medicine certainly helped me in putting the chemistry in perspective. Because to give a very blunt comparison, you can do chemistry because of the chemistry and, let's say, study the hymocianin of snails, but you can do the hemoglobin of man. My purpose then also became to do the chemistry of problems that were of importance in medicine. Therefore, my medical background certainly helped me in putting the things in perspective.

JONES: Yeah, okay, so let's go back then to you undertake medical training, a lot of chemistry courses.

DE CLERCQ: Lots of chemistry and then I was very dedicated to students. Certainly a very good student and I was even writing the courses for the students on chemistry and biochemistry. In my class— at the university these were big classes— there were around two hundred to three hundred students per class. So this was very important. I took care also of the courses and then distributed my course to the other students. [Laughter]

JONES: Do you think you—is this a natural gift, do you think, to be able to just sort of take all this information and quickly—

DE CLERCQ: I mean I was teaching to my fellow students just out of interest and because I liked to teach. That was long before I did or could think about any research. So I was just a teacher to explain the difficult part in the courses and especially chemistry because the students struggled – suddenly students in medicine that had a serious, let's say, aversion to chemistry. I tried to overcome that, even already at that time. So later on it would become my profession.

JONES: Yep, so you made many friends I assume in medical school, people who appreciated your—

DE CLERCQ: Oh, yeah, I think so, yeah. Yeah, last year I got special recognition for that at university, and so when the students refer to—now, those that are still alive – when they refer to how helpful I was in these old days, yeah, yeah. That's it was a special recognition.

JONES: Yeah, that's nice.

DE CLERCQ: No Nobel Prize but that was indeed a kind of satisfaction call it that way.

JONES: How did you do with the other aspects of medical training? There's dealing with bodies and so on? **<T: 15 min>**

DE CLERCQ: That became then a dilemma because that group—I mean I kept my preference for chemistry but in the meantime, seeing patients I also felt very attracted to do a medical career. And in fact I was thinking very seriously of starting to do internal medicine. So then at the end of my medical studies there was a kind of dispute I would say between two of my mentor professors—the professor of internal medicine, who wanted me to join his staff, and the professor, who was my real mentor, in microbiology who wanted me to join him.

Then he came to me, he said, "We have found a solution. You are going to work 50 percent of your time with me on interferon, and 50 percent of your time you're going to see patients with my colleague in internal medicine."

I said, "That's fantastic." But he was of course very smart, but he said, "You start first with me." Then of course he gave me then so many projects that I did not have the time to do the other 50 percent because I was already full 100 percent working in microbiology on interferon. I never went to the internal medicine so it's –

JONES: So the years here, this is the late sixties?

DE CLERCQ: That was in 1966.

JONES: Yeah, so interferon had been discovered about ten years prior?

DE CLERCQ: In 1957. [Alick] Isaacs and [Jean] Lindenmann and Isaccs was even a good friend of my boss but he passed away already in 1964. And [Pieter] De Somer was very – now I should talk a little about [Pieter] De Somer. So Professor De Somer was my real mentor and he was very famous at that time in Leuven [Laughter]. I mean at our place in Belgium actually. Because he was also an MD and he was very much attracted by penicillin. You must see the situation at that time; I'm talking about the Second World War, where there was a real big need for the penicillin production. The discovery of [Alexander] Fleming had taken place in 1929 but had then been very quiet around that and it was really discovered in 1940 by [Howard W.] Florey and [Ernst B.] Chain. Then they got for this big discovery of penicillin, the Nobel Prize around 1945.

JONES: With Fleming?

DE CLERCQ: With Fleming, yeah. And I still have the original transcripts of Fleming accepting the Nobel Prize.

JONES: That made an impact on you later? You came across that.

DE CLERCQ: Yes, sure. Not directly at that time. But what was important to Professor De Somer I was at that time still just ten years old or something, and Professor De Somer, who was very much attracted by the discovery of penicillin. He was always attracted by big problems, you know, not small science but really the biggest possible science. Penicillin had really fascinated him so much that at the time he started his career, he built up a small company by the name of RIT. This is Recherche Industrial Therapeutic all in French, because you have to see the situation. It was typically French. He was able to get some money from venture capitalists.

JONES: They probably weren't called venture capitalists? [Laughter]

DE CLERCQ: At that time it was not called [Laughter]. No, his name was a certain Jacques Lanoir from the puppetry De Jean Valle, indeed, not called venture capitalist. But he an entrepreneur, that's maybe a better word.

JONES: And this is unusual at this time, is it? Or is it not?

DE CLERCQ: It's very unusual, it's very unusual. **<T: 20 min>** In these days, you must see this, this was at the end of the forties. I'm talking now about 1948, '49, fifties. I mean so De Somer, my boss, started as an entrepreneur in a company. He built up the company and he had no, at that time, he had the connection with the University. He did this all just. And made perhaps some money as well.

JONES: He was at the University but started this up and—yes.

DE CLERCQ: As an assistant at that time. He was not a professor yet. He started his company before he was a professor.

JONES: This was already in place and running by the time you showed up at the University?

DE CLERCQ: Oh, yes, yes. I was not there yet and so, but this was the start—

JONES: Forty-eight, '49, okay.

DE CLERCQ: —of antibiotics and that was then the company called RIT, Recherche Industrial Therapeutic. Yeah.

JONES: Yeah, I would just like to ask one other question about context. You're at this point where you have to make a, a decision about your future career, chemistry, medicine. What were?

DE CLERCQ: At that time I was not in research and so the problem, you know I'm talking about nineteen. . . at that time it was 1950 so I was only nine years old.

JONES: No, I mean later though, when you're—

DE CLERCQ: Later on, and then, what happened in the meantime, so De Somer with that company that he had built up then got a lot of money, a reasonable amount of money, with which he then built an institute. And that institute was called The Rega Institute. The name, Rega, that's important, comes from an old figure, president of the university in the eighteenth century and so it is a family name. It is not an abbreviation or an acronym from, you know, royal evaluation or something like that. No, no, it was just a family name of a person that was quite famous in the eighteenth century, so the name was adopted to label the institute. The institute was built on the antibiotic money, on penicillin money, but then De Somer got his second big laugh. That was the polio vaccine.

You must realize polio in the fifties was a very huge problem and I can refer to a book on polio an American problem but that is because it was written by the American journalist, Olitski, who got the Pulitzer Prize for this.[1] I've read this story so this was the time of [Jonas] Salk and [Albert B.] Saben and so we had a local, let's say, interest. Professor De Somer of course was not Salk or Saben but he was, let's say, the European equivalent since he was very much interested in developing the polio vaccine.

JONES: Developing an independent vaccine?

[1] David M. Oshinsky, *Polio: An American Story* (Oxford: Oxford University Press, 2006).

DE CLERCQ: Independent and he was successful in doing this for the European continent. And I remember in these then I had already joined his group.

JONES: At the University?

DE CLERCQ: At this University, and yeah, I never worked in a company at that time. And so I remember the visit of Albert Saben to our institute because he became a friend of Professor De Somer. I was a very young assistant so I had a big admiration because Albert Saben was a very towering kind of a figure. I've never seen Jonas Salk but I know of the situation. Then De Somer, that was his second big laugh. He resolved the problem already in 1960.

JONES: The problem of a vaccine?

DE CLERCQ: Of the vaccine.

JONES: Yeah, how did he make it?

DE CLERCQ: According to the methods of Saben. And so they –

JONES: It was a live vaccine?

