CHEMICAL HERITAGE FOUNDATION

JAMES A. MCCLOSKEY, JR.

Transcript of Interviews
Conducted by

Michael A. Grayson

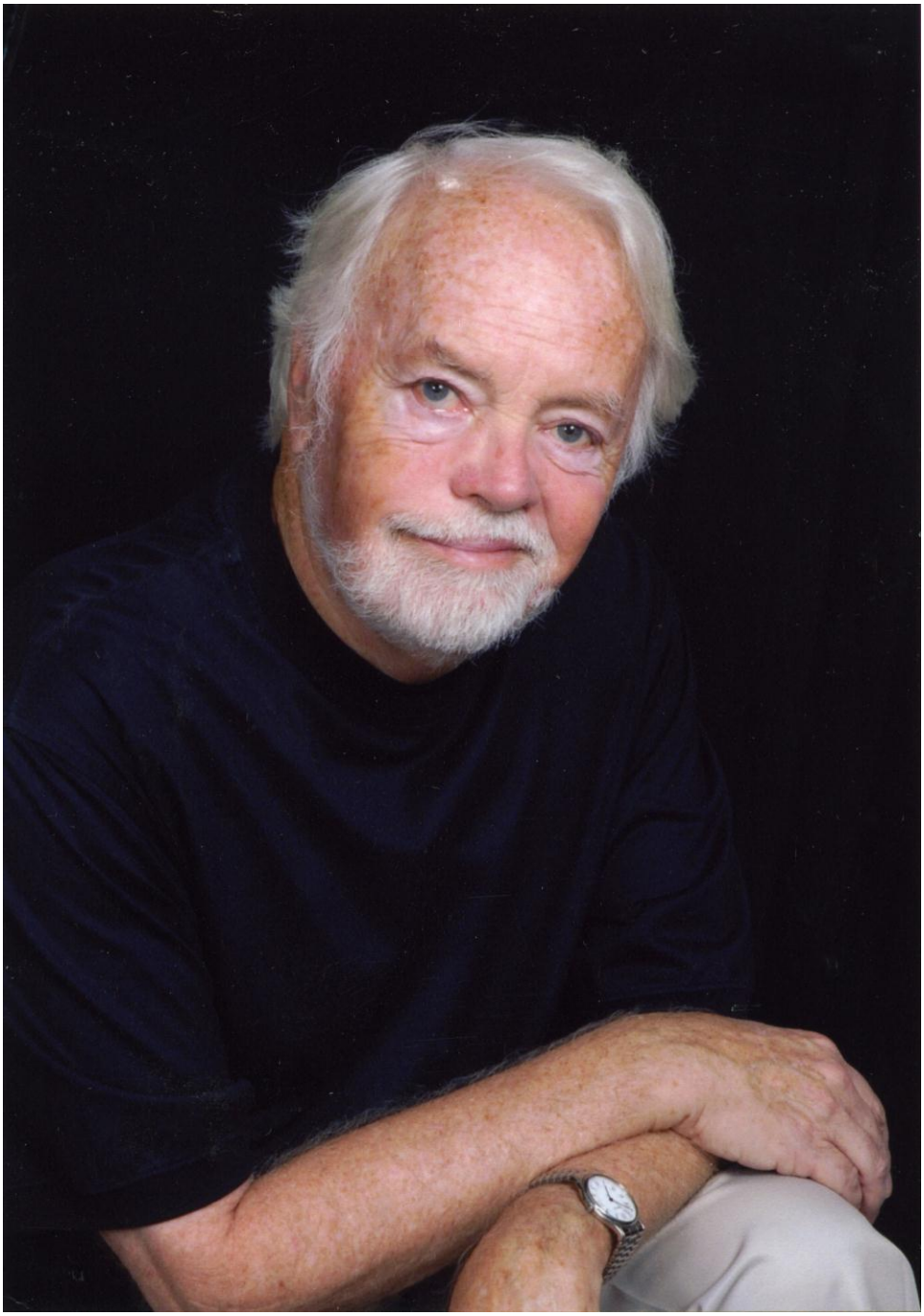
at

the McCloskeys' Home
Helotes, Texas

on

19 and 20 March 2012

(With Subsequent Corrections and Additions)



James A. McCloskey, Jr.

ACKNOWLEDGMENT

This oral history is one in a series initiated by the Chemical Heritage Foundation on behalf of the American Society for Mass Spectrometry. The series documents the personal perspectives of individuals related to the advancement of mass spectrometric instrumentation, and records the human dimensions of the growth of mass spectrometry in academic, industrial, and governmental laboratories during the twentieth century.

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JAMES A. MCCLOSKEY, JR.

1936 Born in San Antonio, Texas, on 25 June

Education

1957 B. S., Chemistry, Trinity University
1963 Ph.D., Chemistry, Massachusetts Institute of Technology

Professional Experience

United States Army Biological Laboratories, Fort Detrick, Maryland
1959-1961 Chemist, United States Army Chemical Corps

Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France
1963-1964 Postdoctoral Fellow (National Institutes of Health)

Baylor College of Medicine, Houston, Texas
1964-1967 Assistant Professor of Chemistry
1967-1971 Associate Professor of Chemistry
1971-1974 Professor of Chemistry and Professor of Biochemistry in the Institute for Lipid Research and the Department of Biochemistry

Tokyo University, Tokyo, Japan
1971-1972 Visiting Professor

National Cancer Center Research Institute, Tokyo, Japan.
1971-1992 Visiting Investigator

University of Utah, Salt Lake City, Utah
1972 Visiting Professor, Departments of Chemistry and Biopharmaceutical Sciences
1976-2003 Director, Mass Spectrometry Facility
1976-2007 Professor of Biomedical Chemistry, Medicinal Chemistry, Department of Medicinal Chemistry
1976-2007 Adjunct Professor of Chemistry, Department of Chemistry
1993-1995 Director, Interdepartmental Biological Chemistry Program
2007-present Professor Emeritus, Departments of Medicinal Chemistry, Chemistry and Biochemistry

Honors

1972	National Institutes of Health Special Fellow, University of Utah
1989	Distinguished Research Award, University of Utah
2005	Award for Distinguished Contribution in Mass Spectrometry, American Society for Mass Spectrometry
2009	Fellow, Section on Chemistry, American Association for the Advancement of Science

ABSTRACT

James A. McCloskey, Jr., grew up in San Antonio, Texas, an only child. His father, a doctor in the US Army Medical Corps, was the first regular army medical doctor killed in World War II, at which time James's name was changed from Robert. He attended public high school, where he was also in Reserve Officers' Training Corps (ROTC). It was always expected that he would attend college, and he entered Trinity University in San Antonio, where he majored in chemistry and continued in ROTC, paying his way with scholarships and with money he earned in summers.

McCloskey realized that he would go nowhere with just a bachelor's degree, so he earned a PhD in analytical chemistry from Massachusetts Institute of Technology. He fulfilled his ROTC commitment by working for the US Army Chemical Corps; he published his first paper there. He also married while in the Army and fathered a daughter while still at MIT. He returned to Klaus Biemann's lab at MIT, where he began his lifelong interest in and study of nucleosides/nucleotides, necessitating different types of mass spectrometers; mass spec was in its golden age. After finishing his PhD, McCloskey persuaded the National Institutes of Health (NIH) to send him to Paris, France, for a year. He turned down the Karolinska Institutet for a job at Baylor College of Medicine in Houston, Texas. At Baylor he continued his funding relationship with the NIH, getting a number of spectrometers for the College. He began a twenty-year collaboration with Susumu Nishimura in Tokyo, Japan, and made his first of many trips there. He learned the biology of tRNA; Pamela Crain began working for him; his lab discovered the nucleoside Q. He began his part of the search for the roots of the tree of life, which consists of bacteria, eukaryotes, and archaea.

McCloskey spent six months of a sabbatical at the National Cancer Research Institute in Tokyo before going to the University of Utah as a visiting professor. He decided to accept a full professorship there, citing common interests, funding, and research freedom. Pamela Crain moved with him, continuing to collaborate on many papers. In addition to running his lab, heading the mass spec facility, and teaching, McCloskey became secretary, vice president, then president of the American Society for Mass Spectrometry (ASMS). He continued collaborating with mostly scientists outside the United States, especially from Japan; his work was primarily with ribonuclease T1 and T2; he studied how organisms modify in reaction to increase in temperature and found that they also modify below freezing.

McCloskey talks about his grants, all of which were approved by NIH and which remained constant; the different types of spectrometers and their uses; collision-induced dissociation (CID); polarity; importance of mass accuracy; his funding and funding in general; Carl Woese and the tree of life; synthesis of a new molecule he named archaeosine or G+; closing down his grants and lab when he retired and moved back to Texas; changes in the field of chemistry, in mass spec, and in students. He explains his editorship of *Methods in Enzymology* and his collaboration or lack thereof with several scientists the interviewer asks about. He laughs over the Prochaska scam. He modestly claims that his contribution to mass spectrometry was "not that great," meaning that he answered difficult questions in a narrow area. He has retired completely but remains interested in the field of chemistry, marveling at its sudden and rapid expansion.

INTERVIEWER

Michael A. Grayson retired from the Mass Spectrometry Research Resource at Washington University in St Louis in 2006. He received his B.S. degree in physics from St. Louis University in 1963 and his M.S. in physics from the University of Missouri at Rolla in 1965. He is the author of over forty-five papers in the scientific literature dealing with mass spectrometry. Before joining the Research Resource, he was a staff scientist at McDonnell Douglas Research Laboratory. While completing his undergraduate and graduate education, he worked at Monsanto Company in St. Louis, where he learned the art and science of mass spectrometry under O. P. Tanner. Grayson is a member of the American Society for Mass Spectrometry (ASMS), and currently is the Archivist for that Society. He has served many different positions within ASMS. He has served on the Board of Trustees of CHF and is currently a member of CHF's Heritage Council. He continues to pursue his interest in the history of mass spectrometry by recording oral histories, assisting in the collection of papers, researching the early history of the field, and preparing posters recounting historic developments in the field.

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ALSO PRESENT: **Kathleen (Kay) McCloskey**

INTERVIEWER: **Michael A. Grayson**

LOCATION: **the McCloskeys' Home**
Helotes, Texas

DATE: **19 March 2012**

GRAYSON: …and it says that we're recording. So as usual, I'll start out this interview stating that I'm in Helotes, Texas, interviewing…

J. MCCLOSKEY: Helotes […].

GRAYSON: Helotes, […] Texas, interviewing Professor James Augustus McCloskey. It is the 19th of March, and we are at his residence, which is a very pleasant place in the countryside here. And so I think with that, we can go ahead and get started. Just for informational purposes, the town is in the northwest quadrant of San Antonio's [Texas] super suburbs. It's really probably not a suburb. It's just a small town outside of the northwest Greater San Antonio area. So James, I usually like to start beginning in the childhood.

J. MCCLOSKEY: Start at the beginning?

GRAYSON: Yes, right. Start at the beginning, and the influence of your parents and other people in your getting directed towards a scientific career. So tell me a little bit about your parents.

J. MCCLOSKEY: I never met, as far as I know, my father [James McCloskey]. I was raised by my mother [Marian K. McCloskey]. He was killed when I was four or so. He was killed in World War II. So I was born here, and as a consequence of being in a military family—he was a physician in the Medical Corps, what was then called the Medical Corps—and we moved with him to the Philippines. And we were there a year and a half or something. I could find out. And…

GRAYSON: So that was while he was alive and he was in the service?

J. MCCLOSKEY: That's right.

GRAYSON: Okay.

J. MCCLOSKEY: So that was, like, 1938 and 1939 or something. The war broke out in what, 1941?

GRAYSON: Yes.

J. MCCLOSKEY: And we came back on the last [maritime] transportation out of the Philippines.

GRAYSON: I see. Well, you say he was…

J. MCCLOSKEY: And he stayed.

GRAYSON: He was in the Medical Corps, so, I mean, he wouldn't have normally been in a position to be killed in the military? Or was he in a dangerous…

J. MCCLOSKEY: Well, I don't know. He was on Bataan [Philippines], I think. By virtue of being there, the risk factor is high, and so forth. So he died, and I was raised by my…not only by my mother as, sort of, a single parent, but my [maternal] grandparents as well. And we lived with them off and on through this time.

GRAYSON: What were their names?

J. MCCLOSKEY: My [maternal grandparents]—these were her parents, not his—her parents were Archibald Koehler, K-O-E-H-L-E-R [and Florence Magill Koehler].

GRAYSON: Archibald and Florence.

J. MCCLOSKEY: So anyhow, we spent a lot of time in San Antonio, and no time anywhere else, when I was in…right before we went to the Philippines, however, we stayed six months at Fort Sill, Oklahoma, and the significance of that was that they had a polio outbreak, and I contracted polio almost surely at that time. And when we left and went to the Philippines, I was the only person within a large radius that had polio, even though it was the thing around here, you know. So they figured that it corresponded precisely to an outbreak that they had at Fort Sill. Anyway, it didn't affect my legs at all. That was a [fortunate] thing.

GRAYSON: Hmm. Yes.

J. MCCLOSKEY: It affected the muscle in my…right [facial] muscle, called the seventh nerve, really, over on this side of my mouth.

GRAYSON: Was that an unusual effect of polio? Most of the time people had leg issues, it seemed.

J. MCCLOSKEY: Not unusual. I mean, it was not common, but less than…you know, there are people who lose arm control and so forth.

GRAYSON: Oh, yes.

J. MCCLOSKEY: The famous ones are the ones who can't walk. And so forth. I mean, still alive. There was a high mortality rate. Anyway…

GRAYSON: So what about your **<T: 5 min>** parents' names? We got your grandparents, so what…

J. MCCLOSKEY: My father was James [Augustus McCloskey. He was the son of a prominent Bexar County judge (Augustus McCloskey) who had also been a United States Congressman.]

GRAYSON: Okay.

J. MCCLOSKEY: [When I was born I was named] Robert. And I became James Junior after he was killed, and it was clear that I was going to be an only child. […] My mother said, […] "Let's change your name," and got a court order to do this, and so forth and so on.

GRAYSON: So if we go back and look at the records, we'll see Robert on the birth certificate?

J. MCCLOSKEY: You'll see Robert on the birth certificate in San Antonio, and I don't remember the year [of the name change]. I, maybe, was five or six years old when it was switched to James. So that started the ball rolling. And I lived here I guess, sort of, continuously until I went to graduate school in 1957. Is that right? And my father was killed in [the Philippines in] March of 1942. That's right. So they named a hospital after him in Temple, Texas, which they then changed the name [years later]. It became a veterans' hospital. He was the first doctor to be killed in the war.

GRAYSON: That's why it was, kind of…but like you said, he was in a very bad place.

J. MCCLOSKEY: Yes. And he was the first doctor, so it was one of those strange things, the claim to fame…kind of crazy. So anyway, all I had as a youngster growing up was the continuous question from family, "Of course you're going to be a doctor, aren't you?" So the automatic reply was, "No." [laughter] And it probably changed my…I may have done that, and that might have…then I'd have had a different life, path, and I never really, you know…and my mother supported me on that and so forth. So I went to […] college here. Lived at home […].

GRAYSON: So your undergraduate was at…

J. MCCLOSKEY: At Trinity University [in San Antonio].

GRAYSON: Okay.

J. MCCLOSKEY: And so that's kind of a home environment, isn't it, all the way through high school and college living at home.

GRAYSON: […] Now your dad was obviously pretty well educated as a physician. Was he just…I guess at that time they didn't specialize too much. He was probably like a general practice…

J. MCCLOSKEY: […] He [went to college] at St. Edward's University in Austin [Texas] [and medical school at St. Louis University in St. Louis]. And, of course, at that time, never dreamed that he would either be in the Army or killed. So. The War was…

GRAYSON: Yes. So was he taken because of his skills, or did he volunteer? Do you recall? Or do you know anything about that part of it?

J. MCCLOSKEY: […] He [chose the Army as a career path.], so I guess what I would need but don't have is the year that he entered the military. All the [military] records, including the details of his death, were destroyed in a fire in St. Louis [Missouri].

GRAYSON: In St. Louis, in the Records Center. Yes.

J. MCCLOSKEY: In…I don't know when it was.

GRAYSON: Yes.

J. MCCLOSKEY: 1959 or something.

GRAYSON: Yes. We remember the fire. I lived in the St. Louis area, and that was a very big news splash, to have the fire at the Records Center, and have so many records destroyed. It was really unfortunate. So there's no way of knowing.

J. MCCLOSKEY: It's just…there are big holes, I think, in the history of the military, and especially the Medical Corps. Anyhow, that's where it all started. And I went then to college with no real influence from anybody, except there was always an expectation that I would go to school and get educated, and whether it was a doctor or not wasn't a serious issue, although I found out as I was going through college that…two things. One was that I enjoyed chemistry, and the other thing was that I found out that people who had B.S. degrees in chemistry were destined for a life of nothing, pretty much. There's nowhere to move, you know, and so forth. Vibes were bad. So that motivated me after college to go to graduate school, and I applied to several places.