DE CLERCQ: It was a live vaccine. **<T: 25 min>** Yeah, that's a very good. You're very well informed in this. [Laughter] That is the method that he followed and he was talking about that in his classes of microbiology. I was in the meantime proceeding to the fourth year and the fifth year. So we have seven years of medical studies in our place. I had to do exams with him. Then he was asking because I was a good student, whether I could join his laboratory. I said, "No." I said, "But what should I have to work on?"

He said viruses.

I said, "No, no, viruses does not appeal to me."

JONES: Ironically.

DE CLERCQ: I like formulas, I like to do chemistry. And then he said, "You can do the chemistry of viruses." But anyway, the first time that he asked me I refused but the year afterwards –

JONES: What did you have in mind? You said, "I'm not going to do that and I'm going to do?"

DE CLERCQ: I wanted to do more biochemistry for the mental work in biochemistry. I had no preconceived ideas, I mean what exactly—but I wanted to see formulas, not viruses. Because viruses were –

JONES: Messy.

DE CLERCQ: Kind of. [Laughter] Not always in a good mood whereas formulas are never changing their mood so. [Laughter]. But then when I talked to my colleagues then they said, "But you have to be stupid to refuse a proposal of a man as important as Professor De Somer," who at that time who was going to be the director of his university. He was already advisor to the director and he was gaining more momentum.

JONES: Yeah, was there any problem in that, his ascent within the University? The fact that he had a commercial operation, was that ever a—

DE CLERCQ: No, that was in fact considered to be already kind of a bonus point. I mean the University accepted the fact that he had done industry first and then moved to the University. Because when the institute was built, it was built with the money coming from industry.

JONES: So they're welcoming?

DE CLERCQ: And they were welcoming, and on the founding stone, which is still present in our institute, that was signed by the rector at that time, who was the most senior magnificus. [Laughter] They were all priests of course and that was very well accepted, so it added to the, let's say, prestige. Also and to the situation of Professor De Somer.

JONES: Right, did the Rega family make any contribution to the institute or is that just—

DE CLERCQ: No, no, no. Only the name from Rega was chosen but all the money came from industry and was entirely devoted to. Yeah, no, we got a lot of money I think, I mean in these old days. So I finally accepted then to come to work with De Somer and he said, "You are going to work on interferon." So, and that was the third laugh of Professor De Somer after penicillin and other antibiotics, then the polio, but the polio problem was resolved so he had then to switch to interferon. His thinking was that interferon would become the kind of penicillin for virus infections. So that was the belief, the panacea for resolving also the virus infections as penicillin was believed to do this for bacterial infections. That's when I joined and decided to join him, Professor De Somer.

JONES: Was your thought at that time that this is a permanent move into research, to basic research, rather than a career in medicine?

DE CLERCQ: At that time?

JONES: Yeah, no?

DE CLERCQ: I was absolutely, no. I just now realized that next year, it will be fifty years **<T: 30 min>** that I've joined the institute. So my career has already started in '64, in 1964.

JONES: Yeah, and you didn't even realize it?

DE CLERCQ: No, no, I just—

JONES: At that time in Belgium, what was the comparative stature of the medical profession and academic science in terms of maybe social prestige or remuneration? Did it matter to you or did it matter to anybody else?

DE CLERCQ: I think normally to gain all the money, or I mean a reasonable amount of money, you have to do it in private practice. And but De Somer, his father was a medical doctor, a physician—not like in my case. But he had seen, you know, this practice of his father and he hated it. He did not want to see patients so that was a big difference with me. I love patients but he, in his case, he did not want to see patients, so he had decided to do research only and not to think about any patients. But normally to make enough money, research was very risky and you could fail whereas, if you did a practice and seeing patients you were always just sure that you would never have failed to get a sufficient amount of money.

JONES: Yeah, so it was a bit risky to go this way for you personally?

DE CLERCQ: It was kind of risky, yes, and certainly for my mother who had been dreaming to see her son become a practitioner, she was disappointed. She has never forgiven Professor De Somer for taking me away from this career.

JONES: Even with, was she able to witness your wonderful success later?

DE CLERCQ: No, my mother died before that happened.

JONES: I'm sorry.

DE CLERCQ: She has never seen it. No, well… and my wife even died, Eva, that's also part of the story. So then what happened by 1966, I graduated as a medical doctor and then I started to work in the laboratory of Professor De Somer on interferon.

JONES: What was known about interferon at that time?

DE CLERCQ: At that time, interferon was really a very mysterious compound. It had of course not been cloned, identified; even the real chemists among my colleagues doubted very much that interferon existed.

JONES: Because you couldn't find enough pure interferon?

DE CLERCQ: And that it was rather based on a principle, on what they called an anti-virus state that interfered—that explains the name of interferon—that interfered with virus duplication. So this is the belief at that time. It's of course later on that it became identified. But at that time it was really mysterious and some of my colleagues' friends they recommended that I should not continue on it, to work on interferon because it was an unsettled compound. It was perhaps not even considered a compound, but only a principle, as something that was in the air or something, yeah. We are talking about the 1960s.

JONES: Did you have any doubts about it? "We don't know what it is. Is this—?"

DE CLERCQ: I had doubts about it, I had doubts, I had doubts about it. Yeah, I was not so convinced that it really existed.

JONES: What about your mentor? Was he certain that it was there?

DE CLERCQ: At that time, he believed that it existed but then to make my belief stronger he said, "You have to go to the United States." See, that was at that time considered to be the mecca for further research, I mean compared to the situation in Europe. So in all of Europe, also including Belgium there was no what **<T: 35 min>** I would say convincing place where to do real research, certainly not on interferon—

JONES: And now, at this time you didn't have a doctorate or the equivalent of a doctorate in chemistry?

DE CLERCQ: No, I never had, I never had. I never pursued any degree in chemistry, no.

JONES: Oh, okay. I've got in my notes here somebody, somebody's identified you as a PhD so that's –

DE CLERCQ: Yeah, that's true, that I am, that I got later. Okay, so, but the purpose of De Somer was very clear. He said, "I send you overseas." Now in retrospect that was to consolidate that I would not get second thoughts and that I would concentrate in research. He gave me three options, to work at Johns Hopkins [University]—

JONES: And he knew people at all these places?

DE CLERCQ: He knew because he had some contact persons at each place. And then the Bronx that was Einstein's College. Albert Einstein College [of Medicine] in New York, and then the third option was Stanford, and of course to work with Tom [Thomas C.] Merigan and yeah, I immediately selected Stanford. [Laughter]

JONES: And the idea of coming to the United States, is that something that had ever occurred to you before?

DE CLERCQ: No, no, it really never occurred but then I immediately realized it was unavoidable if I wanted to make a career.

JONES: And was it an exciting prospect?

DE CLERCQ: It was uncertain but it became very exciting afterwards and so my lifetime in Stanford. In the meantime I got married so, with my wife. She was a pharmacist and she liked the prospect of leaving Belgium and going to Stanford. She persuaded me to go there so I got the fellowship, I got—

JONES: She persuaded you to go to Stanford rather than Johns Hopkins or New York?

DE CLERCQ: Yeah because of the climate I would say [Laughter].

JONES: And what did you know about California at that time?

DE CLERCQ: I did not know anything. I mean, absolutely no.

JONES: It's very different than Belgium.

DE CLERCQ: Yeah, totally different. Everything was a kind of serendipity—the choice of my wife to get married to her and then to go to for honeymoon, I mean this was a honeymoon trip to California. I remembered that trip even. It was PANAM [Pan American World Airways] and I don't know if it exists, and to fly first to London, [United Kingdom] then the very big flight to Los Angeles, [California,] then from Los Angeles to San Francisco, then from San Francisco by helicopters to Palo Alto, [California]. [Laughter]

JONES: Helicopter?

DE CLERCQ: Yeah, it probably does not exist anymore but I remember the last part was by helicopter and I arrived—I think we arrived in the morning but local time was evening here. The phone was ringing and it was, and this is typical, that was the wife of my the boss here, Tom Merigan. And she gave me instructions in the Californian dialect and I did not understand one word, one word, no. The beginning was rather what I would say—

JONES: A little awkward?

DE CLERCQ: Awkward, yeah, and so my wife was asking but she said, "The only thing I know is Joan. Her name is Joan," but that I knew before but what she said, she's saying something about what's going to happen next morning about brown hash potatoes. I said, "I never heard of." [Laughter] I did not know about all this. So for us it was really an adventure. But the thing is, Stanford honestly was like— compared to Belgium or compared to the institute, it was like a heaven on earth. What was possible here, what was not possible in Leuven, that's tremendous.

JONES: And why is that? What was at Stanford? Was it people, knowledge? **<T: 40 min>**

DE CLERCQ: The people, and the intellect, and the drive that was so much easier here than in Belgium. Everything was complicated even if we had to ask for the smallest things. Here at Stanford, I mean you just got— they got a lot of money but they've also got a lot of intellect. And for me it was like falling into heaven scientifically. I had the pleasure of attending the lectures of the biochemist—

JONES: Paul Berg, [Sylvy] Kornberg?

DE CLERCQ: And they all became—Paul Berg is still my friend now but at that time, yes, it was— and I went over to here. [Inaudible] Arthur [W.] Conway was the leader of the group. He was a very good teacher and I now followed all these lessons just as a free student. I did not have the foresight to do a PhD in one year because my fellowship was only for one year. They told me at Stanford that in one year I could not really enroll for a PhD degree. But I followed the lessons and those were very stimulating lessons in these old days; I mean Kornberg and Berg. I've also met Liedenberg at some times but not regularly. But so all those were Nobel Prizes.

JONES: Right, and they're working on DNA at that time?

DE CLERCQ: DNA polymerase. Of course I was not working on DNA polymerase because I was working on interferon and interferon induction with Merigan. I just followed them and their classes out of interest, but it was for me like so much refreshing opening the real world.

JONES: And you had a sense that this is the center of the universe for the entire field?

DE CLERCQ: For biochemistry Stanford was officially I think the best place I guess in the United States; that means by definition in the whole world. [Laughter] Ye**s**, it was the best place. That is for sure. I do not know how it evolved later. So after one year I liked it so much that I asked permission to my boss, Professor De Somer, if I could stay for another one year. and he said, "Yes, but no more than."

JONES: He wants you to come back and help him?

DE CLERCQ: Yeah. [Laughter] And then my wife, she liked it even more than me, living at Stanford and she wanted to stay there. My boss at Stanford, Tom Merigan, offered me a position of doing the clinical virology. When I told this to my boss, De Somer, he flew over directly to see me and said, "You have to come back now." I stayed for a few more months after the second year but no longer than that. [Laughter]

JONES: How did you feel about that? Did you have conflicted loyalties or did?

DE CLERCQ: Yeah, well my parents liked to see me back and then Professor De Somer liked to see me back and so I made a decision to come back. And it was a hard time because for at least six months I had a very time to get acclimatized again to Belgium. Because Belgium had not changed and our institute had not changed. I missed the intellect and the lectures and many lectures that the people came to because Stanford was of course a pole of attraction for the whole world. I mean everybody wanted to come to Stanford to give lectures there. I attended many of these lectures of famous people from the whole world.

So of course as soon as I was back in Belgium that disappeared. But I knew I had to, you know, come back and to start a career at home. [. . .] The first thing I did was to get my PhD. That was based on the work I'd done at Stanford and the work I'd done in Leuven **<T: 45 min>** so it was a combination. In 1972 I got the PhD but also in Leuven, just as my MD. So I never got a PhD from Stanford, no. [Laughter]

JONES: What was your PhD thesis on? What had you learned about interferon?

DE CLERCQ: That was induction of interferon. So half of that was based on the work at Stanford, half of it was based on the work in Leuven. Professor De Somer was my, of course, thesis advisor and Tom Merigan was— he did not come over for my thesis defense. That's right. But he was my boss here at the Stanford University. And he is still alive, he's now seventy-eight, I mean, and he is still alive in Portola Valley, [California,] I believe.

JONES: Which is a beautiful place.

DE CLERCQ: Yeah, but always lived there. That was my Stanford days and I have very good memories of that. Then I started to build up my own career because then De Somer very quickly told me that I could do whatever I liked to do.

JONES: Did you leave interferon at that point?

DE CLERCQ: Not at that point yet. Later on I would leave it but I continued to work on interferon, and I picked up a second what I would say love at that time. That was reverse transcriptase. I remember when at the end of my stay at Stanford I spotted in nature the papers that were published by Mizutani and [Howard] Temin.[2] Then another paper that was published by [David] Baltimore.[3] I found that fantastic. I mean, this had nothing to do with interferon but I was you know, very fascinated by these discoveries.

JONES: Did you think this could help explain viruses and maybe the action of interferon somehow?

DE CLERCQ: No.

JONES: No?

DE CLERCQ: I did not see a connection with interferon but I saw a connection with cancer.

JONES: Yeah.

DE CLERCQ: And my dream was always to find a cure for cancer. [Laughter] You see, I did not fulfill this dream but, let's say, that that was— and the reverse transcriptase at that moment was considered to be at the origin of cancer. So that brings us to some papers that were

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[2] Satoshi Mizutani, David Boettiger, and Howard M. Temin, "A DNA-dependent Polymerase and DNA Edonuclease in Virions of *Rous Sarcoma Virus*," *Nature* 228 (October 1970): 424-427.

[3] David Baltimore, "Viral RNA-dependent DNA Polymerase: RNA-dependent DNA polymerase in virions of RNA tumor viruses," *Nature* 226 (June 1970):1209-1211. See also David Baltimore, interview by Sondra Schlesinger at New York, New York, Cambridge, Massachusetts, and Boston, Massachusetts, 7 February 1994, 13 and 29 April 1995 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript #0198)

published by a certain Saul Spielman based on the Temin and Baltimore discovering that the reverse transcriptase was on the basis of cancer. That was in the 1970s; now we know of course much better but, you know, this was the belief at that – and I could even give you an anecdote to confirm the belief in that. Because totally on my own without having said anything about it to anybody else, I discovered that a certain compound which was known by the name of Suramin—I discovered this—a very good inhibitor of the reverse transcriptase. I had done this with my own hands so, no, I did not have a technician, I did not even tell my boss about it. I kept that—

JONES: What put you onto it? How did you make the discovery?

DE CLERCQ: It was just by serendipity that I was going through the shelf let's say, and in fact the name of the compound Suramin was Moronil, that was the French name. In Germany it was Karmanen, I mean, since Suramin had been used in the old days for sleeping sickness. Totally by chance I found that this was inhibiting the reverse transcriptase. The belief around 1975 was that that could be a cure for cancer. So believe it or not, I was injecting leukemic cells in mice, treating them with Suramin, with the belief that as an inhibitor of the reverse transcriptase, that would stop leukemia. **<T: 50 min>** But it did not, and I was very disappointed.