GRAYSON: Do you recall if there was anyone in your college career that kind of really impressed you with chemistry. You know, I mean, a lot of times a teacher or what not **<T: 10 min>** will get somebody turned on, and…or was it just that you found it to be fun?

J. MCCLOSKEY: So there were two people [both professors of chemistry. One] was a man named William [C.] McGavock. […] And another one named [Earl Cooper] Smith. […] This is a [relatively] small school. You've got six chemists graduating with you […].

Anyhow, [these two] were influential and they encouraged me greatly to go on [to graduate school].

GRAYSON: Okay. So that was a factor in pursuing chemistry?

J. MCCLOSKEY: Yes. Oh, it was quite clear. It was quite clear. And…

GRAYSON: Was the rest of your family beginning to back off on the medical degree thing, or were they still…

J. MCCLOSKEY: No, they said, "Well, okay. It's up to you. Do what you want to do." And as long as I was pointed in an upward sort of direction, they said, "Well, that's fine."

And so there was disappointment in my father's family, that I didn't go into medicine, and furthermore, I changed my name. Oh, no, there shouldn't have been a difficulty over that, because I took my father's name, so I think that wouldn't…

GRAYSON: Yes.

J. MCCLOSKEY: That wasn't a problem. So anyhow, time went on, and I went to Trinity, and graduated from Trinity in four years, a very standard arrangement.

GRAYSON: Small things like what the tuition was and were you financing yourself?

J. MCCLOSKEY: There was trouble here, because my mother never remarried, and her income was confined largely to military pension-type stuff for [military] widows.

Now in those days, however, being a widow meant that you not only had medical care, but…and especially if your husband had been a doctor who was killed, that cemented it in. And I had medical care. This is great, you know. You get orthodontists to look at your teeth [and so forth]. So that was helpful. I had some fellowships—scholarships, rather, [from the Minnie Stevens Piper Foundation]—at Trinity. And I worked in the summers somewhere. Let's see. The one I remember the most was a place called American Lithium Chemicals Incorporated, outside of San Antonio. And I was in there just doing lab work part-time, I mean, just scut work, you know. [laughter] But that suited me, and it was a significant amount of money, I think, over a period of time. But otherwise…

GRAYSON: So your tuition was in the range of…

J. MCCLOSKEY: I don't know what it was in those [days], but it was relatively high, and still is. It was a private university. […] And there's some affiliation with the Presbyterian Church, but not much. And their academic rating is now notably higher after I left. […] In fact, it's pretty good. […] But that's a beautiful campus. It's here in the city.

GRAYSON: Is it still a pretty small school, compared to…

J. MCCLOSKEY: Well, they've got maybe twenty-five hundred students. That's pretty small.

GRAYSON: Yes. By today's standards.

J. MCCLOSKEY: Yes. So anyhow, that was the story there. And I found out that I could also get financial support [from the government] as the [surviving] son of a [person killed in the War]…There was a survivorship thing, […] because of my father and his death and so forth, I had a small stipend that got cranked up and paid me through graduate school.

So I got a little bit there. I mean, we're talking a hundred dollars a month or two hundred dollars a month. I don't remember, frankly. And you add that to normal support the graduate students get; you work in the lab, and they pay you something, maybe it's thesis work, maybe it's not, but everybody contributes, and so forth. And so those were the parameters **<T: 15 min>** up till that stage. [Also, Kay worked at the MIT Aeronautics and Astronautics Library until Lydia was born].

GRAYSON: So you were able to go to school. You weren't living high off the hog, so to speak, but you were…

J. MCCLOSKEY: It was fairly fundamental, and I enjoyed it, except that I found out that there was a sea change, S-E-A change, in culture and everything around me moving from here to Cambridge, Massachusetts [to attend MIT]. This was a big change.

GRAYSON: Oh, yes.

J. MCCLOSKEY: In every way you can think of it.

GRAYSON: So this was graduate school?

J. MCCLOSKEY: Graduate school.

GRAYSON: What made you decide to try to get into MIT [Massachusetts Institute of Technology]?

J. MCCLOSKEY: Well, there were several options. I also applied to Purdue [University] which was a red hot place at that time. I liked analytical chemistry, and that seemed to be interesting. So those were the two places. I was accepted to Purdue, and then was accepted at MIT, and I was always impressed by the fact that the chairman of the department of chemistry at Purdue wrote me a nice letter saying, you know, "Best of luck. Sorry you won't join us." But just, "Good luck in your future endeavors."

GRAYSON: What year would this have been?

J. MCCLOSKEY: […] 1957, graduated from college. And so the wheels also were turning slightly early. I was [fifteen] when I graduated from high school. [For various reasons], my mother decided [when I finished elementary school in the Catholic school system that I should go to public schools. The Catholic schools] were really advanced, and you could just slip over the [seventh grade in public schools], and I did it.

GRAYSON: So you skipped a grade…

J. MCCLOSKEY: Yes, skipped a grade and that put me on a different track, for a long time. Interesting how those tracks work out.

GRAYSON: Oh, yes.

J. MCCLOSKEY: And so I finished graduate school…

GRAYSON: I'm just curious if you […] remember the name of that Catholic school.

J. MCCLOSKEY: Which one? That I went to?

GRAYSON: Yes, the one you went to.

J. MCCLOSKEY: Oh, my gosh. When I was a little tad, a little guy, I went to St. Peter's Prince of the Apostles School [elementary School in San Antonio]. I remember because of the uniform, the little patch on the sleeve.

GRAYSON: So you were in a uniform-type outfit.

J. MCCLOSKEY: Oh, yes. This place was run by nuns. [laughter]

GRAYSON: Yep. Everybody chuckles on that one.

J. MCCLOSKEY: Boy. [laughter] I saw some real human rights violations. You toed the line, and so forth and so on. So…

GRAYSON: Well, it didn't hurt you any.

J. MCCLOSKEY: No, I came away, at least at that time, with a fairly good handwriting, which is one of the things you got, needless to say. They made sure that you could do this. [But I went from St. Peter's to Mark Twain Junior High School and then graduated from Thomas Jefferson High School in San Antonio in 1953].

GRAYSON: Yes.

J. MCCLOSKEY: So anyhow, then on to graduate school…

GRAYSON: So you were really pushing it age-wise in terms of…

J. MCCLOSKEY: A little bit.

GRAYSON: You were kind of the youngest in your classes as you were progressing now at this point in time here. Did you see that as a handicap, or did it work out okay, or maybe you were…

J. MCCLOSKEY: I never thought about it. It didn't seem to be a handicap. After a while, I figured out it may have been an advantage of some kind. I never could figure out how I was going to take advantage of that. But it meant that I was, you know, twenty-one when I [graduated from Trinity].

K. MCCLOSKEY: We had our first date on your twenty-first birthday, and that was [the summer] before you went to MIT.

J. MCCLOSKEY: That's right. You're right about that. Anyhow, so that was the track. And my mother anyhow died in 1988, and so forth. But I was raised essentially by her. One-parent thing. I did have grandparents, but their influence in a parental sense was pretty minimal, you know. **"**Sit down, let's talk about this." There wasn't any of that. So I think I was in a **<T: 20 min>** one-parent family, actually.

And she worked very hard to…you know, [she said], "I couldn't marry anybody else, I couldn't do anything else, because of your father," and the support and so on, and…

GRAYSON: Did she actually have a job in addition to the pension, or was she was able to…

J. MCCLOSKEY: She did not. And I think that's what made life more difficult for her. And, of course, this [was] in an era right then, the 1940s, where women didn't go out and work. I mean, they were either housewives or something. They went to work for the War, or something, but, you know, you didn't have skills that were natural that you could take advantage of.

So anyhow, I somehow made it through MIT. It was relatively difficult because of the different level of education. It just was nothing like I was accustomed to. While I was at Trinity, I found out that some of the courses I was taking were boring, and I didn't do very well, and I found that's because I was bored. But when I went to MIT, all that stopped because you're running on a treadmill night and day.

GRAYSON: Yes.

J. MCCLOSKEY: To keep up

GRAYSON: Yes. Right. High performance.

J. MCCLOSKEY: It's a high end story and you're, of course, also in the presence of the MIT undergraduates, and they are very smart. Very smart. Smarter than the graduate students.

GRAYSON: Yes.

J. MCCLOSKEY: And so that was an interesting experience, the whole thing.

GRAYSON: So what year did you start at MIT, then? That would have been somewhere in the…

J. MCCLOSKEY: 1957, and I had gone…back up one step. I had gone to ROTC [Reserve Officers' Training School] in college; also in high school, I might add.

GRAYSON: Yes. Was this Army ROTC?

J. MCCLOSKEY: Army ROTC. And I did it in college. And so when I graduated as a second lieutenant in the Reserves from college, I accrued an obligation at that point. And the choices were you can pick when you go in, but you've got either six months' or two years' service. And the six months thing you get very little choice in, but the two years, you get a little more choice, and so on. So I said, you know, I found out that one of the most awful prospects would be—because I had talked to people who had done this—is to get a Ph.D. from a school like MIT and then go in the Army. [laughter]

I was an artillery officer, and I thought…they said, "Gee. Whoa. You…" So I said, "Okay, I've got to get out of this deal." So I talked to the people at MIT to take a leave and get rid of the military service and return. They said, "Oh, that's wonderful. That's no problem. Just let us know when you're ready to come back." Very informal arrangement.

GRAYSON: So this was a…you opted for the six months?

J. MCCLOSKEY: No. Well, at that time I opted for the two years.

GRAYSON: Oh, okay.

J. MCCLOSKEY: And because I got transferred to the Chemical Corps; that was helpful. I think it was helpful.

So I did so by actually going to the Pentagon. I went to the Pentagon—big building—and I walked in the front door, and found the Chemical Career Officer, he's the guy that guides people, officers in the chemical career. [laughter] And I knocked on his door, and as a result of this we chatted and had tea and other things, [then] he said, "You know, let me know exactly what your timetable is. I think I can get you out of the artillery."

So I moved out of artillery into the Chemical Corps, and while that didn't…you know, the result of that actually was that I spent…the two [army] years were spent mostly in a lab, and they didn't know what to do with me. This was at the biological warfare place in Fort Detrick [Maryland]. And they weren't sure—there were chemists there and so on and so on—but they weren't quite sure what to do with me. So they pretty much said, "Here's a lab. **<T: 25 min>** Go get 'em."

So that was the [setting]. I published my first paper out of working there.[1] I dreamed up something [in electrochemistry] to do and did it, and published it, and I was happy. So that was that. And I went back to MIT…

GRAYSON: So it was a little two-year hiatus…

J. MCCLOSKEY: Hiatus, and I had done pretty much my coursework before I left, and then

[1] James A. McCloskey, "Direct Amperometry of Cyanide at Extreme Dilution," *Analytical Chemistry* 33(13) (1961): 1842-3.

when I got back, then there [were] exams you have to take to get into candidacy. That was awful. I mean, these are big barriers in life, you know.

GRAYSON: Oh, yes.

J. MCCLOSKEY: And so I came back, and I was married while I was gone, which…I was married while I was in the Army.

GRAYSON: Okay.

J. MCCLOSKEY: So the difference was…of course, another difference was when I returned to graduate school, I was married. When I left graduate school, I was not married. So life was somewhat different there, and both of us were adjusting to New England. The weather, the language. [laughter] You name it. It just was another [culture].

GRAYSON: So your wife is from this area?

J. MCCLOSKEY: She's from the [Texas] Gulf Coast.

GRAYSON: Oh, okay. So both Southern types.

J. MCCLOSKEY: Yep. That's right. That's right.

GRAYSON: Not used to the upper Northeastern [climate].

J. MCCLOSKEY: No, no, no. Northeastern anything. But we enjoyed it. We both thought that Cambridge and Boston [Massachusetts] was a worthwhile experience. For anybody, I recommend it. It's full of all kinds of cultural things that you are not familiar with, right? Music, art, different points of view. […] You go to a big-time graduate school, you meet people from all over the place.

And that's a plus in my book. That is a serious plus. You don't know it at the time, but later on, you say, "Gosh, that was a very positive thing." And it influences me. Later in life even I realized my acceptance of diversity and so forth was partly because I was tossed into this

maelstrom of different people and ideas and cultures and so forth. So then, let's see, where are we?

GRAYSON: So you finally got through with your Army obligation. Now you have to go back to MIT, and you have to…somewhere in there, you have to decide who you're going to work for.

J. MCCLOSKEY: That's right. And they…it was analytical chemistry, and it turned out that at that time their analytical chemistry division had three professors, and unknown to me, one of them [Lockhart B. "Buck" Rogers] had just gotten a job at Purdue, to move—he was a full professor—to move to Purdue. I didn't really know that when I went to talk to him. And then another one was an electrochemist, [David Hume]. He was okay, I thought. And then the third was a totally untested, brand new assistant professor, Klaus Biemann, who worked with mass spectrometry, which I didn't know anything about. And Dr. Rogers said—Buck was his nickname, Buck Rogers—said, "You know, you really should go down…" I had just walked in to tell him I was going to work with him [Buck]. He said, "No, no, no. You really should go down and talk to Klaus Biemann. You know, he can measure ^{15}N contents of amino acids in mixtures." All kinds of things. It sounded a little on the edge, you know. He said, "That's pretty exciting. You should do that." And I went down the hall [to seek out Klaus Biemann] and never came back.

GRAYSON: Yes. Now this Dr. Rogers guy, how does he fit into the…

J. MCCLOSKEY: Well, he then moved, so he…

GRAYSON: So he was the guy who was going to Purdue?

J. MCCLOSKEY: Yes. […] He moved to Purdue…

GRAYSON: So he kind of didn't want to take anybody on because he knew he was about to depart.

J. MCCLOSKEY: Yes, he was walking out the door. I didn't know that [at the time]. But he was very warm in his endorsement of Klaus Biemann.

GRAYSON: Yes. So I still need to…so we figure this is in the early 1960s? So you spent two years with your Army obligation…

J. MCCLOSKEY: […] This is 1960.

K. MCCLOSKEY: [Our daughter] Lydia was born in 1962.[2] So, this is 1961.

J. MCCLOSKEY: I graduated from graduate school in '63. It was two years, **<T: 30 min> s**o I went back in 1961. Must have been 1961, back to school, two years, graduated then in 1963.

GRAYSON: So Klaus hadn't been there…he'd been there maybe…

J. MCCLOSKEY: Two years?

GRAYSON: Not too many. Not too long. [laughter]

J. MCCLOSKEY: But the interesting thing about it was that even in my early stage in life, I could read the jungle drums, and the jungle drums were: be very careful, if you go to work for an untenured assistant professor in this place, because [if] they don't get tenure, then where are you? You are out, high and dry.

GRAYSON: Yes.

J. MCCLOSKEY: And, of course, he had no graduate students.

GRAYSON: At that time, he was… [laughter]

J. MCCLOSKEY: And so they're saying, "Whoa, this is a limb. You're climbing out on a limb."

[2] After the birth of their first daughter, two sons and another daughter were born while in Houston, Texas.

GRAYSON: You were his first experiment?

J. MCCLOSKEY: Yes. And I said, "Okay, I want to do it anyway." And so I did, and I remember going back to see him after he had interviewed me, and I had gone back, and I said, "I want to work with you." He looked kind of amazed at this. He said, "You're sure you want to work with me?" I said, "Yes."[3] So that was, for him, a big deal, because being an assistant professor, you don't get anything done without hands. You need hands.

And in his case, the hands were from graduate students, which then rapidly followed. He wrote [a] book, and that gave him an element of fame, called *Mass Spectrometry*,[4] and so he gained students. But he understood what to do, and it was to import, in this case Austrian—Swiss and Austrian—postdocs, that had come in ready to go. No training. And no mass spectrometer. That's not important. They do chemistry things. But they went into mass spectrometry pretty fast, because it was being learned at that time that mass spectrometry was chemistry. These were gas phase reactions of organic molecules. There were rules. Nobody understood them too well, but there were rules. And it was a new day. So…

GRAYSON: Yes, because my recollection is that he really had this chemical synthesis route to make these compounds he wanted to study that weren't really amenable to the mass spec volatile, so he would derivatize the things to get them into volatile form. But his earlier training was in all this chemistry technology.

J. MCCLOSKEY: Right. So he was really a microchemist. He worked for [a] man named [Hermann] Bretschneider, and was a microchemist with peptide research in mind. He saw the problems, and he saw, you know, this is a different sort of game. And he sold me on the idea, initially, that the enemy here is volatility. We are really up against it, because we're now making these derivatives to do GC with and so forth, and wow, there must be a better way to do this. And the better way is to try and find a more direct route to making gaseous ions, especially of biological molecules. And he said, you know…and that's where I got into the nucleoside, nucleic acid, arm of things, because they were terrible. It was the worst case. They were more polar than peptides, and it just was horrifying. So…

GRAYSON: So, but, I mean, my recollection was Klaus was focused on peptide work initially. So…

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[3] Klaus Biemann, "The Massachusetts Institute of Technology Mass Spectrometry School," *Journal of the American Society for Mass Spectrometry* 5 (1994): 332-8.
[4] Klaus Biemann, *Mass Spectrometry: Organic Chemical Applications* (New York: McGraw-Hill, 1962).