Otherwise I could have told my boss, "Look, I have fulfilled your dream to find the cure for cancer." [Laughter] I could not tell anybody and I buried the data— classified the data until 1978, when the Bob [Robert C.] Gallo—this is an authentic story—visited me and Gallo was very curious about what I was doing and about, you know, and I told him.

JONES: He knew about you and your work?

DE CLERCQ: Yeah, he somehow knew about me and I told him that I had discovered – that Suramin was a very good inhibitor of the reverse transcriptase so that was fun. But that it did not have any effect on the cancer or on leukemia, and that for that reason I thought that this was not publishable. He said, "Yeah, but you should publish, I mean, in my journal, *Cancer Letters*, on the Suramin, not for leukemia but for its effect against the reverse transcriptase. Maybe one day it will be picked up." And in fact, years later after HIV [human immunodeficiency virus] had been discovered, then Suramin was the first—

JONES: That Gallo tried?

DE CLERCQ: That Gallo tried. [Laughter] I was not told and in fact I got at a certain time a phone call at home from Sam [Samuel] Broder who was working with Gallo at the National

Cancer Institute [NCI]. And Sam Broder, he congratulated me on Suramin, and I said, "I forgot all about it. What did you find?" And the reason that he congratulated me, actually he congratulated himself because his paper in science was just accepted. [Laughter] And that was in 1984 and it was on the inhibition of HIV replication. Later on it was shown that actually Suramin worked more by blocking the entry of the virus into the cells rather than the reverse transcriptase. But at least the reason that I tested it against HIV was based on my data.

JONES: But it did inhibit reverse transcriptase if you put in?

DE CLERCQ: It did. But that is quite often in science you find "A" and "B" and you always try to causally link these two things, but quite often they're all just by accident. By accident, and that happened in this case. But for me it gave me of course a satisfaction and you can see the name of Bob Gallo on that paper which was then—Sam Broder was on the paper and then Mitsuya, Hirowaki Mitsuya, who had done the experiments with HIV.[4] So of course, I was very attracted and then Sam Broder even on the phone invited me to come to work at NCI. But at that time, I mean I'm talking about 1983, 1984 –

JONES: In the seventies had you started working on retroviruses?

DE CLERCQ: Actually, yes. I actually already worked on retroviruses at Stanford. Because I developed a system based on Moloney [murine] sarcoma virus to induce tumors in mice. I had done that at Stanford. Of course then I brought the system with me and we further worked with that model in Leuven. But that was a murine virus and not with the human. Because then Gallo, I mean, described it first, the human TLV, the TLV1. But that is the system that I never worked with. I mean, so we worked with the murine system. So we worked with it but unfortunately I tested some **<T: 55 min>** of the reverse transcriptase inhibitors in that system but not Suramin, I mean so somehow after it did not have an anti-leukemic effect.

Somehow forgot about it and didn't ever further explore it. I explored in these days but not against leukemic viruses. Otherwise we should have discovered. [Laughter] So let's say that I missed some very important discoveries. Now I'm going in too many different directions so I was back and it was already clear that I would never go back to Stanford or to the United States. Because at that time, I got also more and more interested in small molecules as anti-virus because always my inclination [was] to work on molecules rather than interferon. Now, interferon, I had not given up on it because it must have existed since the group of Maurice Hilleman at Merck [& Company, Incorporated] tried to purify and were able to purify it to a certain stage. So that was evidence that interferon existed, and then there was a second big breakthrough in the interferon field, is that you couldn't use it with double-stranded RNA.

[4] H. Mitsuya, M. Popovic, R. Yarchoan, S. Matsushita, R.C. Gallo, S. Broder, "Suramin Protection of T Cells in *vitro* Against Infectivity and Cytopathic Effect of HTLV-III," *Science* 226, no. 4671 (October 1984):172-174.

So from then on, I became convinced that this molecule really exists. I talked about it with a man in the University of Ghent, Walter Fiers, who had also spent some time at Stanford in the group of the biochemistry. Walter Fiers, he is a real brain. I mean he believed in the existence of interferon and he said, "We are going to clone it and to express it," and so on. And so in our collaboration between three groups: Fiers, then my own group, then also the group of Jean Content at the Pasteur Institute that is in Brussels. We succeeded in 1980 in cloning interferon, the beta interferon, and in expressing it. We were not the first for interferon.

JONES: That was Weizmann. Yeah, was Fiers involved with that? Because he was also in Biogen with Weizmann.

DE CLERCQ: He was at Biogen, yes, but he— I never knew about his precise links with Biogen [Incorporated]. I mean my role in this here was just to induce interferon with double-stranded RNA. That was the big breakthrough for the double-stranded RNA, poly-I, poly-C as we called it, and that was the breakthrough that was made at Merck. So we used this technology to induce enough of the messenger RNA. Then we were able to extract the messenger RNA. That work was done by the help of Jean Content in Brussels. Then they produced interferon starting from the messenger RNA, and then we again tested the production of interferon with this system. So it was really a collaboration that was going with Fiers and some of his guys had presented it as a train that was going— like it's always like that. But it was not really a train, it was a car who was always driving between these three places. [Laughter]

But we were the first for the beta interferon but as Wiesseman had done it for the alpha interferon. By a few months we were second but these were hectic days because, you know we prepared two *Nature* papers on this and so Fiers was in continuous correspondence with the office of *Nature*. [Laughter] We got two papers in 1980. So for me that was also a little bit of the end of the story because then as a side **<T: 60 min>** product, we also found the beta to interferon, also produced in the same system. Beta-2 interferon later on became IL6, Interlugen 6. So that was a co-discovery or, let's say, a coproduct of the beta interferon.

JONES: But that was your last involvement with the interferon?

DE CLERCQ: And it was my last involvement and there were two reasons for that, is that in the meantime, I got too much involved in the small molecules in the world. I already was, let's say, starting to discover new compounds there. The second, De Somer himself had lost his belief in interferon so he—

JONES: Just when the rest of the world is. [Laughter] There was a lot of hype about interferon at that time.

DE CLERCQ: At that time, there was a lot of hype. There was a certain time there was a belief that interferon would have an anti-cancer activity, but you know we never believed in this and as you can see also, this has not been followed up. Then De Somer just had a moment like all big inventors, injected once interferon by himself.

JONES: Did he get sick?

DE CLERCQ: And he got a very big Shwartzman reaction, allergic reaction. [Laughter] And then he said, "What an awfully toxic compound, so this is never going to make to be a drug," and he lost his belief. And he did not make, let's say, many people good friends, but you know. [Laughter] Because he officially at a meeting, and I think it was in at the Weizmann Institute Rehovot, he once officially declared that he had lost his belief in interferon at an interferon meeting. That was like— what do you call that, insulting the church? [Laughter] But anyway I had also at the same time lost my belief in interferon and [I was] working with new molecules—

JONES: And did you think that it made sense to work with small molecules rather than big macromolecules?