J. MCCLOSKEY: That's right. For a long time; even while I was there. The peptide thing went on full force.

GRAYSON: Oh, yes. Yes. So why did you get…did you select the nucleoside/nucleotide side of things, or did he suggest that, or how did you get into that?

J. MCCLOSKEY: No, I thought it looked very interesting, and the biochemistry seemed to be endless.

GRAYSON: Oh, yes.

J. MCCLOSKEY: And other…more endless than I knew.

GRAYSON: But for mass spec, they're more difficult to deal with.

J. MCCLOSKEY: Yes. That's right. So this was an opportunity. He said, "Well, let's start by…there is a mass spectrometer that is on the market that we can buy," and he was trying to get money from NASA [National Aeronautics and Space Administration] at that time to do it, which is a Bendix time-of-flight mass spectrometer. [And he was successful. It was intended ultimately to analyze moon rocks for involatile organic matter, a topic of great interest about then].

GRAYSON: Oh, yes, yes.

J. MCCLOSKEY: And it has a probe that comes in from the bottom, like this. And they did inorganic thermal things with it. And [Klaus] reflected that he had met or heard of a man in Scotland named Reed, [Rowland] Ivor Reed, who had some success with some polar molecules, putting them on the **<T: 35 min>** end of a probe like that and putting them in and just flashing them off in the mass spectrometer. And he said, "That's an interesting thought." It would be subliming them. They would be sublimed, in other words, if they didn't decompose.[5] So let's try that, and that worked, and it was gold.

[5] Klaus Biemann and James A. McCloskey, "Application of Mass Spectrometry to Structure Problems VI. Nucleosides," *Journal of the American Chemical Society* 84 (1962): 2005; Klaus Biemann and James A. McCloskey, "Mass Spectra of Organic Molecules. II. Amino Acids," *Journal of the American Chemical Society* 84

GRAYSON: So this was…now, one of the things I've been trying to sort out personally is who really is the responsible entity for the creation of the direct insertion probe for putting samples into a mass spectrometer. Sounds like…I mean, I'm getting a sense that Bendix was the one that pioneered this.

J. MCCLOSKEY: Well, they pioneered it, but not for organic molecules.

GRAYSON: No, not for organic molecules.

J. MCCLOSKEY: They had a device you could use, and so since…I made it work, and then Klaus had just gotten a 21…

GRAYSON: 110?

J. MCCLOSKEY: CEC 21…I don't know.

GRAYSON: 103?

J. MCCLOSKEY: 103, and he said we should be able to do the same thing […].

GRAYSON: So when does he…well, but I mean, when he first came there, he was already doing mass spec, so what was he using?

J. MCCLOSKEY: That must have been with his [21-]103.

GRAYSON: With…well, yes, 103. Okay.

J. MCCLOSKEY: And that's the bottom rung of…

(1962): 3192-3; and Klaus Biemann, H.K. Schnoes, and James A. McCloskey, "Application of Mass Spectrometry to Structure Problems. Carbohydrates and their Derivatives," *Chemistry & Industry* (1963): 448-9

GRAYSON: The 110 [was]…

J. MCCLOSKEY: CEC 21-110…

GRAYSON: Okay. Yes. That's the big Mattauch-Herzog puppy?

J. MCCLOSKEY: Yes. That's right. So he was working in the Stone Age. [laughter]

GRAYSON: Yes. So he was trying to get money for…

J. MCCLOSKEY: And he did. He did. He got it from NASA. And so I was kind of on a parallel track, and …

K. MCCLOSKEY: NSF [National Science Foundation]. It was funded by NSF and CEC.

J. MCCLOSKEY: By NSF. Oh, okay […].

GRAYSON: NSF. Okay. […] The 110?

J. MCCLOSKEY: At that time, he had also…Al [Alma L.] Burlingame then joined […] after I did, and he worked on alkaloids. So he also had a track that was destined to not be the mainstream in Klaus' work, although Klaus really enjoyed the alkaloid work. It worked well for him, and it wasn't entirely [wasted time].

GRAYSON: They didn't have to do so much messing around with the, like, derivatization and all that kind of stuff.

J. MCCLOSKEY: Yes, and you get families of reactions, and you can place substituents by the same [procedures as for other organic molecules].

GRAYSON: Yes. Yes.

J. MCCLOSKEY: The shift technique. The shift technique. It was a gem for the shift technique.

GRAYSON: So that shift technique does what?

J. MCCLOSKEY: It means that you take the mass spectrum of a simple model and you understand it. Now you look at its neighbors or its homologues and analogues, and you see some peaks stay the same and some shift.

GRAYSON: Oh, okay.

J. MCCLOSKEY: If they shift by 14 daltons, you have a methyl group, and so on, and so on. While it doesn't give you total structure, it's a very easy way to obtain a large [amount of information very easily].

GRAYSON: Easy way to what's going on.

J. MCCLOSKEY: …amount of information. I mean, these guys spent years with alkaloid things. I mean, whoa. You know, and they were being used for cancer, vinblastine and vincristine and these things. So it was a good line for Klaus, and he rode it for a while, and then realized, I think, that its time had come and gone.

GRAYSON: So did Al come after you were there or about the same time, Al Burlingame?

J. MCCLOSKEY: No, after I was…oh, let's see. […] He was there when I came back from the Army. . […] So I joined Klaus' group first. [Al] was second. , but he graduated before I did. So he's the earliest product on the Ph.D. list and so forth. So anyway, let's see. Where are we […]?

So I was doing…that was the days when we were doing direct probe analysis, and we could get spectra of compounds, including amino acids. We got the first mass spectra of three amino acids, and the first mass spectra of underivatized carbohydrates, and all this is lost in the fog of history. And we published a paper in *Chemistry and Industry*, I think it was, about the

fact you could measure the spectra.[6] But, of course, there were still [volatility] limits. Nucleotides were still out of the question.

Add a phosphate, and you just put a barrier around yourself. , and if you made oligonucleotides, where there were a series of **<T: 40 min>** nucleosides connected by phosphate bridges, the polarity didn't…it would get worse.

So even after a while of that, and then…well, let me see. I spent a lot of time trying to understand the mass spectra of simple nucleosides, and we did. We spent a lot of time doing that.

GRAYSON: So these were…you just take the simplest ones that you could come up with and they were fairly easy to get spectra from?

J. MCCLOSKEY: They were easy to get spectra from.

GRAYSON: From the simple ones?

J. MCCLOSKEY: And you could then find out how to get labels in them. There was a chemistry already out there, and you could get deuterium [incorporated], and you could find out ways to get ^{15}N in, or buy something that had ^{15}N in it. And so you had a route to take to understand [the mass spectra]. Still, there was the problem that they're polar, and when you have a mixture of these things, life is terrible.

Just like the peptide people were finding, that you can take a large protein and make peptides out of it enzymatically, and all of those guys are very polar, and you still have to separate them, and so on and so on. So one thing leads to another, and you see the necessity for improvements in the methodology that is led by those facts.

GRAYSON: Yes. If you didn't have to make gas phase ions out of samples, then mass spec would be a…

J. MCCLOSKEY: I'd be selling shoes, or maybe life insurance. I don't know. That's right.

[6] Biemann, Schnoes, and McCloskey, "Application of Mass Spectrometry to Structure Problems. Carbohydrates and Their Derivatives."

GRAYSON: So you were still…all this time you were using electron ionization?

J. MCCLOSKEY: [Electron] ionization. That's right.

GRAYSON: There was no…you hadn't gotten into any of the other ionization business.

J. MCCLOSKEY: CI [chemical ionization] came along just at the end of that, if we're trying to categorize this. And of course, if you look at the history, the real history of mass spectrometry, organic mass spectrometry, it rides on the back of volatility. Everything was controlled by volatility, and its history, and what people did, chemical ionization and field desorption, field ionization and field desorption, and then electrospray, and it went on and on. And those were all invented and used and exploited because of the volatility problem. That was the fundamental backbone of necessity.

And it's interesting, because so many papers have been published on variations of those things, and they're most…many of them are not very good. But they were steps forward, you see. "Well, look, two years ago we couldn't do anything, so give me a break."

GRAYSON: Yes. Well, looking back on it, when you've got, you know, modern techniques at your fingertips, then it looks like a minor advance, but at the time it was a step…an important step in the right direction.

J. MCCLOSKEY: That's right. And I remember riding in a taxi in Baltimore [Maryland], it was, with a fellow named [W.] Alan Wolstenholme, who was a salesman for [the VG Company].

GRAYSON: Well, at the time it was probably Kratos [Analytical] or AEI [Scientific Apparatus, Ltd.]. Probably AEI, back then.

J. MCCLOSKEY: I think it was AEI, and he told me, he says, "Jim, let me tell you about this. I just came back from England, and I have to tell you this. There's a method where you can make polar things fly very easily by mixing them with glycerol, and then you shoot it with a beam of something." And he said, "It's just amazing." And I said, "Okay. I'm…you know, this sounds interesting." And, of course, it exploded [onto the scene] after that. It was the thing [to do].

And it was, I think, the first look…understanding that people had that there is, you know, numberless, limitless possibilities. Once you get into that sort of thing, the world is getting rosier than you know.

And of course, that was before you could even connect a chromatograph of any kind. And that led to another big branch of the tree, right? And so forth and so on.

GRAYSON: Yes. Well, the one you're talking about of course is FAB, fast atom bombardment.

J. MCCLOSKEY: Yes. Fast atom bombardment.

GRAYSON: Yes. So were you going to…they were ASTM [American Society for Testing and Materials] meetings then at that time. You were…

J. MCCLOSKEY: There were ASTM meetings, E14, committee E14 [Committee on Mass Spectroscopy].

GRAYSON: Yes.

J. MCCLOSKEY: And I was going to those. The first one I went to was in [the 1950s in] New Orleans [Louisiana]. Klaus told me about this and said, "Why don't you go to this, see what's going on?"

And I went to this, and I **<T: 45 min>** found out that there was a world of oil chemists, and I don't mean fats and oils. [laughter]

GRAYSON: Oil in the ground.

J. MCCLOSKEY: Oil in the ground chemists, who did a lot of mass spectrometry. All kinds. And they didn't worry about funds or anything. [laughter]

And it was very impressive. But the chemistry was sort of limited in a certain sense. There were few people looking at hardcore chemistry issues, and that was Joe [L.] Franklin and then Frank [H.] Field, and so forth. [M.S.] Burnaby Munson. And that…

GRAYSON: Did it strike you as strange that these guys worked for petroleum companies at the time?

J. MCCLOSKEY: Yes, it did a little bit. Then I began to realize that they went where the problems are, and where the problems are, the money is, and oil people have just nothing but cash flowing out of holes in the ground. [laughter]

You want two mass spectrometers? In academia you were lucky if you get one in your lifetime. And these guys had two and three lined up on the floor, and that was pretty impressive. So you realized that there was a dynamic here that one had to pay attention to.

GRAYSON: Yes. Well, that was…my earliest recollection of those meetings were pretty much similar, is that the oil people, you know, kind of dominated things, but there were always these…this group of people doing fundamentals, and as you say, Franklin and Field and Munson and…

J. MCCLOSKEY: Right. Of course, even the fundamentals were pretty fundamental in the sense that they're worried about bond strengths and simple stuff, in ethane and propane and so on…

GRAYSON: Right. Yes. In hydrocarbon molecules.

J. MCCLOSKEY: But, you know, that's where you begin. And of course, that was—whoa, that was—I have to look at the date…

GRAYSON: Well, New Orleans, I can get the date for that, because I have all those dates. That was in the ancient history, kind of. I think that was the last meeting they had in New Orleans. That was one of the earlier ASTMs…

J. MCCLOSKEY: Only one, you think, or was there…

GRAYSON: Well, they had two in New Orleans, and that was…I think, it might have been the second of the two, and they had a problem with one of their attendees couldn't get a hotel room or whatever, you know, because he was black, and…

J. MCCLOSKEY: Oh, Lord.

GRAYSON: They opted not to go back to New Orleans.

J. MCCLOSKEY: Isn't that interesting?

GRAYSON: Yes. Yes. Well, you know, that was the tenor of the times, you know.

J. MCCLOSKEY: Yes. Absolutely.

GRAYSON: So the governing group made a decision to, you know, essentially blackball New Orleans because of that. Well, I know the meeting hasn't been there. I've got the whole list of, you know, meeting sites and dates and everything.

J. MCCLOSKEY: Impressive. It's impressive. And so…

GRAYSON: So did you learn anything from these oil chemists?

J. MCCLOSKEY: I didn't learn…well, yes. I did. I realized they were doing quantitative work and that there were ways to make quantitative measurements, when you understood ionization efficiency, and you could make mixtures and do those sorts of things, and while you would say now that's pretty simple chemistry, it was…for those guys, it was gold.

And they had to deal with awful things like fragmentation.

GRAYSON: Yes. Well, all those hydrocarbon molecules broke up…

J. MCCLOSKEY: Especially if they're branched.

So you can see where they came from when electrospray hit the world. Whoa. They said, "Oh, our problems have just gone away. The biggest problems have just gone away." And they did. They had gone away. I don't know where they were with fast atom bombardment. They were in it, but not…

GRAYSON: Yes. So much of the stuff they dealt with was not…was non-polar.

J. MCCLOSKEY: Yes. So FAB didn't do too much for them.

J. MCCLOSKEY: That's right. But once again, there were signs that better times were coming. And that sign that better times were coming was a flag starting to be carried by the biological people, who said, "Whoa, we're really solving problems. We can solve unusual problems, ground-breaking problems, you know, with these methods, and we're going to take the ball and run with it." And that became, then, a section of ASTM E14. And a very healthy one, rapidly growing, to the point now where I think it has squeezed out everything.

GRAYSON: Well, yes. The focus of the conference has always been kind of fluid, you know. I mean, I remember the period when environmental issues had a huge…you know, you'd go to the meeting and **<T: 50 min>** papers on environmental analyses would be pretty dominant, you know. They would take over a large section of…but my recollection is biologicals didn't really come home seriously until electrospray and MALDI [matrix-assisted laser desorption/ionization] got on the scene.

J. MCCLOSKEY: Yes. Then they were going to solve famous problems. I mean, it wasn't just…

GRAYSON: Yes. But you guys were a kind of advance guard, using solid probes and FAB. So did you actually use FAB while you were at MIT, or did you…

J. MCCLOSKEY: No. No. Never did. That came after. That came while I was in the Army. I think. Wait a minute. No.

GRAYSON: I've got some dates on FAB, but I don't know…

J. MCCLOSKEY: No, I was never…there was a guy named Guy [P.] Arsenault. Remember him? […] He worked in Klaus' lab, and he was, I think, the first one to try FAB in Klaus' place.

GRAYSON: So was he—I've heard his name before—was he like a lab tech person?

J. MCCLOSKEY: No, he was a super postdoc or something.

GRAYSON: Oh, okay. Super postdoc. Okay. Yes. Those things happen, but this is kind of early in the timeframe of what we're doing to…yes, he was…I think he did a lot of stuff, you know, with Klaus and pushing the limits of things.

J. MCCLOSKEY: Yes. But not a lot with Klaus' people. He was an island…

GRAYSON: He was his own shop?

J. MCCLOSKEY: …pretty much unto himself, which is fine. I didn't worry about how that came to be. But he was the front man to do some of that stuff. I'm pretty sure that FAB was one of them.

GRAYSON: He was a French-Canadian, wasn't he?

J. MCCLOSKEY: Yes. And he left MIT to go to Quebec [Canada] or someplace like that […].

GRAYSON: Yes. I remember. I actually looked at some of his papers when we were doing some things, so the name is familiar to me, Arsenault. So he was…eventually he left Klaus' lab and went on to…

J. MCCLOSKEY: In the 1970s, I guess. According to this. Yes. So he went then and got a different kind of job in Canada. So…

GRAYSON: So some of the fundamentals work probably was a little bit interesting to you guys…you as well, right? Because of how these guys were approaching understanding ionization efficiencies and so on, and using it for quantitation.

J. MCCLOSKEY: Yes. To do things. And then all of a sudden there was this business that I never gave much thought to about the dissociation chemistry of simple hydrocarbons. And it turned out that CH5+, that I had never heard of, became one of the most famous ions in analytical chemistry, because it was the reagent ion for chemical ionization for methane. It was

the principal product of methane dissociation, and the higher the pressure, the more CH5+ you have, and it was a powerful acid. It donated the proton to all kinds of things, making protonated molecules in the gas phase. If you're doing that in a mass spectrometer, you're doing it in the right place, and that, of course, was Joe Franklin. Those guys were doing those kinds of things.