DE CLERCQ: Yeah, yes, sure, that was the reason also that I was working with polynucleotides to induce interferon. But then if interferon would not be useful, then uses of interferon would not be useful either. For the chemists that I collaborated with it was a relief that they learned that they did not have to produce huge molecules, that small molecules may do the job. That is the reason why I shifted also interest from larger molecules to the smaller ones. Then I drifted away totally from the work that I had initiated at Stanford and went my own way to collaborate with many chemists all over the world. So it's something that I also announced yesterday in my talk. The biggest discovery that I've ever made was that I discovered the chemists. [Laughter] And the chemists would make the compounds for me. So it is a [inaudible] and if I would say the chemists, and I would single out one chemist and that is Antonín Holý. I mean so he is a compatriot of Mendel.

JONES: Did you meet him at this time?

DE CLERCQ: That was in 1976.

JONES: Early?

DE CLERCQ: Already at that time. I had already collaborations with a few other chemists over the world including David Shugar. That was in Warsaw, in Poland [inaudible] that was at the [Institute of Biophysical and Biochemistry, or Medicine and Chemistry.] You have two Max Plancks in Göttingen. There was a Max Planck for medicinal chemistry and the other one is biophysical chemistry. But then based on my work on **<T: 65 min>** interferon induction, I was invited at a meeting at a rather small symposium in Göttingen of the biophysical alchemy of the Max Planck Institute of Biophysical Chemistry. There I think I made this discovery of being an MD, to be there with only chemists. So they must have thought of me that is "What is this MD doing here? He probably lost his way." [Laughter]

That is where I met for the first time also Dr. Holý. You must see this in the situation at that time. This was the hiring person. I mean he came from the Czechoslovakia Academy of Sciences in Prague, and there were a few other. These were also American chemists there. I mean John [W.] Moffat was there, John [T.] Montgomery. These were very big names in the nucleotide chemistry. And also of course a few West Germans with the name of Fliederer. These were giants in their field and incidentally they're still alive. I was there, the only MD that had lost his way among all these chemists. [Laughter] But that is where I arranged with Holý that we should work on small molecules and to see whether we could—that were anti-metabolites—and to see whether we could get them to work against the viruses. But it's how I made my first arrangement. Holý as a person was in the beginning rather suspicious because he was like the others saying, "What is this MD coming to do here? I mean, he is to steal our compounds or what?" [Laughter]

JONES: But you explained to people, "No, I've been at Stanford. I know all of these things."

DE CLERCQ: At least I could read the language and I could understand the formulas, so it was not like [that] for many other MDs. Things that only existed, you know, with the formula. I enjoyed formulas, I've always and still do. That I have a chemical mind, and that made me to understand the chemist. So we could talk, and what made me perhaps attractive for them is I could explain diseases at least. [Laughter] That made them a little bit at ease.

JONES: And had Holý been doing anything with anti-viral chemistry? Or was this something completely new that you were introducing to him or proposing to him?

DE CLERCQ: Some existed I think. I'm talking about 1976. At that time we had three or four anti-viral compounds that had been described. IDU [idoxuridine] had been described, TFD [trifluridine] had been described, then ribovirine had been described. That was in 1976. There was a first clinical report on the activity of r-a thurtharpine but this is it, these were only four. There was not much belief that viral infections could be cured by anything, certainly not by anti-virals. Still the belief was interferon would do it.

JONES: Yeah, because that's the natural role of interferon if they're. . . ?

DE CLERCQ: Incidentally, it was just in 1976 that [Richard J.] Whitley published for the first time the use of vidaramine or ara-A in the treatment of herpes. That was published in the *New England Journal of Medicine* in 1976 and that was the very first.

JONES: But did you have to persuade Holý that this is something, this is a good way to go? "Help, come, let's work together on this." Did he say, **<T: 70 min>** "I don't believe this could work"?

DE CLERCQ: No, he started very cautiously. He wanted to test me, so he sends me only three compounds and he said, "Do it with these three compounds and then see what happens. If anything, let's decide what you find with these three compounds."

JONES: How were the compounds selected?

DE CLERCQ: Just at random, just at random. In fact, the two compounds that he thought would be effective were not and the one compound that he thought would be ineffective was effective. Believe it or not, that only one compound— it was called DHBA [2,3,-dihydroxybenzoic acid]—that compound, we published on that in *Science* in 1978. Only one out of three compounds. We published only on that compound because the two others were inactive. And when we published it, it was at that time a direct, let's say, competition with acyclovir Because the Valcom Laboratories had just published a few months before we published on this in *Science* of another compound that was somewhat similar. Well I'm not going to explain all the differences in chemistry but it was somewhat similar and that became acyclovir.

And this was to work actually with through the [Gertrude B.] Elion for other work she got together with George [H.] Hitchings; in '88, she got a Nobel Prize. But so acyclovir was the major discovery and that changed the anti-viral field. I mean, and that was a discovery that was made in 1977 or '78. I mean there were two papers, one was published in the *Pioneers* and the other paper was published in *Nature* a few months later that explained the activity. We were then with another compound, just a few months after that, also in 1978, and that we were able to publish in *Science.* That was together with Holý. And so –

JONES: Did you have a big group at your place?

DE CLERCQ: No.

JONES: No?

DE CLERCQ: I did this all by myself with the technician. Only one technician. Later on my group would grow to forty people but at that time, no, it was only one technician.

JONES: There just weren't resources for that? You didn't have the work being done on that scale in Belgium at that time or –

DE CLERCQ: There was not even. I was the only one that ever had touched the anti-viral field. No, my only, let's say, competition was in the US. I mean, acyclovir was discovered in the US because Wellcome Laboratories were at both places, in the US and UK [United Kingdom]. And so originally, I mean to give credit to those that deserve it, it was done in the UK. Interferon was UK. Penicillin was UK. I'm not British. [Laughter] But you have to give, you know, honesty where it is due. The discovery of the anti-viral activity of acyclovir was done in the laboratories of Wellcome in the UK and then descended for further exploration, for mechanism and action and so on, to the US. But that is off the record.

JONES: So the 1978 paper, then this is—you've got some success and this for you. Is its recognition, "We're on the right track, there's something to pursue here"?

DE CLERCQ: That is true. I mean then we resolved mechanism of action and Holý himself, who was more enthusiastic about this compound so that he commercialized it even in Czechoslovak Republic [Czechoslovakia]. That was his first compound and now it is off the market. I mean it's no longer on the market, but it was between a local Czechoslovak company that did no longer exist, and it was used for fever blisters. [Laughter] **<T: 75 min>** But it was the beginning, it was the beginning. Then really the major breakthrough was around 1985. Nineteen eight-five that is when we discovered the principle of the phosphonates and that brings us back to the chemistry. [Laughter] In a normal nucleotide analog you have a phosphate group attached to the sugar ring with what is called a POC bond. POC means phosphor, oxygen, carbon.

Now, that is an ester bond so when it comes to, let's say, metabolism in the cells, in the organism, that is easily cleaved because the phosphate group is cleaved at the level of the POC with water and then you split off the phosphate group. The real discovery of Holý was that he had replaced the POC by a PCO, where you have a direct linkage between the phosphorus and the carbon.

JONES: And that's a more durable bond?

DE CLERCQ: And that is stable as a rock and cannot be cleaved by water, cannot be cleaved spontaneously, it cannot be cleaved enzymatically. So you would say that's very simple but that is actually the crux of the story.

JONES: How did he make the discovery?

DE CLERCQ: He was not the first one because the PCO technically or chemically was also known by others. But he was the first to apply this to a group of compounds that were isosteric to nucleotides [. . .] or to those that can be used in a normal metabolism. So it had been sensitized. So Holý never was the first of course but –

JONES: But he was the first in—

DE CLERCQ: In the nucleotide business.