And I remember being puzzled by the whole thing, but I could sit back and look at what they're doing and think about this business about the pressure, what happens when you go up in pressure, and some of these curves were going down. Others were going up. And it was a challenging, fascinating thing, and I don't know if Joe even understood what this stuff was. Frank Field did after a while, but I think they were happy investigating the fundamentals. And it wasn't until later that somebody said, "Hey, wait, wait, wait. These ions you're making can do many things. Let's look at this." And so forth.

GRAYSON: So that did help in the ionization of some polar compounds, or compounds that were somewhat polar, right? The adaption of the chemical ionization technique.

J. MCCLOSKEY: Oh, yes. Depends on…so the whole acidity scale was created. So you had then the mild acids, like CH5+, and you had…I'm sorry. That's a **<T: 55 min>** strong…no. That's a strong acid, and a mild acid would be NH4+. So the NH4 is reluctant to give up its proton to somebody, unless they were very basic. And a CH5+ was promiscuous. It would give protons away…

GRAYSON: Give them away all over the place.

J. MCCLOSKEY: …to all kinds of things, including the…you know, but it made everybody aware of this gas phase ranking. Once again, chemistry, real chemistry, was at the forefront, and was understandable. It had been worked out by people who had no great interest in applications, but the applications people soon realized that these were…"let's look at that paper again."

GRAYSON: Yes. [laughter] What are these crazy guys up to?

J. MCCLOSKEY: What…what is going on here? And…

GRAYSON: I guess…I don't know if Burnaby Munson ever told you, but that first paper that

they tried to publish in *JACS* got…one of the reviewers just essentially, you know, blasted it as being total junk…[7]

J. MCCLOSKEY: Yes. I remember this. I remember him telling…

GRAYSON: These guys are a bunch of petroleum chemists that don't know what they're doing. [laughter]

J. MCCLOSKEY: Yes. And that's easy to understand. You're out on a…

GRAYSON: They were way out…

J. MCCLOSKEY: …brand new story here, and are they trying to pull the wool over somebody's eyes? "Maybe my eyes?" [laughter] Says the…

GRAYSON: Well, like you say, CH5+, what the heck is that? [laughter]

J. MCCLOSKEY: What are we talking about here? And CH5 became famous. Famous ion. That was the harbinger…

GRAYSON: So the meeting did give you some kind of intellectual agitation and get you to thinking about different ways to think about…

J. MCCLOSKEY: For those things, yes. People working on what I was working on at those meetings were far and few between. And so especially…

GRAYSON: There are not that many of them today, are there?

J. MCCLOSKEY: No, not…well, there's a bit more. I had coffee with a few of them.

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[7] M.S.B. Munson and Frank. H. Field**Error! Bookmark not defined.**, "Chemical Ionization Mass Spectrometry. I. General Introduction," *Journal of the American Chemical Society* 88 (1966): 2621.

But at that time it was slow going. And I developed an interest, a deep interest, in nucleosides and their chemistry and what they're being used for, and how we can do things for structural work with mass spectrometry, which made me less interested in following the horrible stories of carbohydrate fragmentation, and really some other things, where they're very meritorious, but complicated. I just never got excited about that. But there are a number of people, of course, who would follow those fields because they were new, and just scrape the initial information off the top and drive on.

GRAYSON: I think one of the…there's a guy at Washington U[niversity] I think that still does a lot of that stuff, Fong Hsu, I think does a lot of that.

J. MCCLOSKEY: Fong-Fu Hsu. He was my graduate student.

GRAYSON: Oh, really? […] I wasn't aware of that. Yes. He's been at Wash U [Washington University] for a long time.

J. MCCLOSKEY: A long time. So I guess he's part of the facility, the facility exists…

GRAYSON: Well, you know—excuse me—the Mass Spec Research Resource still is in its umpteenth year, and just got renewed a couple of years ago for another five-year lick, but they're cutting back. The initial aliquot of funds that were to be given has been reduced, you know. So it's been…

J. MCCLOSKEY: Well, welcome to the…

GRAYSON: There's been a reduction in staff as a result of that, so it's having real…

J. MCCLOSKEY: Who's the PI […]?

GRAYSON: Oh, that's Mike [Michael L.] Gross. It used to be…

J. MCCLOSKEY: Oh, of course.

GRAYSON: It used to be that that was run out of the medical school with Denny [Dennis M.]

Bier and Bill [William R.] Sherman and those guys, and Mike was hired to come in and take that over.

J. MCCLOSKEY: Yes. Associating him with St. Louis is still alien to me. He…

GRAYSON: Oh, he's kind of back in Nebraska.

J. MCCLOSKEY: His fame was what he did in Nebraska. That's what got him really [recognized].

GRAYSON: Yes. No, Mike's been at Wash U probably for 20 years now, and so he's taken charge of that operation. He actually has…there's a wing that's in the medical school, and a part that's in the chemistry department at Wash U, and so he's the head honcho for that.

J. MCCLOSKEY: I've been there on a number of site visits, and it was always a very interesting proposition, because whoever was PI, they were in the middle of **<T: 60 min>** great problems to solve. You know, fabulous people there. And so it wasn't they were just looking for something to do. There were things to do.

And that was…Do you remember meeting Denny Bier?

K. MCCLOSKEY: In Shanghai [China]. […] It was at the Peace Hotel.

J. MCCLOSKEY: That's right, in the restaurant. […] I approached his wife and introduced myself. He was in the restroom. I said, "Are you with this guy? Are you his wife or something like that? Dennis Bier?" She says, "Yes." I said, "Oh." Then he came out, and we had a big reunion and so forth. I don't know where he is now.

GRAYSON: So now let's get back to our…

J. MCCLOSKEY: So I was just pointing out here that my father went to [St. Louis University Medical School].

GRAYSON: Your dad did?

J. MCCLOSKEY: He went to St. Edward's University for undergraduate work, and then [St. Louis for medical school]. Used to be a Catholic…

GRAYSON: Yes. St. Louis University is the Catholic school—a Jesuit school, I should say, rather than Catholic—in St. Louis, and Wash U is the other. Of course, Wash U's a big powerhouse university and St. Louis is…St. Louis U has done okay. They're doing okay.

J. MCCLOSKEY: Yep. So anyway, where were we?

GRAYSON: So you've completed your graduate work with Klaus by this time, and you're kind of hooked on nucleosides and nucleotides, and you're ready to start your career, and so what are you going to do?

J. MCCLOSKEY: Well, the first thing I was going to do was something that was a little bodacious, and that was I applied for an NIH [National Institutes of Health] postdoctoral fellowship to go abroad, and those were pretty rare in those days; very rare in those days. And I went to Paris [France], and that just was an interesting thing.

GRAYSON: So this decision to do this, was it just…there weren't that many of these. You just decided you were…

J. MCCLOSKEY: No, I had heard, actually, through Klaus that there were interesting things going out at a lab in Gif-sur-Yvette.

GRAYSON: Where is the lab?

J. MCCLOSKEY: CNRS [Centre National de la Recherche Scientifique]. It's outside Paris. […] That became a hotbed of mass spectrometry, actually, at a time when it was struggling in Europe for relevance and so forth.

GRAYSON: Who was the principal to get it going there? Who was the…

J. MCCLOSKEY: There was a natural products chemist, named Edgar Lederer, L-E-D-E-R-E-R, and he was a well-known guy who knew how to get things done.

K. MCCLOSKEY: And Walter was there.

J. MCCLOSKEY: And Walter Vetter…that's right. I had forgotten that.

GRAYSON: Walter?

J. MCCLOSKEY: Walter Vetter […] was one of the Austrian postdocs that Klaus had imported to help get the ball rolling. So Walter ran the mass spectrometry lab in this Institute, so the Institute of Natural Products [Institut de Chimie des Substances Naturelles]. You'll see it on my CV, its full name there. And so the idea was in that case I would kind of replace him, but we had sort of a showdown after I got there, and I wasn't interested in just standing around and running samples for people.

GRAYSON: Sure.

J. MCCLOSKEY: There were advantages to doing anything where I was. I mean, all kinds of things. But the idea of just doing this, you know, I mean, coming in, is it done or isn't it done, where is it, and so forth, so we had a frank talk. Actually, the frank talk was done by NIH. I went to see the NIH man at the Embassy in Paris.

GRAYSON: So they had somebody representing NIH at the French Embassy?

J. MCCLOSKEY: That's right. The American Embassy.

GRAYSON: American Embassy in Paris.

J. MCCLOSKEY: Yes. So he dealt, I guess, with NSF as well. So he said, "Yes, we know, there are **<T: 65 min>** problems like this that exist there," and he encouraged me to tough it out.

GRAYSON: So they wanted a lab tech and…

J. MCCLOSKEY: That's right. They wanted a lab tech.

GRAYSON: And you wanted…you were a Ph.D…

J. MCCLOSKEY: And I wanted to do real science, because I just came from a science laboratory where you worked on real problems.

GRAYSON: Yes. Well, was that part of the European scientific…I know, like, in Germany, they had the *Habilitation*, where you get your Ph.D. degree, and then you're kind of an indentured servant to some bigwig dude for another ten years before you actually get to do your own research. And that's…I mean, my understanding, that's why Klaus, you know, after he'd experienced what was going on in America, he said, "To hell with those Europeans. I'm going to, you know, pursue my career in the United States where I can be a scientist now."

J. MCCLOSKEY: Yes. The French did something similar, but the Germans have it much more refined.

GRAYSON: Ah, more refined. I like the… [laughter]

J. MCCLOSKEY: It's a more refined system, and it works well for them. There's no question that people who finish the *Habilitation* are really well-trained. Some of them are fantastic, right? But they have spent a lot of their career in chains. And they sort of know that.

GRAYSON: Yes. So you got that straightened out pretty early on, that you weren't going to be a lab tech for this…

J. MCCLOSKEY: So I did work on some science problems there, and that's reflected in several papers in my CV.[8]

GRAYSON: Was that a year…a one-year appointment, or two-year, or…

[8] For example: G. Lukas, J.C.N. Ma, J.A. McCloskey, and R.E. Wolff, "The Constitution of Two New Sesquiterpenic Ketones: Furopelargones A and B," *Tetrahedron* 20(7) (1964): 1789-801; and Ginette Jauréguiberry, John H. Law, James A. McCloskey, and Edgar Lederer, "Studies on the Mechanism of Biological Carbon Alkylation Reactions*," *Biochemistry* 4(2) (1965): 347-53.

J. MCCLOSKEY: It was one year, and when it was due to be renewed or something, I was getting antsy, and had went to visit…there were two people who became famous at that time named Ragnar Ryhage and Einar Stenhagen in Sweden. And the two of them had become well-known because of their work on [mass spectra of] fatty acid esters. They had spectra of everything, and they understood a lot of things, and it was quite an interesting story. And so I went up there to visit.

GRAYSON: This was in Stockholm [Sweden] or…

J. MCCLOSKEY: Yes, Stockholm. And they offered me a job, and it wasn't clear who that was going to be with. And it turned out that [the job offer was from Stenhagen]. I wanted to work with Ryhage. He was the instrumentalist, and I thought I would learn more with him. And Stenhagen was the chemist and so forth. And I had met—what's his name who got the Nobel Prize? Worked in prostaglandins, he was from Karolinska [Institutet], Sune [K.] Bergström. […]. Sune Bergström [Physiology or Medicine, 1982]—and he encouraged me to go work with Stenhagen. But what happened was…so I went to talk to the NIH people about this conundrum, and they agreed that I could switch [out of Lederer's lab], that they would bankroll another year in Sweden. I thought, "Go." Because this is not…it was just an expansive thing to do. And so we actually…I don't know if we got started on that or not. I went and visited those guys [in January], and […] I went to Stockholm in January, February.

GRAYSON: That wasn't a good time to go. [laughter]

J. MCCLOSKEY: Oh, my gosh. I didn't know what cold was.

GRAYSON: Yes. Right. [laughter]

J. MCCLOSKEY: People go outside? I'd open the door and run. That was news to me, that you could exist, and they did it very well, so I was impressed by that. But anyway, in the midst of all this, I became aware, or someone had tipped someone to write a letter to me about a position that was going to open…or was opening up at Baylor College of Medicine [in Houston] in a laboratory called the Institute for Lipid Research. The director was Evan Horning, E-V-A-N. You've met him before.

GRAYSON: Yes.

J. MCCLOSKEY: Horning, and his wife, Marjorie […]. And he says, "You know, we're about to get into mass spectrometry, and we've got funds for an instrument." What did they get? They had to have a CH5 or something. But they then…he was friends with **<T: 70 min>** Stenhagen in Sweden, and they then immediately found out that there was an instrument that was going to be produced by LKB [Instruments, Inc.]. A 60 degree sector instrument. And they were convinced that was the way to go. And then they did that…where the CH5 [instrument] was in that [arrangement] I don't remember. I would have to ask somebody who knows, and I don't know who that would be.

GRAYSON: I was just curious. You said you went to Stockholm to visit the lab that Ryhage and Stenhagen were at. Did…

J. MCCLOSKEY: It was separate labs, but…

GRAYSON: They had separate labs. Okay. Were they both doing mass spectrometry, or just Ryhage?

J. MCCLOSKEY: Well, they were both doing mass spectrometry, but Ryhage was the guy who made the instrument work [and produced the data].

GRAYSON: Hmm. And he was using what kind of instrument, then?

J. MCCLOSKEY: Oh, gosh, he was using a large homemade sector instrument that [produced] marvelous spectra, and so forth and so on. And he didn't care much about the chemistry, but Stenhagen did.

And so there were papers coming out, joint papers, lots of joint papers. And they were such that Stenhagen started to interpret the spectra…

So…wait a minute. I'm missing part of the picture here, because one of them…Ryhage was in Stockholm, Stenhagen was not in Stockholm. Stenhagen was in [Gothenborg, Sweden], on the other coast.

GRAYSON: They had a…was it part of the ETH [Eidgenössishe Technische Hochschule Zurich] or was that in…somewhere…

J. MCCLOSKEY: Nope. He was on another coast, the other side of Sweden. And so there was a question there, [that] was if I went, if I moved there, which one would I work with, and where would I live? And I thought it was a bad idea to try and do both. But it was never quite resolved when I got wind of the job that was opening up at Baylor College of Medicine [in Houston]. So I abandoned the Swedish plan, before it started.

K. MCCLOSKEY: We went there; we were there for about six weeks […].

J. MCCLOSKEY: Is that…oh, so it began? I think it began, actually. They actually switched it.

K. MCCLOSKEY: August, yes. August and September. We came home in October.

GRAYSON: So you actually started?

J. MCCLOSKEY: […] That's right.

GRAYSON: So the work…

J. MCCLOSKEY: It didn't get anywhere in this few weeks. […] Six weeks. And [during that time I] was in Stockholm [at the] Karolinska Institute [and Hospital].

GRAYSON: And then you decided that it was too cold. No, you wanted to take up the opportunity at Baylor?

J. MCCLOSKEY: Baylor College of Medicine. […] Now there's no relationship to Baylor University. At that time, there was a tether between the two, but the tether was then cut while I was there, and they're not related anymore.

GRAYSON: So that's interesting. But it's still called Baylor College of Medicine?

J. MCCLOSKEY: Yes. And it's one of the few freestanding medical schools in the country. It has no [undergraduate] university affiliation.

GRAYSON: Hmm. That's weird.

J. MCCLOSKEY: Yes. But they found out they could do graduate work, the students could do graduate work and take courses at Rice [University]. And Rice is literally [just] across the street.

GRAYSON: Sure.

J. MCCLOSKEY: And, you know, it has some very good people there.

GRAYSON: So we're talking about Houston [Texas], then, as a…

J. MCCLOSKEY: Yes.

GRAYSON: Yes, okay. Baylor's in [Waco while] Baylor College of Medicine is…

J. MCCLOSKEY: In Houston. That's right. Texas Medical Center.

GRAYSON: Yes. Baylor University is in Waco [Texas], isn't it?

J. MCCLOSKEY: Waco. Yes.

GRAYSON: Okay. That makes sense.

J. MCCLOSKEY: Famous for other…

GRAYSON: Yes. Well, yes, Rice is no slouch of a school, so…

J. MCCLOSKEY: Yes. And that's before the buckyball phenomenon, right, which must have…

GRAYSON: Yes. One of my sons went to Rice, undergraduate.

J. MCCLOSKEY: …must have lit them up. Oh, it's very…yes, it's a rigorous school.

GRAYSON: Oh, yes. No, it's a very nice place. Yes, he had a fun time there and did well.

J. MCCLOSKEY: There used to be a time when I was in high school, [that] they had no tuition.

GRAYSON: A good friend of my wife's, [her] husband went undergraduate there tuition free, and then went on to medical school. But, I mean, he would have gone through there in the 1940s or 1950s…late 1940s, early 1950s.

J. MCCLOSKEY: Rice Institute, it was. And then [became] Rice University. And I guess one day someone opened their eyes and said, "Whoa, we're really handing out a lot of education here."