JONES: Yes. And which was not well developed so nobody had –

DE CLERCQ: That was a real discovery that— not what you could call something that others would find. No, he was, let's say, the first one to do it there. My contribution has been only secondary to his, I mean because he synthesized it and I recognized it. [Laughter] I then applied it and made it useful in terms of applications. I could immediately see that this could lead to a lot of. . . well, I did not claim I could see this but let's say that gradually then we were able to show it, that it worked in these very different conditions.

JONES: Where did you start?

DE CLERCQ: We first started to see that this was active against herpes virus, the easy virus, but at that time, we had of course also HIV, so from then on we had the HIV system. So then, we immediately realized that it was also active against HIV and then later on we extended it to hepatitis B and to other DNA viruses.

JONES: And the mechanism of action in each case is similar?

DE CLERCQ: It is always based on that same principle. The compound is built into the DNA and cannot be cleaved anymore because of the presence of the phosphonate. It a rather simple principal and the fact is that you could ask why is it only active against the DNA viruses, not RNA viruses or not DNA of the cells. That is even not an all-or-none phenomenon but it is in the DNA of the viruses. There is a much faster turnover so you get a profitable, let's say, attack on the viruses compared to the cells. That is the idea that has been growing of course for all these years. **<T: 80 min>** The first compound in this series was a compound which we called HPMPA and that is the compound which was never commercialized because it was considered to be too toxic.

JONES: You had found that or had you tested it on animals?

DE CLERCQ: At that time we did not know about the toxicity but finally because of toxicity, it was not the—I'm talking about the long run—some of the principle was published and that was published in *Nature.* That has become our standard paper published in 1986 in *Nature.* I believe that I sent that paper first to *Science.* [Laughter]

JONES: What were their objections to it?

DE CLERCQ: Lack of space. [Laughter] Their objection is too many papers had too much, let's say, pressure for publication. *Nature* accepted it and of course it has become the standard of principles. Later on we published of course many, many more papers on this. I must never lose it. Yeah –

JONES: A few more minutes, yeah.

DE CLERCQ: Yeah, okay, no, no, till eleven. It's okay because it takes longer to return for me since I'm going so slowly so. [Laughter] What I would say the most fascinating part is the beginning. Now, the question that you would ask, you realize how I got in touch with Holý, how did Gilead [Sciences, Incorporated] get involved? This is a very interesting part because at this moment Gilead did not exist yet.

JONES: Gilead was founded 1987?

DE CLERCQ: Nineteen eighty-seven by a certain man, Michael Riordan, with the help of [Donald] Rumsfeld—you probably know him—in 1987. But what happened is in these old days, there was a kind of a compound-hunter by the name of Julius Vida and that came once to our laboratory in 1985. He asked me about whether I had any compounds—he was from Bristol Myers [Squibb Company]—whether I had any compounds that could be of interest for development. I was very careful of not getting involved with such techniques of companies.

JONES: No, why not?

DE CLERCQ: Why not? Because I was in an academic institute and not eager to jump into contact with companies.

JONES: But there was some history at your university?

DE CLERCQ: That was helpful. In 1985 what had happened is that De Somer had died earlier this year but so I had this legacy of making contact. He told me when to make contact, I had to be very careful. I told to this man called Julius Vida that I had probably a compound that I could be interested in. Then I said, "This compound is not mine. This has been synthesized in Prague.

I did not know that Julius could speak Czech, because he was actually a Czech. And he said, "No problem."

JONES: Did he know about Holý?

DE CLERCQ: No, no, I told him much later. Then he asked me and then I told him about the potential of these kinds of compounds, and that meant that he had to travel to Prague to get in contact with. Because I was not going to sell compounds from Holý without telling anybody. But then he also told at home at Bristol Myers to the director of research and that was a certain John [J.] Martin, and so John Martin was the first one to be informed by Julius Vida. And then John invited me to come over to give talks **<T: 85 min>** at Bristol Myers he visited me, he then went on further to Prague.

JONES: He must have been very young at that time, yeah?

DE CLERCQ: At that time, yeah. [Laughter] That's true, I still have the pictures or because he had just been – and that's probably what you do not have covered I think in your reports. He was at Syntex [Corporation]. He started his career with a certain Julian Verheden, also Belgian

origin, at Syntex. He was the one who discovered again acyclovir, and then he moved over to Bristol Myers. Then at Bristol Myers he was very much attracted by this compound, what I called the Holý's compound, and was immediately very much interested. And then at Bristol Myers there signed up a lot of papers, I mean with us, that they were going to develop it and the one that was responsible for the development would be John Martin and all at Bristol Myers. What changed the situation in 1990, that is that Scripps [Research Institute] moved in and actually Scripps took over Bristol Myers. From then on it was BMS, and the first thing that John Martin realized, that is that he was going to lose his job as director at this new company BMS. And he quit in 1990.

JONES: So how far had this gone? Did Bristol Myers, they had control of the compounds? At this point? Or not?

DE CLERCQ: Bristol Myers had complete control of the compound. Oh, yeah, he had that signed and that was all signed by Julius Vida and so it was easy for me because I sign always immediately but people in Prague were very suspicious.

JONES: Government people or university people?

DE CLERCQ: No, the lawyers, the attorneys, and they took, I had to study this agreement very carefully so that took months and months.

JONES: Is that because you think they didn't have experience with this kind of transaction?

DE CLERCQ: The thing is, they considered Bristol Myers as an imperialist company coming from an imperialist country. Without telling me, they were preferring to have deals with the Germans, in this case with [Richard R.] Erst. Erst once invited me to talk about these compounds and I figured out that they knew more about it than I did. The reason was very simply because the people in Prague had contacted Erst and had told them all the secrecies about this.

JONES: So had Holý been in contact with them?

DE CLERCQ: Holý of course was involved, and then I said, "You cannot continue like that. I mean you cannot continue with Bristol Myers—"

JONES: Doing both, yeah.

DE CLERCQ: "— and with Erst." And I told that to the people at Erst too and I said, this is, "They're playing on two horses in the Czech Republic. I mean, you cannot continue like that." Or they can – and then they stopped and Erst later on disappeared from the scene but you know, it's good that they stopped so they continued at Bristol Myers.

JONES: Yeah, why did they go one way rather than the other? Do you have any notion of that?

DE CLERCQ: Why? No, that I do not know. [Laughter]

JONES: It's interesting, yeah.

DE CLERCQ: Yeah, it's – now, that was also because maybe the situation at Erst was not very clear and they were going to be taken over themselves by other companies. So that was, you know, you come in at kind of a treadmill of company management and company business that for a poor scientist cannot follow. [Laughter] Anyway, the Erst business was stopped, and so all the papers were then further done to Bristol Myers. And so then **<T: 90 min>** John got his offer to become Vice President of Gilead.

JONES: Did you hear about that after the fact?

DE CLERCQ: Yes, after that. Gilead had independently already contacted me for a collaboration before that. But that is but that had nothing to do with these phosphonates.

JONES: It was the antisense?

DE CLERCQ: That was antisense but I would collaborate with them on antisense. But –

JONES: What did you know about antisense? Had you worked on any work on it?

DE CLERCQ: No, I never really. I followed a little about the antisense but I never worked on the antisense, so I was not interested and I did not see any druggable approach in that. I wanted to see drugs.