GRAYSON: Well, but my understanding is the guy in <**T: 75 min**> his will specified that there was not to be any charges for…

J. MCCLOSKEY: This is true. This is true. […] They broke the Rice will, and it was a big deal. There was all kinds of things about, well, what…are we going to close the doors? We're going broke […].

GRAYSON: So you were now in Houston at Baylor College of Medicine and working with Evan and Marjorie Horning.

J. MCCLOSKEY: Well, I was working in [the] Institute [for Lipid Research], and we were there ten years. I was there ten years, and rose to the rank of full professor there. But I never published a paper with Evan [or Marjorie] Horning.

GRAYSON: Oh, really?

J. MCCLOSKEY: Which is strange, because he was very prolific, and he would have welcomed it, but I just wasn't interested, and I had these other strange interests, which were not biopharmaceutical in any way. But […] I think his game was there that my work was going sufficiently well that I was an asset to the program, i.e., raising money, so I was there for all that time, and helped him raise money. We got new mass spectrometers and many things evolved from that [arrangement].

GRAYSON: So you were going to NIH for these funds?

J. MCCLOSKEY: He did. […] I never did. I never did [at that time apply to NIH for funds].

GRAYSON: But he was using your work, the results of your work…

J. MCCLOSKEY: Oh, in part, yes, plus his [work]. He was a prodigious [raiser of grant funds].

GRAYSON: Oh, yes, yes. But NIH was the primary funding for this, and…

J. MCCLOSKEY: Yes. Absolutely. Other funds he would take advantage of, but he was running a pretty good lab there, based just on [his] NIH work. He had money from other sources, but I think NIH was the main one […].

[END OF AUDIO, FILE 1.1]

GRAYSON: I think we are working again. That's pretty nice. I only had to push one button. Well, I think you were talking about the beginning of your career after graduate school, where you went to Baylor College of Medicine and were beginning to interact with the Hornings in their laboratory there.

J. MCCLOSKEY: Never really interacted with them. In other words, I went there and did my thing, and I helped recruit Dom [Dominic M.] Desiderio and Paul Vouros, [both of whom contributed successfully to the Institute for Lipid Research]. And they were there for a while. And they also decided it wasn't in their interest to collaborate very much with Evan, [so in general they followed their own research interests].

GRAYSON: What did Marjorie do? Did she work…

J. MCCLOSKEY: Marjorie [was] a totally independent…well, semi-independent. She worked with him and by herself. She had [her own good NIH] grants, NIH grants on metabolism in newborn infants, [for example].

GRAYSON: Ah, okay. So you were kind of like free to do what you wanted to do there?

J. MCCLOSKEY: Yes.

GRAYSON: When you went there, that was because of your expertise in mass spectrometry, was that [therefore] attractive to them?

J. MCCLOSKEY: Yes.

GRAYSON: Okay. But I mean, they weren't interested in someone who was going to be a lab tech. They wanted somebody that had the skills that they could use [for the overall goals of the Institute].

J. MCCLOSKEY: Yes, it was a faculty job. I was an assistant professor when I moved there, and [was professor when I left ten years later].

GRAYSON: Was the NIH okay with you kind of absconding or disappearing from your Stockholm position? You know, I think you'd kind of suggested that you were going to…

J. MCCLOSKEY: Yes. [I was cleared by NIH to work in Sweden for another year if the Baylor position didn't work out. I'm unclear on some of those details].

K. MCCLOSKEY: They were still driving on the other side.

J. MCCLOSKEY: They were still driving on the left. I was there…I visited there once, one week after they moved from the left side to the right side. Whoa.

GRAYSON: Oh, wow. Oh. That must have been exciting.

J. MCCLOSKEY: Yes. They called it H Day. The word is "höger," or something like that for right, and they told me road accidents just went to zero. People just were so up on the…

GRAYSON: So careful. [laughter]

J. MCCLOSKEY: …saying, "Whoa, I don't trust myself to do anything."

GRAYSON: Yes.

J. MCCLOSKEY: And that was the problem. It was a question of reflexes. You get into a traffic circle and you need to make a quick right, and then boom.

GRAYSON: Yes. So you were…

J. MCCLOSKEY: Okay. So Baylor, let's see.

GRAYSON: You were still interested in nucleosides and nucleotides?

J. MCCLOSKEY: Yes. And we published some very good papers in that period, kind of more basic mass spectrometry. I say basic, not in the Field and Franklin sense, but understanding fragmentation pathways and the like.

That worked well. But at the same time, we became rather experienced in microscale derivatization, so that your route into getting useful data was still to make a derivative, because many of the things you work with, whether you're working at a monomer level, then nucleosides, or up, nucleotides, whatever, you can't deal with, so you need to become volatile. And so there are ways to do that through…methylation was one.

GRAYSON: So what would…what part of the…

J. MCCLOSKEY: Silylation was one.

GRAYSON: What part of the molecule got derivatized?

J. MCCLOSKEY: The top…both the sugar and the base [and the phosphate moieties, if present].

GRAYSON: Okay. You could do either one or both?

J. MCCLOSKEY: You can…yes. What you want to do is probably do both and drive the reaction far enough that you know what you have, and…which is to do both. If you stop in the middle or something goes wrong and you've got thirty percent of the bases aren't derivatized and the rest of them are…oh my gosh. And it's a mixture. You'll end up spending your life trying to keep…

GRAYSON: Trying to sort it out.

J. MCCLOSKEY: …stuff like that.

GRAYSON: So you used silylation, you used, like, I **<T: 5 min>** think, tetramethylsilane or trimethylsi…there's a couple of silanes were…

J. MCCLOSKEY: Yes. Trimethyl…well, it was trimethylsilyl acetamide. So-called BSA. And then there's one called BSTFA, which is a more powerful silylating reagent. And we actually got pretty good at that, and because we were starting to work then increasingly on real unknown structures, just not known. And so it was necessary in those cases to make a derivative and understand the spectrum that you get. And if the structure is really, truly not known, then you can get a lot of mileage out of that. But the problem still was initially that you had to be one step away from a mixture. You could isolate it, or somebody could isolate it, and [one additional point, we used trimethlylsilylation successfully for a number of years. It was originally Dick Stillwell's idea].

GRAYSON: Was chromatography part of the act in this…

J. MCCLOSKEY: Not yet. No. That was a later thing. Those were the Vestec [Corporation] days. And I became [a liquid chromatography/mass spectrometry proponent]. At that time also I

began to have serious long-term interactions with a Japanese scientist named [Susumu] Nishimura.

GRAYSON: […] And how did you meet up with this gentleman?

J. MCCLOSKEY: That's an interesting question. [It began by his writing to me, asking for help in identifying a tRNA nucleoside his lab had encountered]. He was interested in modified nucleosides, natural nucleosides that were modified, and there were a lot of them in transfer RNA. The structures weren't known. And someone had put the bee in his bonnet that mass spectrometry might be a useful thing, and we were already starting down that line. [We collaborated for more than twenty years, until I retired].

GRAYSON: So you had some publications that he would have tripped over in the literature that would have…

J. MCCLOSKEY: [Yes, they piqued his interest], plus, you know, of course, he has dozens upon dozens of papers. He's very prolific, was very prolific. But he was very interested in microscale methods, because it was gold to the biochemist who was trying to isolate these [compounds] from RNA. And although they got very good at it, you know, what do you want? I want a microgram of stuff clean.

GRAYSON: Yes. Clean. Got to be clean.

J. MCCLOSKEY: Now wait a minute. Two problems there. One is you want a microgram.

GRAYSON: Yes.

J. MCCLOSKEY: And the second is you want it clean.

GRAYSON: You want it clean.

J. MCCLOSKEY: And sometimes we got it, and he could do it because he would do isolations from tRNA on a very large scale. So I began going to visit him, and…

GRAYSON: This is while you're still at Baylor College of Medicine?

J. MCCLOSKEY: Still at Baylor. Yes. And multiple visits. I must have gone dozens of times.

GRAYSON: Where was he in Japan?

J. MCCLOSKEY: He was in the National Cancer Center Research Institute.

GRAYSON: In the city?

J. MCCLOSKEY: Tokyo [Japan]. Right in the middle of it.

GRAYSON: So how was your…you went to Japan, what was your impression of your first time there?

J. MCCLOSKEY: Oh, it was interesting, because those were early days then, and the Japanese had not ascended to the lofty place they were when they had all these financial troubles. , before they became famous for being better than we and so forth. So it was interesting, and I've got an interesting picture. I don't know where it is, Kay, of…the group picture of his group at the National Cancer Center one year…

K. MCCLOSKEY: Oh, I've got it in here.

J. MCCLOSKEY: And there were a hundred people in the whole…sorry, it's the whole Institute, a hundred people or something like that.

One foreigner. One foreigner. So my little face stands out. [laughter] But it wasn't that way fifteen years later; there were a lot of foreigners. So I was the only one, and it was kind of fun because it was a real adventure. It was just an <**T: 10 min**> out-and-out adventure. And I became fairly familiar with getting around in Tokyo and what to do and how to do it and, you know, things that made me more relaxed. You have to learn, for example, that you can never become lost.

GRAYSON: Oh, really?

J. MCCLOSKEY: Yes. If you think you're lost, stop somebody, or whatever. It's so easy. People fall all over themselves trying to help you.

GRAYSON: Oh, wow.

J. MCCLOSKEY: And you never… there are places in Europe where you get lost and say, "I'm lost." [laughter] And so that is helpful for a foreigner in particular who doesn't speak…

GRAYSON: So were—excuse me—at this time of your initial visits to Japan, were you, like…did you see very many Westerners there, or…

J. MCCLOSKEY: No, very, very few.

GRAYSON: So you were kind of in the…

J. MCCLOSKEY: Now I wasn't around the tourists, you see. I was in the National Cancer Center Hospital and all that. , and occasionally I'd see somebody's Italian postdoc or something. We would eye each other and nod, but…you know, secret handshake stuff.

GRAYSON: Yes. Yes.

J. MCCLOSKEY: Anyway, those were exciting days, and the science was coming along nicely.

GRAYSON: So what did he bring to your collaboration? Did he bring making these compounds, or…

J. MCCLOSKEY: Oh, we each scratched each other's back in a curious fashion. So he would isolate compounds or mixtures that have compounds in them of unknown structure, and we would work on the structures. And sometimes a little bit was known; sometimes much less was known. And we would [often] deliver a full structure, a complete structure. Sometimes we could make it, improve it to make…synthesize it as a [proof of structure].

GRAYSON: The classical…

J. MCCLOSKEY: Yes. Or not. It depends on what you know and what position did it come from in the transfer RNA. What's known about the variation in that position, and other things that would give you confidence that your assignment was probably correct.

GRAYSON: Yes. So the size of these molecules at this time was in the area of a couple hundred [daltons]?

J. MCCLOSKEY: [Yes, or 80 daltons higher if phosphate was present].

GRAYSON: Okay. Was volatility an issue?

J. MCCLOSKEY: Two to three hundred [daltons].

GRAYSON: You had to derivatize…

J. MCCLOSKEY: Well, [in most cases] we were derivatizing at that point, and so we got fairly good at it, and we could do okay. But we were…the whole thing loosened up enormously after LCMS [liquid chromatography-mass spectroscopy] became possible. Wow. And I thought we had the bull by the horns doing…

GRAYSON: […] So you were doing this work on a mass spectrometer at Baylor…

J. MCCLOSKEY: At our place, right. They did finally get a mass spectrometer in Tokyo, but [they lacked the experience to use it effectively…] **<T: 15 min>**.

So I had a long way to go to learn things about the biology of RNA, and even at the time I started on it, it was not recognized about the widespread importance of RNA. It was known to be, you know, kind of a mirror of DNA. You have DNA here and you have RNA here and you have transfer RNA and you have ribosomal RNA. Since then in recent years it's become RNA as some master molecule controlling all kinds of [biological reactions involving protein synthesis], and they're not full, big RNAs, they're little RNAs doing this, and it's become a big thing. I never worked with those, but we worked with the big ones [that occur in the ribosome].

We don't have a poster here, do we, Kay? I should have a poster, but I don't, of the structures. Remember all the…

K. MCCLOSKEY: It's somewhere. The RNA poster? Yes. Let me go somewhere and find it.

J. MCCLOSKEY: We had one… Anyway, so I began to learn more about why they were doing [their experiments], which made it much more interesting to me, but I found out that I could never do their work well at all. I went there and spent months and months trying to learn to isolate things, and the skill required to do some of that is so high that you could read about what to do and do it and find out that you can't find the product, or it's lost, or it's gummed up, or it's…so I…

GRAYSON: So this was all kind of wet chemistry kind of stuff that they were doing…

J. MCCLOSKEY: Yes, wet chemistry to isolate something from a large molecule and put it over. You'd do multiple chromatographies to get it pure and so forth. But it became clear to me that in those days that a method where you could use chromatography seriously in conjunction with mass spectrometry, not just, you know, the day before, but…oh, here we go.

GRAYSON: So now you're talking GC or LC?

J. MCCLOSKEY: Well, it turned out to be LC. There's the cast of characters.[9] [Pam Crain, my long-time associate, became the isolation expert.]

GRAYSON: Oh, wow. Okay. [laughter]

J. MCCLOSKEY: Absorb that?

GRAYSON: Looks like…yes, I can absorb that. Remind me to take a picture of that later. It looks like a spider landed on there with ink on its feet.

[9] P.A. Limbach, J.A. McCloskey, and P.F. Crain, "Enzymic Sequencing of Oligonucleotides with Electrospray Mass Spectrometry," *Nucleic Acids Symposium Series* 31 (21st Symposium on Nucleic Acids Chemistry, 1994): 127-8; and P.A. Limbach, P.F. Crain, S.C. Pomerantz, and J.A. McCloskey, "Structures of Posttranscriptionally Modified Nucleosides from RNA," *Biochimie* 77 (1/2) (1995): 135-8.

J. MCCLOSKEY: Yes. No, so we published that and printed it.[10] So it turned out that we figured that at the time I quit doing this stuff, that we had contributed seriously to 20 percent of the known structures. And there [are] some real interesting molecules in there. Really interesting. And…

GRAYSON: So you kind of had to rely on them to do the wet chemistry and isolate the…

J. MCCLOSKEY: Well, to isolate it, until we reached the point where we could take crude RNA and isolate it ourselves. We could do that. Pam [Pamela F.] Crain, who worked with me for years—you know Pam—and she became very good at the isolations. And she'd isolate an RNA that had the goods in it that we wanted. And then you enzymatically degraded something, nucleosides or nucleotides or whatever, and then perform on that LCMS. And that's when electrospray really came into its own. You could work with some real small amounts of material, and you knew what you could get out of it, and it was just…it was marvelous. So that was…and we're reaching a point where I meet people who've said, "Aren't there…have you not discovered all of the nucleosides in RNA?" You know, see this list or…and I'd say, "Well, probably not." And I think that was correct. There are minor, minor variations of these that could go on forever, but I don't see any point [in making a major effort to go further]. The main thing would be if there are new families. And so there are a couple of major new families that I was involved in and that we had solved learning…

GRAYSON: Major new families of RNA?

J. MCCLOSKEY: Of nucleosides in RNA. I will show you some. Let's see. The most famous **<T: 20 min>** is Q.[11] Where is Q? Hmm. See, what you have here are bases connected to sugars. The [designated] sugars are mostly ribose, but not always. The bases are sometimes simple and sometimes methylated: [rustling] like that.

GRAYSON: Oh, here's Q.

[10] P.A. Limbach, P.F. Crain and J.A. McCloskey, "Summary: The Modified Nucleosides of RNA," *Nucleic Acids Research* 22(12) (1994): 2183-96.

[11] H. Kasai, Z. Ohashi, F. Harada, S. Nishimura, N.J. Oppenheimer, P.F. Crain, J.G. Liehr, D.L. Von Minden, and J.A. McCloskey, "Structure of the Modified Nucleoside Q Isolated from *Escherichia coli* Transfer Ribonucleic Acid 7-(4,5-*cis*-Dihydroxy-1-cyclopenten-3-ylaminomethyl)-7-deazaguanosine," *Biochemistry* 14(19) (1975): 4198-208.

J. MCCLOSKEY: This became a poster child because we worked on the structure and solved it mostly by mass spectrometry. You see, it looks like a purine. It looks like guanine, but there's no nitrogen [in this ring at position seven]. Whoa, wait a minute. See, you should have a nitrogen in that position, everywhere, everywhere. All of a sudden you have a family where there is no nitrogen at position seven. It's a carbon. It goes into your nucleoside chain, then there are more.

Then there are more. And then there are the precursors, biological precursors. So it generated a nest of other work to do to find out what the route was to making Q, and then there's one…

GRAYSON: Is this still hot…I mean, is that still active, that website?

J. MCCLOSKEY: I don't think so. You know, it should be. What we did was we shut it down when I left, and, oh, somebody called me and said…

GRAYSON: Those are all [in] transfer RNAs?

J. MCCLOSKEY: No, these are from all RNAs. The modified nucleotides of RNA, from all kinds of RNA. And I can give you the current URL for what they're doing.[12] So I kind of gave it away to a [biochemist named Paul Agris] in North Carolina [State University] who was interested in it. And I probably shouldn't have done that quite so blithely, but he now has taken it over […].

GRAYSON: Well, it'd be good to include in here. So, I mean, basically it's through your work with this Japanese collaborator that all this information is…

J. MCCLOSKEY: Much of it. Oh, a chunk of it.

GRAYSON: A big chunk.

J. MCCLOSKEY: When I started working with him, probably half of these were known, and then we together worked on most of the other half, and some of them were really killers. One of them is, one called archaeosine which is probably one of the best things I've done, and you

[12] Available at: http://mods.rna.albany.edu/ (accessed on 21 January 2014).

wanted a list of papers that were notable, and…where's…? There's the G+.[13] We gave it the symbol G+. It too has no nitrogen here, but…and then what's on there looks like the fork of the amino acid arginine. So it's charged, and it's just fascinating. That [occurs in only] one whole kingdom, evolutionary kingdom, that nucleoside is very common in its tRNA. [Some] tRNAs from every organism have it. And that's what led us all to say, "Whoa, this is universal." And at that time, we were getting interested in another angle for all this, and that was the [modification] differences [defined by evolution] between the three major branches of life, different life. [In] living things, there are three kinds of [organisms, called] bacteria, eukaryotes, and archaea […].

And so there would be debates going on about where do you put the branch of the "tree of life", and how does this [relate to we humans]…all kinds of questions. But I became very interested in that. So we would follow some of these things by going out on the branches of the tree to see what we found, and were they related to the position of the branch, another large segment that we got into was working with thermophiles, and I collaborated a lot with a microbiologist in Regensburg, Germany, named Karl with a K, Stetter […]. **<T: 25 min>** He was one of the hotshots [in that field. He not only grew them, but collected them from different parts of the world, wherever very high temperature organisms occur (volcanos, submarine thermal areas, et cetera)].

[…] Someone recommended him to me, because I was working on the edge of the [thermophile family], just in that family, archaea, the branch. I'll show you a map, what it looks like. And a well-known person in that field said to me, "You know, you really should work with…you really should meet Karl Stetter. He is a young guy in Germany." He wasn't that young. I mean, he was…he was my age. […] And worked on hot organisms.

He would grow them for us. So we had a number of these that we grew once or twice ourselves. Otherwise, we had someone grow them, and that was painful. We could get out the RNA ourselves and start working at that level, but some of these are really unusual organisms, and they're hard to come by, hard to culture. They're very difficult to culture. But because of the temperatures at which they operate, some of them can grow successfully above the temperatures [around] the boiling point of water. [We collaborated fruitfully with Karl Stetter for over ten years].

GRAYSON: Wow.

J. MCCLOSKEY: Above the boiling point of water.

[13] J.M. Gregson, P.F. Crain, C.G. Edmonds, R. Gupta, T. Hashizume, D.W. Phillipson, and J.A. McCloskey, "Structure of the Archaeal Transfer RNA Nucleoside G*-15 (2-amino-4,7-dihydro-4-oxo-7-β-D-ribofuranosyl-1H-pyrrolo[2,3-d]pyrimidine-5-carboximidamide (archaeosine))," *Journal of Biological Chemistry* 268(14) (1993): 10076-86.

GRAYSON: That's weird.

J. MCCLOSKEY: Now that means on the ocean floor, right? Otherwise, you're not at that temperature. So it turns out there are [RNA] modifications like this that are virtually unique to those organisms.

GRAYSON: Well, I would imagine so.

J. MCCLOSKEY: Yes. Well, it turned out there are. We didn't know that, and we discovered a bunch of them that are, and we determined their structures, and we were able to relate the structures to their resistance to degradation at high temperature. Ah, that's where you really want to go. You have lots of [different] structures, but what are they doing?

GRAYSON: So you're getting to a structure/property relationship?

J. MCCLOSKEY: Getting to the structure/function relationships. And I had a grant once; it was from NIH, where they said, "You know, Dr. McCloskey, it's really very…" whatever it was, "amazing that you determined all these structures, but what are they good for?" And I thought, "Gad, that's an insulting thing to say."

GRAYSON: Yes.

J. MCCLOSKEY: And then I thought, "Hmm, what are they good for?" Some we know what they're good for. Some we don't know what they're good for. We don't know the [sequence] positions. You've got to know sequence position to make sense out of that, and just because you know the sequence position doesn't mean you can infer function. And…

GRAYSON: So this is all while you're at Baylor?

J. MCCLOSKEY: No, this is…oh, I left all that. This is after I moved to Utah.

GRAYSON: […] Okay. So do we want to…is there anything else at Baylor…I mean, did you first get…you met the Japanese guy at Baylor?

J. MCCLOSKEY: I did. I did. And I went to work in his lab actually for six months.

GRAYSON: In Japan?

J. MCCLOSKEY: In Tokyo. And I had a year off from Baylor, and the other six months was in the chemistry department at the University of Utah, [as visiting professor].

And of course, that was a deadly thing to let me do, because the Utah people, especially the College of Pharmacy, opened their arms and said, "Whoa, brother." [laugh]

GRAYSON: Now somewhere in here, Marvin [L.] Vestal fits. Was that at…

J. MCCLOSKEY: Yes. Marvin Vestal was a collaborator of sorts at that time of people in the chemistry department [in Utah].

GRAYSON: […] Because he ended up going to Houston, right?

J. MCCLOSKEY: No, no. [Somewhat later].

K. MCCLOSKEY: He was a student of Jean's, right?

J. MCCLOSKEY: Yes. But he became a graduate student of Jean Futrell's […] in Utah, in chemistry. So Marvin became his student, and there was a joke going around about the fact that this student of Jean's had more publications than Jean did, which may have been true, but that doesn't tell you an awful lot.

Anyway, he was a highly accomplished, respected, well-known chemist, dealing more with fundamentals [than applications]. But Marvin had talents for dealing with instrumentation, and at a time when mass spectrometry's progress, its explosion onto the scene, **<T: 30 min>** was carried largely by radically new instrumentation. He was in the right place at the right time, period.

So he then got a Ph.D. at the University of Utah, and…I have to look at his CV to see when that was.

GRAYSON: I think he ended up in Houston, University of Houston.

J. MCCLOSKEY: Yes. He then went to University of Houston, and then formed the Vestec Corporation, and sold mass spectrometers. And finally then left, gave that up, and now is kind of a consultant.

GRAYSON: Yes. So back at Baylor…you had your first interaction with this Japanese fellow there, but then you carried that relationship on…

J. MCCLOSKEY: On forward [rather extensively].

GRAYSON: […] Okay. And then was there anything else that you did at Baylor that we need to cover at this particular point in time, besides you were still doing…

J. MCCLOSKEY: Well, I had an association, some cross-publication, […] with Dom Desiderio and Paul Vouros, who had independent reputations outside of [the work of Marjorie and Evan Horning].

GRAYSON: So they were there on the…not…what, you were on the faculty…

J. MCCLOSKEY: I was on the faculty, and I recruited them.

GRAYSON: Okay. And you recruited them as faculty members?

J. MCCLOSKEY: Yes. And they followed my track into the Institute for Lipid Research, bankrolled by Evan Horning's efforts [and grant money].

GRAYSON: And when you say faculty, did you guys teach anything, or was it all research?

J. MCCLOSKEY: Mostly research, but there was no undergraduate degree. […] So most of it in those days, most of it was just research. I'd do a little bit of stuff at Rice from time to time. That was the…

GRAYSON: So, like, adjunct professor type thing, or just…

J. MCCLOSKEY: No, not even that much. And I had graduate students who would take their Ph.D. courses at Rice.

GRAYSON: Okay.

J. MCCLOSKEY: So they got a Ph.D. [in biochemistry] under me, but they had nowhere to go to get fundamental courses. , so we would farm them out to Rice, and they would take p-chem, for example, and certain courses in organic chemistry.

GRAYSON: So there was a kind of…was that a kind of informal relationship between Rice and the Institute [for Lipid Research]?

J. MCCLOSKEY: Yes.

GRAYSON: So they were okay with that?

J. MCCLOSKEY: Yes. So what happened, what was…

GRAYSON: [responding to an outside noise] That's some critter out there.

K. MCCLOSKEY: That's our birds. […] I'll go feed them. We have [several] guinea fowl […].

J. MCCLOSKEY: So where were we?

GRAYSON: So you were a total research environment. You didn't have to deal with classwork, or did you…

J. MCCLOSKEY: Very little. […] But it taught me early on that if I wanted to get things done, I would do it with postdocs. So I had in general more postdocs than graduate students, and

once again, the usual advantages of postdocs, namely they come educated and ready to roll. , while the graduate students, you have to teach, they have courses to take, they have other [distractions…] **<T: 35 min>**.

GRAYSON: So you brought Desiderio and Vouros to the Institute there?

J. MCCLOSKEY: To the Institute, but we rarely collaborated. We…Paul Vouros and I did some interesting things on response, on photographic emulsions and photographic plates, to ions of the same mass but different structure.[14] That was so interesting.

GRAYSON: Oh, wow. That's pretty subtle.

J. MCCLOSKEY: It was fascinating. Oh, there were some real differences. , and we began to look at that, but decided there wasn't anything that we could make a lot of…

GRAYSON: This was because of…you were using…

J. MCCLOSKEY: Conformation. One is balled up and the other is stretched out, and you can…

GRAYSON: Wow. But you were doing…I mean, you were using the 110 for this, or what kind…what we're using for…photographic detector or…

J. MCCLOSKEY: Oh, for that, well, we raised money for a MAT 731.

GRAYSON: Oh, okay.

J. MCCLOSKEY: And we had a 110. Yes, we had a [21-]110. We bought a 110 right after I went there. But we had raised the money then for a MAT 731, which was a really nice instrument.

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[14] P. Vouros, D.M. Desiderio, J.G. Leferink, T.J. Odiorne, and J.A. McCloskey, "Ion Detection in Mass Spectrometry. Dependence of Ion-sensitive Plate Response on Ion Structure and Composition," *International Journal of Mass Spectrometry and Ion Physics* 10(2) (1972): 133-42.

GRAYSON: And this is a photographic detection?

J. MCCLOSKEY: Yes, photographic recording. So we worked with that for quite a long time, and we did electrospray, lots of FAB, and so on and so on. But then…

GRAYSON: So you could actually tell the difference between a structure that was tightly coiled and one that was extended based on the…

J. MCCLOSKEY: Darkness of the plate.

GRAYSON: …darkness of the photoplate, even though the ions had the same mass? And…well, obviously, then, the same energy.

J. MCCLOSKEY: It's very interesting. He and I realized we were really getting into kind of new territory here. But when we published a paper, which I…but we weren't sure where it would go.[15] In other words, we could even do more of it, but we had no thesis. What is our basic thesis here? Is it related to structure and charge density? Probably. And charge shape? You know, where is the charge? Over here, or spread out? But even if we did all those things, it wasn't clear that we were on a fundamentally different thing. But it worked, anyway.

GRAYSON: And this was structure of the nucleosides/nucleotides?

J. MCCLOSKEY: These were not nucleosides, not nucleic acid things at all. I'll show you the pictures. I'll show you the spectra. They're all kinds of molecules […].

GRAYSON: So was that the extent of your collaboration with these guys?

J. MCCLOSKEY: Yes, I think it was […].

GRAYSON: What was [Desiderio] doing there?

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[15] Paul Vouros, D. M. Desiderio, J. V. M. Leferink, and James A. McCloskey. "Selective Response of Photographic Emulsions to Ion Structure," *Analytical Chemistry* 42(11) (1970): 1275-7.

J. MCCLOSKEY: Well, he was recruited into that operation just like Vouros was […]. And they proceeded independently. And they operated, as far as I know, pretty much off of grants of Evan's; NIH grants, which is, after all, what I did. And we were very successful with it. And he realized, too, that when he goes to get these grants renewed, having strong publication records with people not working closely with him, working on really very different things, could be an advantage, could be seen as an advantage.

GRAYSON: **<T: 40 min>** So having a diversity of projects was better than just being…

J. MCCLOSKEY: Yes. It was NIGMS, National Institute of General Medical Sciences. Ah, it's the National Cancer Institute. Ah, that's different. Whereas the cancer-relatedness of this work, and…

GRAYSON: So he was going to a specific branch of NIH primarily, Horning?

J. MCCLOSKEY: No, a lot of it was General Medical Sciences. That's what got us into it. But he had money to do pharmacology from other branches. We got to a point where one of my grants [after I moved to Utah], which was the structure grant, doing structures of nucleosides, had gotten to a point after about its twentieth year, fifteenth year, they called me up one day, NIH, and said, "You know, Dr. McCloskey, we're looking at your publication record, and it's really nice," and this and that and this and that. "But we think you are not a good fit for…" at that time that was a cancer grant. "You are not…it's not a good fit for the National Cancer Institute."

And I don't know why I'd gone that direction, but I had originally. And he said, "We would like to move it." And I said, "Be my guest." And they said, "Okay, it'll happen," and so they moved my grant. Just never knew it would happen. You never knew it happened. But the funding source was from one pocket to another pocket [and that is from one Institute to another]. And it became broader in that sense.

[…] That means that you've not done well with reviews. But it turns out… at one time there was a close association between nucleoside modification and cancer, both because there are modified nucleosides from tumors that are different, and because modified nucleosides became anti-cancer agents, were being used as anti-cancer agents. , so my work on modified nucleosides would fit under their umbrella. Until finally one day they said, "It's not…you know, we have so many things to fund and this one has moved out a little bit. Why don't you…" he says, "I talked to the NIGMS person, and they'd be delighted to fund it."

GRAYSON: So they moved you over into the National Institute of General Medical Sciences?

J. MCCLOSKEY: Right. And it stayed there [kind of forever] until [I retired in 2007].

GRAYSON: […] Okay. I just want to make sure that we wrapped up anything of importance or interest at Baylor before we get up to Utah. And I don't know, you talked about, you know, kind of recruiting a couple of people there, and this is where you got connected with the Japanese researcher that you spent a lot of time with […].

Why did you decide to go to Utah?

J. MCCLOSKEY: Well, that's an interesting question. It didn't have to be, in the sense that there was nothing special about Utah, and if I held on long enough, I probably could find a position at some other university, because mass spectrometry was just getting a toehold in 19…what was it, Kay? When did we move to Utah?

K. MCCLOSKEY: Well, we moved to Utah in 1974.

J. MCCLOSKEY: But it was…other things looked very good about it. I would have freedom. I had research freedom.

GRAYSON: But you were a tenured professor at Baylor?

J. MCCLOSKEY: Yes.

GRAYSON: So you would be moving as a…with tenure?

J. MCCLOSKEY: As a full professor.

GRAYSON: As a full professor. Okay. To Utah.

J. MCCLOSKEY: Yes. And I did that. And there was money [initially] to fund me through Evan's grants, and those were not the days where you said, you know, "I lost all my grants." It

didn't happen in those days. So that was…to answer your question, that was the attraction, was that there was funding, enormous freedom to do what I wanted, and they really liked…they <**T: 45 min**> liked what they saw in me.

GRAYSON: So did they kind of recruit you, or, I mean…

J. MCCLOSKEY: Yes. Yes. [I kept in touch with the folks in Utah after my six months there and they had professed an interest in talking to me about a position. We clearly had common interests].

There was an interview trip to […] Utah.

K. MCCLOSKEY: The medical school in Houston had not yet started up, and the one in San Antonio was just in the early stages in 1974, so those two were, you know, kind of in limbo as far as what they [could offer]…

J. MCCLOSKEY: Yes […].

GRAYSON: So there was a chance to stay in this area and go to some new institutes that were starting up in Texas, but, I mean, was it…

K. MCCLOSKEY: It was far down the road.

J. MCCLOSKEY: By leaving Texas…well, there's two stages here. One is what attracted me to Baylor, and then there's what attracted me to leave Baylor and go to the University of Utah.

And so what we were really discussing was the Utah thing. And I had some interests similar to theirs. They had people, a long history in that department that I went to, Department of Medicinal Chemistry, of nucleoside synthesis. And I think they believed that if we're interested in nucleoside synthesis, and they had grants, big-time grants, that having a person with credentials in doing mass spectrometry on these molecules wouldn't be bad at all.

And I said, "Well, I agree with you, and I've got…there are people to talk to," and I came up, and I thought, "Well, those are gorgeous mountains." I didn't realize that you had to shovel snow.

GRAYSON: Yes. [laughter] Mountains are pretty, but it was summertime.

J. MCCLOSKEY: I found that out later on, when I had to get rid of the snow in the driveway. So that was, anyway, the theme that was attractive.

GRAYSON: And so…let's see, University of Utah is in…

J. MCCLOSKEY: Salt Lake City, [Utah]. […] So we moved to…

GRAYSON: Now did you take any grants with you?