JONES: Why did you think antisense wouldn't work? Be it, it's just you couldn't deliver the oligonucleotides?

DE CLERCQ: That is because of delivery problems. You could not get them to the target so it is simple reasoning but working with polynucleotides, I knew that making antisense or making drugs out of antisense would be a terrible and difficult problem.

JONES: That's difficult. Tomorrow I'm going to talk to Stanley Crooke down in San Diego, [California,] yeah.[5]

DE CLERCQ: Oh, yeah, I know him in.

JONES: Do you?

DE CLERCQ: Yeah.

JONES: I haven't met him, yeah.

DE CLERCQ: It's a long time ago that I've seen him. I've even played tennis once with him.

JONES: Is that right?

DE CLERCQ: Yeah, but no, I do not do that anymore. But that was how Gilead started but then John Martin was hired as their vice president. At that time, the compounds were in the hands of Bristol Myers, so for a year we were in a very difficult situation that the champion of working with the phosphonates was already going over to Gilead. Whereas the compounds were still at Bristol Myers at that time. And so at Bristol Myers Corp— that was in '91 in May— they invited Holý and myself to come to Wallingford, [Connecticut,] their headquarters, where they were going to tell us how they saw the future of these compounds. We, Holý and I, were in a good mood. We said, "Now we are going to find out [what] they are going to do with it." As it

[5] Stanley Crooke, interview by Mark Jones at Carlsbad, California, 14 May 2013 (Philadelphia: Science History Institute, Oral History Transcript #0994, in process).

is normal when we come over to the US, they treat us with a dinner that is always the day before.

JONES: Is that the custom elsewhere?

DE CLERCQ: That evening, I mean I remember it was around 11:00 [PM], just when we were eating the dessert, and Julius Vida said, "I have to tell you guys,"— he was talking to Holý and myself— "tomorrow you are going to hear how Bristol Myers Squibb is seeing the future but that's not very bright. You are going to return the compound to the owners," in this case to Tony Holý and myself.

JONES: That's good news, yeah? [Laughter]

DE CLERCQ: We were of course said that was good news in a certain way. I mean if you look at it from today, I mean it was good news.

JONES: You were hoping to hear that they were going to they were going to put a lot of resources—

DE CLERCQ: And that they were going to put a lot of resources and going to develop it and so on. And David told us, "We are closing the groups."

JONES: Why did they bring you to dinner in the US? To be courteous at least?

DE CLERCQ: Yeah, yeah, I think so. The man who was responsible for that was Holý. I mean, apparently – I heard about the story from Julius Vidal later on. There was a split voting for it. It was something like three to three. And then since it was seven in total had to vote, then the last vote was against it. Julius said, "I'm not responsible. I voted for it but they did not accept it," so Piers got the one from Bristol Myers. Scripps voted against it. And within one week, **<T: 95 min>** John Martin was already calling us.

He said, "What did I hear?" I mean the bad news, it's like you said. "So the good news," he said, "for us, because now we offer you the situation that you transferred, the whole package of all these compounds from the deal that you had with Bristol Myers now to Gilead."

Then we had a meeting in July. In the meantime, this approval of the compounds was in May. By the second of July we had a meeting which I consider still as the most historical

meeting that I ever had. It was in Paris, [France,] and was somewhere on the street in a Best Western, where we were with four: John Martin, his boss at that time, that was Michael Riordan, the one at Gilead, and then Tony Holý and myself. I had to interrupt my—

JONES: I think we have a photo with the four of you together.

DE CLERCQ: I do not even. Yeah, but that was not at that meeting.

JONES: Yeah, but later. Yeah, yeah, much later.

DE CLERCQ: Yeah, I always considered this like an equivalent to Yalta in the Second World War, but in Yalta they separated East and West. Here they united the East and West. And that memorable day, I mean, we signed. Holý and I signed the agreement with Gilead.

JONES: And the terms as good as the terms you had with Bristol Myers?

DE CLERCQ: They were exactly the same, so that was the easiest. And Tony and I, we discussed it and I said, "We take a big risk because now we are going from a very big company, Bristol Myers, to an unknown company, biotech company." I mean we did not know what that was going to get.

JONES: For a while was it faith in John Martin? Is that it?

DE CLERCQ: It was faith in John Martin. I think.

JONES: Is that the main thing?

DE CLERCQ: I think he was the main reason, yeah. now I am cutting the story short in the sense that then Mike Riordan stayed with company 'til around 1986, I think.

JONES: Ninety?

DE CLERCQ: Ninety, 'til around '96, '97.

JONES: This is ’91 where –

DE CLERCQ: This was ’90. The deal and agreement in Paris was in ’91 and then you know, I must say that for Gilead this was a question of survival. For us, it was a real blessing to know that Gilead really pushed so hard. But they did not have an alternative. You know, they had the antisense but for them that was not going to make any sense.

JONES: But they maintained that program for some time?

DE CLERCQ: For some time but not for much longer, and as soon as they had, let’s say, faith in the phosphonate, then they rejected the antisense.

JONES: And I think they sold it to Stanley Crooke.

DE CLERCQ: Yeah, yeah.

JONES: I think so. Is that right? I think –

DE CLERCQ: Well.

JONES: I have to check but I think it went to ISIS [Pharmaceuticals].

DE CLERCQ: It happened later but they had a deal with Glaxo [SmithKline plc] originally on the antisense and then they stopped that deal. Then later on they made a deal with the ISIS. . .

JONES: I think they did. They sold the patents.

DE CLERCQ: But then they really devoted, and I must say this is real genial approach of John Martin with. . . Robert. I think they’ve always formed and are still forming a very good thing.

JONES: Did he come from Bristol Myers as well?

DE CLERCQ: No, no, John brought some other colleagues like [Michael] Mick Hitchcock and also [Muzammil] Muz Masuri. He followed John Martin from Bristol Myers to Gilead but independently Robert came from Genentech [Incorporated]. He was at Genentech so they were not linked at that—

JONES: And Gilead?

DE CLERCQ: —only when they were there. Then I have been there numerous times. I mean I do not know how many times but at least twice a year. I've been at Gilead and in the beginning, I mean **<T: 100 min>** this was very tough. I mean to push these compounds to the market, that was a long process. Of course I mean it has only been increasing now in in terms of, let's say, intensity. But based on the phosphonates, let's call it the phosphonate groups, they have enlarged from twenty people up to three thousand or four thousand people. So I did not create this company. [Laughter] I played a major role in getting this company, you know, up to this stage. So what do we have at this moment? I mean we have a total of eight compounds or seven compounds.

JONES: How many were there originally that were transferred from Bristol Myers to Gilead? How many at that time?

DE CLERCQ: There was no output yet. No, we only had at that time, the technology, we had – the first one that we had coming along was the Cidofovir and Cidofovir was the first to be officially licensed in 1996.

So that was the first. The second one was actually Adefovir; that was finally then licensed in 2001 and then the tenofovir came in 2000. That was then further pursued in combinations, so then in 2004 we had Truvada that was approved, then in 2006 we had Atripla. In 2011— now I'm already speaking about the recent times— we had Complera which is on the market also in the European Union as Eviplera. Then we had in 2012, we have had Stribild, that is the latest one. Also in 2012, ironically the day that Tony Holý died sixteenth of July, we had the Truvada approved for prevention. And a few other combinations are still coming.