J. MCCLOSKEY: I took no grants with me. So the issue was there, I thought it was unfair for me to attempt to take money with me, because we had raised the money as a joint effort, Vouros, Desiderio, the Hornings, and other people there. And I thought, "This is crazy." Plus the instruments were not spring chickens. So I thought, perhaps we'd…people said, "Well, this is foolish," but I did it, nevertheless, I could raise the money and get new ones, new instruments. More modern instruments.

GRAYSON: No…okay. So you showed up at Utah with no grants and no instruments?

J. MCCLOSKEY: [That's right.] I didn't have a dime. […] And so I said…well, I immediately cast out for money. I went to NIGMS initially…

K. MCCLOSKEY: And Pam moved.

J. MCCLOSKEY: Yes. Pam moved. Pam Crain had worked with me at the Baylor College of Medicine, and she was a B.S. level person, but she…I convinced her she should come to Utah, so she came and got a job…we managed to make her a research associate, which is normally a postdoc title. I said, "Well, she's doing a postdoc's work, so let's do that." [Utah paid for her until I was funded].

And [after I got grants] I paid her. I mean, she's paid by my grants. And so Pam came. And we launched the whole thing, applied for new money, and got it. Bing. I was…oh, was that helpful. That was for a 110, and although some people felt that that was old, old science you're dealing with here. , my response was, "Yes, but we're familiar with it. We know exactly what we're getting into."

GRAYSON: Yes. You can get the ball running.

J. MCCLOSKEY: We're going to make hay very fast, if we're **<T: 50 min>** dealing with that mass spectrometer. And we needed, of course, a densitometer to read the plates.

GRAYSON: Sure. Yes.

J. MCCLOSKEY: Whoa. [laughter] People forget that, right? The unknown parameter is that you've got to have a densitometer for automatic reading, and you need the programs and all of that. So we got the money for the densitometer, bought it from the same place, the only ones, I guess, at that time that were really selling them, and we got the software from Baylor. I mean, it was written under my jurisdiction anyway. , and [we] changed it so that we could use it at Utah.

GRAYSON: So you had actually had some software development at Baylor. You had people working for you to do that? To get the automatic transfer of the mass spectra or photographic plate…

J. MCCLOSKEY: Yes. And we did other things, too. We were into some interpretation of rules using computers and the like. And I had a…let's see. That was at Baylor. Right. I had a programmer working for me.

GRAYSON: So it's the time frame when everyone was kind of doing their own thing, because there wasn't that much out there, in terms of software, if you wanted to…

J. MCCLOSKEY: Yes. Yes. And I wasn't trying to invent any new wheels here. Let's get it out…

GRAYSON: Get the data.

J. MCCLOSKEY: …get it running very fast, and I had proposals, after all, to do certain kinds of work, an NIH grant, and writing software *de novo* wasn't in my plans. I could see the merit in it.

[…] There are demerits if you're trying to move fast.

GRAYSON: Yes. Well, I thought they put an electrical detection scheme on the 110 at one time, or is that my…

J. MCCLOSKEY: Yes. No. It had one. Yes.

GRAYSON: So did you get it with that electrical detection as well, or…

J. MCCLOSKEY: Yes. Yes. [We] weren't bound to the photo plate.

GRAYSON: And they had also put an EI [electron-impact] source on it?

J. MCCLOSKEY: Yes. We had it…just an EI source [to start with].

GRAYSON: Just an EI source?

J. MCCLOSKEY: To start with. But the fact is that, you know, coming through the halls of MIT, I was already, you know, tinged with the photo plate idea, although it was clear after very long that there are other ways to go. You don't need to do that. But it has certain advantages between…

GRAYSON: Well, it's an integrating detector.

J. MCCLOSKEY: Yes. So you can […] do things at different points and still gather the data. And that turned out to be true. You could work with real mixtures, very hairy mixtures. , whether you moved the plate or not between exposures. You may move the plate or you may keep it in the same location and continue to collect data. There's various ways to do it, and we got fairly adept at doing all those things.

GRAYSON: It sounds to me like money came pretty easily in this era. I mean, it seems like if you had established yourself and had the credentials and had problems that were of interest to the funding agency, this…you got it.

Of course, now you were a graduate from Klaus Biemann's group. I assume that all those people had kind of like…I don't know what you want to call it. Extra recognition?

J. MCCLOSKEY: Yes. […] And I had been at Baylor then for ten years and published a fair number of papers at Baylor. , so the track I was on looked fairly good for a guy who's moved without any grant money and has tenure but [so what]!

GRAYSON: Yes. So that's kind of risky in a way.

J. MCCLOSKEY: […] Well, and it was risky, and I didn't realize the level of risk until I looked at it hard in the process of getting it reviewed, thinking, wait a minute, if this goes south […] what do we got going on here? And it did not go south. We were successful. And then it was renewed multiple times. That grant ran [continuously] for thirty years.

The initial grant ran for thirty years, and that ended when I left University of Utah in [2007]. That was year thirty, coming into a wind-down.

K. MCCLOSKEY: […] We were in Utah from 1974 to 2007.

J. MCCLOSKEY: […] After Utah is retirement, so retirement is total wind-down.

GRAYSON: […] And you ended up getting funding and getting going, and how long did it take you to get underway? I mean, you've got to get…I mean, you've got to wait for money. You've got to get the instrument. You've got to get set up and running.

J. MCCLOSKEY: All those things.

GRAYSON: Yes. That took a year or two, didn't it?

J. MCCLOSKEY: Yes. It took a year plus, and I had certainly…I had manpower, because I moved, Pam Crain moved. , and so I had [a person], and [Utah] agreed to pay her initially.

GRAYSON: Yes. Because you didn't have any money…

J. MCCLOSKEY: […] That's right. So that worked out pretty well.

GRAYSON: Now you're in a true university environment, though, in terms of education. So were you required to do any teaching?

J. MCCLOSKEY: Yes. And I did some teaching, and I spent more time with academic things, like I ran the seminar program a few years, and I had another thing I…there was a committee started under me that ran, or monitored, or whatever, all the graduate programs in the college, and I was chairman of that for fifteen years.

GRAYSON: Oh, the graduate programs in…

J. MCCLOSKEY: In the College of Pharmacy. Which there were five departments. So there was a Graduate Programs Committee, it was called, and I bet I spent a fair amount of time at that, actually, when I quit it. But that was fine. That…and it played out. It had its uses at a time when departments are falling down on one side or another, you need to give them a boost.

And we had some, you know, get-togethers where they could talk to each other, that sort of thing. So in parallel with all this, there's yet another plane with all this, and that was ASMS [American Society for Mass Spectrometry].

GRAYSON: Oh, okay. So you were…

J. MCCLOSKEY: So I became secretary…that's on my CV.

GRAYSON: Yes. We can get the dates out of the…

J. MCCLOSKEY: So I was secretary, and then vice president. Then I…because I was then president-elect, that made me vice president for the programs for two years. So then I had those two, then I was two years as president, then I was two years as past president. Yes. It was only when all that was finished that I realized by going to the meetings that I really hadn't gone to the meetings very much, in my huge amount of time, because there was no staff.

Whoa, whoa, whoa. Now wait a minute. At the time it was E14 and all of that, everything was done by [volunteers].

K. MCCLOSKEY: And there was no Judy.

J. MCCLOSKEY: …or living off of somebody's secretary, or doing something, but you didn't have a dedicated staff to get things done, so people who made the programs, did things to the programs, did a lot of copy work and folding papers and yakking on the phone to arrange this and arrange that. So my job at that stage was…let me think when that was. I can look.

I started making phone calls to…and I looked up this other society's name and…other societies, national society of about the same size, not that radically different, and called them with a proposal to ask them if they'd like to co-join. What if we share an office? And we have persons running all that, and we paid into it and you paid into it by some formula, and so forth and so on, and hopefully they would already have a place, so you would say, well, we'll just pick up part of the rent, and go on with that.

And so that was quite interesting. That was a **<T: 60 min>** real education for me, because I talked to a lot of people in other societies of all kinds.

I didn't know how they operated, but I found out by discussing their business with them, about what went where. And I came upon Judith Watson, and I hired her. So Judith […] Sjoberg…

GRAYSON: Right.

J. MCCLOSKEY: […] But she was working for an eye institute, an eye…yes, an eye institute of some kind. And, you know, running their program and stuff like that. And so we got together and we realized after a little while that we were talking about a job that would suit her very well with her personality and with her experience level, and that we were certainly in need of help. I was drowning in my second year as vice president for programs. We had to have those things printed, folded up into…remember the St. Louis meeting?

GRAYSON: Yes.

J. MCCLOSKEY: That was when I was on the plane flying to St. Louis and opened up the program, which I had printed and then got, and realized that it was wrong, pieces had been left out [at the printing stage]. And so I called…who did I call at that point? Gerry [G.] Meisels or somebody, and said, "There's bad news. The programs that were delivered yesterday by air freight to the hotel," whatever hotel it was. I remember it being round.

GRAYSON: Yes. It's down riverfront…one of the riverfront hotels. It's changed names three or four times, or owners or whatever.

J. MCCLOSKEY: Those won't work. And so the printer was at fault, and the printer knew it, and the printer agreed to have them redone and send us pieces, big pieces for the [missing] center. So when we got there, several of us went and ripped apart the programs for a whole night. I don't know how long it took. We ripped out the centerpieces and put in the new ones and stapled them. Oh, my gosh, that was a nightmare.

GRAYSON: Yes. That would have been…

J. MCCLOSKEY: Judith was not yet [hired]. That was at the tail end of […] my sanity, at that point. realizing that these are things that can be taken care of by a staff person, if they're good. And I should have…you know, I could have, I guess, checked all those things at the printer when I picked them up, but whoa, I had other irons in the fire. Going through those wasn't part of it. , but now I learned.

GRAYSON: Well, being part of the…a shop that runs the meeting, you end up missing a lot of the conference, some of the time, too, because you're always running around…yes.

J. MCCLOSKEY: And we're always having meetings of our…of the board of directors, and who is going to check the suites to find out who's not in compliance with which rule.

There are a list of rules of who can do what in what. And this went on and on. And we were…I was vice president of programs. We were the ones who went and enforced this. And go and tell them…[you] can't do this. And I thought, "Gad." So one of the…what I thought was a major accomplishment, but it didn't occur to me as being that until much later, was hiring her, because it gave the society something it had really needed, and it let the society recruit by one means or another its officers without…if they were too smart, they would find out that there's a lot of work associated with this stuff. If they weren't so smart, you were better off, because they could work on the…

GRAYSON: I've got the figures. I don't know what they are offhand, but I guess the meeting at that time size-wise would have been in the multiple, five hundred, six hundred, seven hundreds, I guess. Would it be as much as a thousand? I actually have the numbers. I'll have to check that out.

J. MCCLOSKEY: […] Oh, [that was] a big deal. We had all kinds of hotel problems.

GRAYSON: **<T: 65 min>** Yes.

J. MCCLOSKEY: One of them was the time we were set to meet in Houston at the Rice Hotel. And someone called me…oh, no. Pam Crain is the one who spotted it. She said, "I just looked at an article in the *Victoria Advocate*, and it says that the Rice Hotel is closing. What?! [laughter] We had no idea. They never informed us. Just we were back to square one. , and so that was a panic time.

And it really…it…[they] pulled it [off and moved it to the Shamrock Hotel. But the only time they had available was on the Memorial Day weekend]. That was the first of many Memorial Day weekends, because we found out—that was the lead example—that you can get all kinds of deals. You can get into hotels you couldn't get into otherwise. The rates will be 20 percent less. And so forth. And of course, that was taken…all those decisions at that time were made by the officers, in particular the vice president for programs, touring around and saying, "I like this hotel better than this one. Let's line up the issues here." So finally we got rid of that onerous job by having a staff.

GRAYSON: When you proposed the idea of hiring someone like Judith to run the kind of like nuts and bolts, day-to-day business of the society, how did the board…I mean, was that a popular idea amongst the board members at the time, or were they more or less…

J. MCCLOSKEY: It was popular. They talked about it, and they knew I was out fishing around. It wasn't quite clear how this was going to work. What are the financial arrangements? Is it a deal or not a deal? And I said, "Gosh, it's a step up. no matter how you slice it. It's a step up. We have to do it." And…

GRAYSON: No, I mean, it would be impossible today to do it under the old way, where you had, you know, a volunteer staff that did everything. That would be totally disastrous.

J. MCCLOSKEY: Oh, boy. It used to be you just…I remember…anyway, I had the honor of being the first vice president for programs who rejected an abstract.

GRAYSON: Oh, wow. [laughter]

J. MCCLOSKEY: That had never been done before. That tells you something. Nonsense. What's that guy's name? Nonsense abstract. He was going to take mass spectrometers and run them to see which one was better here, better there, and make a poster out of it. And I had to call him up and say, "This is not research. This is not stuff you want to report at." Anyway, so no.

GRAYSON: Yes. Because they never…hardly ever rejected an abstract. I mean, they do now on a pretty regular basis, but not in the past. They hardly ever rejected abstracts. I think mostly what they were trying to do is keep out advertisements for instruments.

J. MCCLOSKEY: Well, Kay points out I was not an ASMS officer at the time of Houston. I was…

K. MCCLOSKEY: That's when they recruited you.

J. MCCLOSKEY: Recruited me to be secretary. That sets the dates. The date frame then moves a little bit. Okay. Let's see, where are we?

GRAYSON: What do we think? Lunch?

J. MCCLOSKEY: Yes. Anyway, the ASMS thing was a parallel deal to everything we're talking about, because it didn't require science, it didn't require whatever, but it was […] time-consuming, and it was a contribution to the community to do some…

GRAYSON: […] Did you ever teach any classes at Utah?

J. MCCLOSKEY: Yes. I taught some analytical biochemistry classes to the pharmacy students early on when I was there, and that sealed my conviction that I was not…

GRAYSON: You were not meant to be a teacher?

J. MCCLOSKEY: I was not meant to be a [pharmacy educator]…for that course. , and I had no interest in the pharmacy program and how it worked. And that was at a time when the pharmacy program was **<T: 70 min>** changing radically, and they were making what's called a Pharm.D. program.

GRAYSON: Pharm.D.?

J. MCCLOSKEY: Yes, doctorate of pharmacy. […] So you had the undergraduates, they were

there for five years, and you had then the others who were picking up on this new thing. And endless hours spent in committee meetings trying to decide how to do that, right? I mean, just…and I was spared that because I just…I aced myself out of it.

So I had a…whatever it is, biomedical instrumentation course that I invented and talked about, taught this for mass spectrometry, and I had an NMR [nuclear magnetic resonance] guy come in, faculty member, and do an NMR section, and that sort of thing. That was a graduate-level class, and it lasted for quite a while, actually. , and I ran it for quite a while. , but it wasn't a draw on my time, like it would be if I taught a real pharmacy class. Whoa, right? Five times a week, and whoa, they're on you.

GRAYSON: So these are, like, three [credit] hour courses?

J. MCCLOSKEY: Yes.

GRAYSON: And did you teach that for a long time, or was that just…

J. MCCLOSKEY: That one was for a long time. That was more than a decade, I think.

GRAYSON: Oh, okay. And the enrollment [for the course] was, what, a handful of people, a bunch, or…. […] Eight to fourteen is my recollection.

GRAYSON: Okay. So a friendly group. Now is Utah a state school?

J. MCCLOSKEY: Yes, it is.

GRAYSON: Okay. So is that another one of these land grant schools, or do you know, or…

J. MCCLOSKEY: […] Utah State is the land grant.

GRAYSON: So University of Utah is a state school but not a land grant?

J. MCCLOSKEY: That's correct. That's correct.

GRAYSON: And the enrollment typically?

J. MCCLOSKEY: Typically, twenty, twenty-two thousand.

GRAYSON: Okay. So it's a typical…

J. MCCLOSKEY: Size for that…But not these humongous things with sixty thousand. […] You know? Which to me would not be very comfortable.

GRAYSON: Okay. Well, you want to take a break here and do the lunch thing?

J. MCCLOSKEY: Yes. Let's do a lunch thing […].

[END OF AUDIO, FILE 1.2]

GRAYSON: Okay. We're back after lunch, and I think we've got you to Utah, and you're kind of getting an idea about your obligations there in terms of teaching and…

J. MCCLOSKEY: So this is a reminder that Kay gave me which was a listing, teaching courses and things…fellowships and professional societies.

GRAYSON: But I mean, you really weren't a big time teacher, so to speak?

J. MCCLOSKEY: Oh, no. No, never a big time…never big time. If I spent eight hours a week on it or in a week, that would to me be pretty much.

Let's see. I ran the seminar program for the Department of Medicinal Chemistry for some years, five years, I guess. And a course…there's a multi-departmental course called Biomedical Research Techniques, and I developed that and ran that for probably ten years. Here it says 1984 to 1986, but that's not…

GRAYSON: So a lot of extracurricular stuff?