The new compound, the new, let's say, tenofovir is tough for tenofovir alafenamide and that is scheduled for next year or the year afterwards. This is all in terms of the original agreement that says that we should also be entitled for products of not only the phosphonate compounds but also for the products. That may be synthesized by the company. That was also transferred. So let's say that we got also good agreement of this, the approach.

JONES: And that's helped immensely in Belgium yeah? With research at the university?

DE CLERCQ: Let's say that based on this deal, we are entitled to royalties. But the royalties are going to the university, not to the inventors. It's different in Prague. So there, the royalties are in the first place going to the inventor and he has an agreement then with—and I do not know how this has now been restructured now that Holý has died. But then this is an agreement that he has with the academic or the institute. In our case, all the royalties are going straight to the university and then I must make an agreement with the university to get part of the royalties to myself, which has been uphill. Last year it was not settled but you see, these things take some time for long time. I mean this is now settled so I've so far not become a rich man on that. **<T: 105 min>** I mean there are people that have become rich but that was not really the purpose.

JONES: Yeah, that's not the objective. [Laughter]

DE CLERCQ: That was not the objective.

JONES: And how did, after the nineties, in the early nineties, these compounds go under development at Gilead and how does your work progress in Belgium, in your lab?

DE CLERCQ: All the efforts then from, already from the 2000 I think, was done at Gilead and we have continued to use some of the money of course that we are getting from this deal, I mean to do research. Not on these compounds anymore because that is finished.

JONES: Right, right, so what have you been working on?

DE CLERCQ: I personally cannot work anymore since the rule—

JONES: They passed the mandatory age—

DE CLERCQ: At the age of sixty-five which is already a few years ago, I mean since 2006. So it is going to the laboratory and there are many different projects I mean so…I cannot work anymore. I mean I can still write and I still do write and I can still teach, but not in Belgium. So I keep teaching in ironically, in the Czech Republic. [Laughter] So where I've found another very good friend—actually it was also a friend of Tony Holý—a certain Liebor Gruphoffer. And he is the now Director, President of the University of Ceske Budejovice. And that's where—

JONES: In Prague?

DE CLERCQ: In a place called Ceske Budejovice, which is south of Prague, it's about two hours' drive from Prague. So if you have ever the occasion to visit me and also to visit him, I mean that would be great. You would be very well received there because these are places where people do not come. I mean this is not Harvard [University] or MIT [Massachusetts Institute of Technology], you know. [Laughter] This is very far from everywhere in the world.

JONES: How much time do you spend there? Do you go back and forth between Belgium?

DE CLERCQ: It is in season. I mean I'm teaching there a total of thirty hours per year. I mean around October and November. Then I have to go a few times, so I mean, and then I'm spending two days there. It's not really cumbersome. I mean it's easy and also I get always transportation from the airport to the place because otherwise to get over there in Ceske Budejovice it's not obvious. [Laughter]

JONES: Right.

DE CLERCQ: So this is not San Francisco. [Laughter] But I get a very warm feeling. I mean so people are very helpful and they know that. And this is also a joint project with Austria so it's not only Czech but also Austria, and so students are mixed—Czech, Austrian, and some even international.

JONES: Anti-viral conferences like the one being held here, you're in demand these days, yeah?

DE CLERCQ: No, but there was a very special reason for that. That was because I was in a special symposium in honor of Holý. I cannot guarantee I will be at all of these meetings. These are annual. It just happened I was there also last year in Sapporo, [Japan,] but then for a few years I have not been there, but now it was—the special reason was that it was dedicated to Holý. Of course [that] was for me a very, what I would say, necessary reason to be here. I've in the meantime built up a very nice relationship with also the ambassador, the Belgian ambassador in Prague. She has been very, let's say, instrumental in this collaboration with Holý.

JONES: From the beginning?

DE CLERCQ: No.

JONES: Or from—

DE CLERCQ: As soon as she was ambassador, since 2007. Now her term is finished because 2012. So she's **<T: 110 min>** passed ambassador but the title, you can keep. We do not say ambassador in emerita or so no retired ambassador. [Laughter] Once you are ambassador, you can keep the title.

JONES: So she's here visiting Gilead with you?

DE CLERCQ: Just in a half an hour. The driver is waiting at eleven at hotel there.

JONES: And I'm sure you're a very honored guest at Gilead?

DE CLERCQ: At Gilead I'm a, of course, let's say –

JONES: A hero?

DE CLERCQ: A usual guest so there, but now I'm very— for her it's the first time and she is with her husband who is a journalist or was a journalist at *The Washington Post* and is still involved in journalistic affairs. It's interesting and who knows, maybe one day she will write a [story] on this, on the history of—

JONES: Yeah it's a great story. We'll write something on this, we will be telling the Gilead story. It's great to have it from you. Thanks for coming, thanks for coming early.

DE CLERCQ: [Laughter] Okay, I'm very grateful that. . . yeah.

JONES: I think what we have here is perfect, okay?

DE CLERCQ: No, no, I will you know, take away. Sorry that is has to be so fast but if you need further information just keep in touch. I do not know how and where you're going to write the stories. I've written your stories on other people and so, they are very big because some of them I've known and you may not even know. One of them I've known very, that is Jan Vilček.

JONES: Yes, yeah.

DE CLERCQ: He is a Slovak but, you know, in these days Czechoslovak, we are united, and he was a good friend of mine at that time.

JONES: Yeah.

DE CLERCQ: Yeah, so that is—so

JONES: That's another fabulous story.

DE CLERCQ: That's another one.

JONES: Yeah.

DE CLERCQ: Yeah, sure, yeah, I could tell you more about that even because he has also written on De Somer. Then you can see, sometimes you make associations between famous people. Because he has known De Somer and De Somer has even been instrumental in him flying out of the country. Because that was arranged— he was from Bratislava, Bratislava to Vienna, [Austria]. He was allowed to go on vacation but as soon as he was in Vienna then he has come to Belgium and then De Somer got a little bit scared about getting into problems and so Vilczech had to continue to fly to New York, [New York].

JONES: Yeah, that's, that's a great story, maybe we'll hear more details about that.

DE CLERCQ: That by itself is a very nice story. I did not know whether young Vilček is still in good shape.

JONES: I think he is. He's actually been in touch with us so –

DE CLERCQ: Oh?

JONES: I don't know, I haven't met him in person, but I would like to talk to him also and get in touch.

DE CLERCQ: Yeah, I mean that should be very great. I've also read what you wrote about some of the others. I was fascinated by this book of yours.

JONES: It's a wonderful job for us to, to be able to do this. It's difficult, we have to learn about so many different technologies and we have to get it right. [Laughter]

DE CLERCQ: And you have to always keep it within two pages.

JONES: For that book, yeah, but we're writing a much more detailed scholarly history of the commercial industry. We're also collecting these oral histories. We'll put a transcript together and send it back to you. You can review and correct it. And then with your permission we'll publish it in our archive with all of the others, yeah.

DE CLERCQ: No, but for any further information I think it would be great. Okay, and if you ever have a chance to come through Belgium or to come to Prague—in Prague, Holý has of course disappeared. But I mean if you go from Prague a little bit further to Ceske Budejovice, you will have a very warm reception there. He also came over here yesterday, Libor Grubhoffer, but he has already **<T: 115 min>** left, he is no longer here. But he is a very warm person and being the president of his university also, he's worth a complete coverage.

JONES: Yeah, very good, thank you.

[END OF AUDIO, FILE 1. 1]

[END OF INTERVIEW]