J. MCCLOSKEY: Oh, I mean, a modest amount. I was the departmental graduate advisor for all graduate students, from 1982 to 2004. That's a long time.

GRAYSON: That's a lot of advising.

J. MCCLOSKEY: Methods in Structural Biology was a multi-department course that I developed and taught in between 1992 and 2006, and Medicinal Chemistry 656 was Biomedical Applications of Mass Spectrometry. That was between 1976 and 2006. So that's not a lot of teaching [for two courses] in a certain sense, but [they] lasted for some years.

GRAYSON: It seems like it's a lot related to mass spec and the interpretation of…

J. MCCLOSKEY: Biomedical Applications of Mass Spectrometry, now that's a whole course on mass spectrometry. But Biochemistry 649, Methods in Structural Biology, that included X-ray crystallography and NMR and all of that. And I would get different people in to [cover those topics]. So I was the manager of the course and so forth. It was for…1986, it's fourteen years […].

GRAYSON: Well, let's talk about your students at Utah. There you were able to get funding right away, pretty much, and with that, you were able to get equipment…a [21-]110, and you were able to get some students I guess…what kind of students were going to this school of…this is a **<T: 5 min>** School of Pharmacy?

J. MCCLOSKEY: It's in the [College] of Pharmacy, but all the graduate students, really, most of them are chemists [and have a molecular orientation]. They're not…they're very…pharmacists are rare and usually don't have the background. So the students, my students, I would normally have one or two at a time, and that's not a lot.

GRAYSON: So how did they find you? I mean, you're in pharmacy.

J. MCCLOSKEY: Well, there's a population of them in the department, and they interview faculty to see what the story would be if they worked for them. What would they do? What's…you know, what's up. So you make a spiel to them, and they then make a decision about who they want to work with. Of course, you've got to make sure you have the money to support them for years. I mean…

GRAYSON: […] So mostly it's…I mean, you're kind of in a cross-disciplinary area here. You're in analytical chemistry, chemistry, biology.

J. MCCLOSKEY: [That's correct].

GRAYSON: And you're doing…I mean, your research is still in nucleosides and nucleotides, right?

J. MCCLOSKEY: Well, nucleic acids and…

GRAYSON: …nucleic acids. Okay. So they come to you because they want to do that? They know you're known for that?

J. MCCLOSKEY: [Essentially, yes]. They come to me…some of it is that, yes, it turns out, I was told by them. And some of it was mass spectrometry. And if they had an involvement with mass spectrometry, for example, as an undergraduate, they worked somewhere and ran samples, they'd say, "Golly, this is pretty neat stuff." So that would take that tack. Otherwise, the biological part, they would not know much about it. Let's see.

Missing pieces here. I was director of the mass spectrometry facility for the University of Utah from 1976 to 2003. Okay? That is a campus-wide…[fee-for service facility].

GRAYSON: So you had equipment…obviously, you're ending up with more than a 110.

J. MCCLOSKEY: Not mine. No, this is…no, this equipment's not mine. University money. I made sure that I didn't use any of my equipment for that. And that was…

GRAYSON: But were you the arbitrator to say which to buy in this…

J. MCCLOSKEY: Yes, I was. And I would make the rules about what samples are submitted, and we charged them. Most things are never free. They can be free if it helps, but, you know, mostly not. , and so there would be a fee schedule that I would have to keep up year after year. And then there was the interdepartmental—I'm looking at this thing I haven't seen for a while—interdepartmental biological chemistry program. That's run…goes through twenty-some odd departments. Twenty-seven, twenty-eight departments. So I was the director of that from 1993

to 1995. All other things were kind of fallout from those. Visiting professor, visiting investigator, the National Cancer Center Research Institute. That's to work with Susumu Nishimura. And I had the title of visiting investigator between 1971 and 1992. Okay? So that's [a pretty good summary].

GRAYSON: You made a lot of visits [to Japan]?

J. MCCLOSKEY: …21 years. Well, I made probably a dozen. So the advantage in that, if you're going to Japan, is that it's a remarkable thing to see it change. Just, you know, every year, every other year, you'd see changes, changes, changes.

GRAYSON: So when you say changes, is that…what…

J. MCCLOSKEY: The buildings, the dress, the things that represent societal [matters].

GRAYSON: So they were becoming more Westernized in dress?

J. MCCLOSKEY: To some extent, but otherwise, just better at what they do, more sophisticated. Factories of this and that. So…

GRAYSON: Now I understand it's a very dense population in Tokyo.

J. MCCLOSKEY: Very dense.

GRAYSON: So is that…was that an issue, and did that kind of feel…

J. MCCLOSKEY: It did originally, and the bigger problem there was taking the public transportation. When I went…I went for six months the first time to work for Susumu Nishimura. That's when I had an NIH fellowship, **<T: 10 min>** and I took public transportation. That's an hour and a half each way, and sometimes you couldn't…when you stand, you couldn't move your arms on the train. You could not move your arms. So this comes to some…leaves you with some hilarious situations sometimes, when you're boxed in tightly. I'll describe this more tonight at dinner. Anyway, but I got used to that, and being stared at. If you're the only foreigner on the whole train—on the whole train—there are a thousand people on that train, and you have a feeling of…

GRAYSON: Who's the oddball?

J. MCCLOSKEY: …being very…gawked at, is a better word […].

GRAYSON: So these students that you did get [in Utah]…

J. MCCLOSKEY: They had backgrounds mostly in chemistry, [although several of them wanted a PhD in biochemistry which indicated that their interests were more biological than chemical].

GRAYSON: [Did this result in having fewer graduate students?]

J. MCCLOSKEY: Yes. And I had a total while being at the University of Utah of about six, I guess, my whole career at University of Utah, six graduate students, and another five from Baylor, and the rest were all postdocs [or something similar].

So, one could take a slice [of my lab] population at any one time - it'd [have] one or two graduate students. , and I had graduate students from biochemistry, too…Biochemistry Department. So I was also professor of biochemistry, and that was…I always thought it was a generous thing on their part. And when I moved there, there was a deal made about my having an appointment in the medical school. It was a pre-concocted deal. But when I went there, I thought, the worst thing is for me to walk in the door and announce what I [wanted], and so I didn't. And I went to see these guys, and they said, "Well, why don't you hang around for a year, see how things are going, and then we'll talk about it." And I did that, and they voted, I guess, and I became a professor of biochemistry. So I became professor of biochemistry, if you see the dates, a year after I got there, because I didn't rush into it, even though a deal had been prearranged. And [so in the end that arrangement worked well].

GRAYSON: And this was on the medical school faculty?

J. MCCLOSKEY: Well, they're both, because as professor of biochemistry, that's in the medical school. Professor of Medicinal Chemistry is in the College of Pharmacy. So I was in two departments in two colleges, that's two different buildings. But I got a lot of intellectual benefit from the biochemistry department, much more than other places. So I had students from there, and I went to those seminars, and all the full trappings of the biochemistry department. And that was enjoyable.

GRAYSON: Yes. So generally speaking, getting any degree of recognition in the medical school is difficult compared to, you know…I mean, at least that's the way it is at Washington University. [Wash U was divided into two different campuses.] If you have a joint appointment and you're able to have one of your appointments in the medical school, then that's super good, you know… Is it the same way at Utah that you got extra credit…

J. MCCLOSKEY: Yes. Somewhat, yes. I would say so.

GRAYSON: So you continued to focus on the nucleotides and nucleosides work, the research.

J. MCCLOSKEY: Yes. So that developed along […] increasingly biological lines, and also things related to evolution. , because **<T: 15 min>** as I mentioned to you before, the world is divided into three compartments for evolution: archaea, bacteria, and eukaryotes. We are eukaryotes.

And it turned that a lot of characteristics of modification of nucleic acids is unique to one or two, sometimes three, sometimes one, sometimes two, of those domains. And so we kept up with those, and we published pictures showing what [RNA modifications are] in which domain.

GRAYSON: So this is kind of like an overarching guidance to your research.

J. MCCLOSKEY: Well, we were interested in what's unique to this, what's unique to that, but the main driving force was when we started working on high temperature organisms, and…

GRAYSON: When was that? That was with this fellow…is that Stetter?

J. MCCLOSKEY: Stetter. Part was with him and part just was me doing stuff on my own, without his [input]. I remember the very first [modification we encountered that could be subject to such classification]. It was in about 1985. 1987. No, it would be before 1987.

GRAYSON: And this is [1-methylpseudouridine, which is strictly archaeal].

J. MCCLOSKEY: So let's say 1985, 1986, would be the opening gun on that count.

GRAYSON: By this time, how many other people were doing mass spec of nucleosides, nucleotides? Or was there anybody else?

J. MCCLOSKEY: Well, depends on what your level of seriousness would be in order to designate that. But I think there were never more than half a dozen. At one time it became fashionable to think you could sequence nucleic acids by mass spectrometry. And they were interested mainly in DNA, because that was a gold mine if it worked.

It didn't work. I never said it worked. In fact, I was interviewed by *C&E [Chemical and Engineering] News* and quoted that, you know, it was destined not to work, that that was not a way that was going to be fruitful for large-scale sequencing of RNA or DNA.[16] And it turned out to be true. So once those people dropped out, those were the ones who drop in with…you can get involved with DNA for a couple of years and find out it wasn't getting them anywhere, so they back out maybe. And so…let's see, beyond that, you had some things like we published at the same time Franz Hillenkamp did on some things. His interest was never that much in the nucleic acids, but he published a paper or two and so forth.

GRAYSON: Yes. So it's…I mean, you're kind of like a lone wolf out in this area.

J. MCCLOSKEY: To some extent, yes. Over a period of time, I may have been just about the only person, and I became the only person really working to look at these modifications. There are other angles you can pursue. The one of making modifications on RNA. DNA instructs the cell what the sequence is going to be of proteins and of RNA.

So there are separate genes for those two. And once the RNA is made, it is then—most of the RNA—is then subject to further modification, methylation, replacement of O by S, side [chain synthesis] of various kinds, and there are special enzymes that do that just in RNA. And so when you get to that level and you're worrying about where they're coming from somewhere, I may have been about the only person, certainly the only one doing mass spectrometry. There may have been a few people along the way, but not…it wasn't that it was a great idea of mine that made that so, but it was true that I spent a lot of time finding out how to do it [on RNA]. Knowing these people and so forth, that made it a fruitful avenue of research.

GRAYSON: Were […] there difficulties in actually getting these guys to fly?

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[16] S. Borman, "Biochemical Applications of Mass Spectrometry Take Flight," *Chemical and Engineering News* 73(35) (1995): 23-32.

J. MCCLOSKEY: Not after you had things like electrospray. And what I started to say earlier was that what really **<T: 20 min>** uncorked the dam was LCMS with electrospray. That was the greatest single moving event, because you could take nucleic acids and you could hydrolyze them down to small pieces and analyze the whole thing in one shot, right?

That's the typical advantage of chromatography-mass spectrometry. The same thing holds for GCMS [gas chromatography-mass spectrometry], only in this case you're working with molecules that probably are very, very polar. And once we had worked out the [ion] dissociation chemistry, then you could marry that into collision-induced dissociation, and they were getting now a huge amount of information from one of several chromatographic runs. I mean, really a lot. And you could identify forty or fifty nucleosides, different nucleosides, in one organism, by doing that. Before, that would be several years' work. But you never had to worry about the number of these things, because chromatography separated them, and even if they didn't separate them totally, you learned to read [chromatographic] shoulders and everything else, and you could figure out where they had [originated]. So that was the story.

GRAYSON: So when you electrosprayed these guys, did you have a…it seems to me I recall a young woman working in Mike Gross's lab that was working with oligos, and she found them to be a challenge mass spectrometrically compared to the peptides and the protein things.

J. MCCLOSKEY: Yes. Probably so. They're still more polar than proteins and peptides [of similar size].

GRAYSON: And they seemed to be prone to…[her] viewpoint was you had to have very pure, clean equipment to do the wet chemical preparation and so on, and you couldn't have any dirt around, or else it would…

J. MCCLOSKEY: Well, there's an element of that. It depends on what her problem was. If you're going to use enzymes to cut it up, then you need to have things that are reasonably clean before you add the enzyme because once they're hydrolyzed, these small pieces, and you look at the pieces [using MS], you're not sure whether you're looking at something that came from a nucleic acid or a piece of junk. , or even a peptide or something like that. So…

GRAYSON: So when you went into these, what size…how many units did you start out with? I mean, so did you kind of get to bigger and bigger things with time, or…

J. MCCLOSKEY: No, there wasn't any merit to it. We got to where we could…there was a very useful enzyme called ribonuclease.

GRAYSON: What was that?

J. MCCLOSKEY: T_1 ribonuclease. That's one word. The two were ribonuclease T_1 and ribonuclease T_2, capital T in both cases, usually done with a subscript T_1, T_2. And T_2 is useful because it cuts [the chain] only at G. So now think of a large nucleic acid. You have an enzyme that cuts at G, since G is one of the four major bases, it means that you're going to do a lot of cutting, right?

And if you have stretches of nucleotides that don't have Gs in them, you'll end up with some big pieces. , but when you encounter that piece, you're fairly sure that the terminal nucleotide is a G. Now that's [good starting] information. That's information-bearing. And you can find modifications in there by various means, but if they're modified, that may be a really devil of a situation without LCMS. I mean, LCMS is made for that sort of thing.

GRAYSON: So you're continuing to push the state of the art in this whole time period and also applying as much information as you can get from every possible…

J. MCCLOSKEY: Well, the progress we made was very…of decreasing importance in the field of mass spectrometry, but increasing importance in biology, and people who deal with nucleic acids and the enzymes that make them…that modify them and so forth, and…because **<T: 25 min>** once you had electrospray LCMS and furthermore, if you did the experiment right, you could do CID on pieces that way. If you had enough sensitivity to do that, whoa, you've really got the bull by the horns, and I don't know what else you could do to develop something. I mean, little trivial things.

But then the action comes in what you're doing. What is the application you're then making with it? And so that's where the action is, and that's where the action was for me, was in those cases.

GRAYSON: Now I noticed in some of these papers it seems like there's…these are mostly Japanese collaborators that…looking at the list of papers and the authors, there's…

J. MCCLOSKEY: Yes, a number of them.

GRAYSON: …quite a few…but, I mean, they're not…they're from the Far East, but they're mostly…I mean, they're Japanese.

J. MCCLOSKEY: Japanese. Yes.

GRAYSON: They're not Chinese or…

J. MCCLOSKEY: No, no, no. Japanese. But they're not always in Nishimura's laboratory. There was another group headed by a man named Isono […] Kiyoshi […]. Those were antibiotics of various kinds, some of which were nucleic acid related, some of which were not. And we published papers. They were nice papers. And so you would see a Japanese name, but it wouldn't have anything to do with the nucleic acid business or with the Nishimura group. So I probably published with him a dozen papers like that. I could count them.

GRAYSON: Did many or any of those people come to your lab in Utah, or…

J. MCCLOSKEY: To work, you mean?

GRAYSON: Yes, to work…

J. MCCLOSKEY: Occasionally. Oh, I had…yes, I had, early on, two postdocs [who] were from Japan who came, but they weren't the offspring, or a part of the groups of people I worked with otherwise. They just came on their own, and I supported them through [existing] grants and things like that. And we published a few papers, and…So…

GRAYSON: Now all this time you're being funded primarily by the…

J. MCCLOSKEY: [In Utah], NIH.

GRAYSON: NIH? And how is that level of funding working for you as a function of time? Is it constant? Is it increasing?

J. MCCLOSKEY: It's fairly constant. It depends on whether you're asking for a mass spectrometer or not.

GRAYSON: [laughter] How many mass specs did you ask for?

J. MCCLOSKEY: If you're content with what you have, then the budgets obviously get much smaller. If you've got a half-million-dollar mass spectrometer in the budget, then many things happen. , but it means that you're in a special category and so forth.

GRAYSON: So how many…I mean, you had the 110 for starting your research. Did you kind of…

J. MCCLOSKEY: Then I had the 731. And we had an LKB [9000S]. For conventional…what was it? Conventional…

GRAYSON: Was that a GCMS LKB?

J. MCCLOSKEY: It was mainly GCMS. Right.

GRAYSON: LKB 9000S?

J. MCCLOSKEY: LKB. 9000S. 9000SS, it was called, because it was made by Shimadzu.

GRAYSON: Oh, it was done by Shimadzu.

J. MCCLOSKEY: Corporation. That's when they were in the business of using the patents provided by Ryhage to make the [interface]…

GRAYSON: [My understanding] was that the 9000S was fashioned after a MAT machine, if I'm not mistaken. It was, like, LKB's version of the MAT 60 degree…

J. MCCLOSKEY: Well, that's what I heard, but, I mean, 60 degrees is 60 degrees. So you can say… [laughter]

GRAYSON: Just because it's…

J. MCCLOSKEY: Well, I mean, it's geometry that has use because of the optical…ion optical problem that you had. But saying that that was copying someone, I…that's only true to an extent, and I think probably that's right. But that's not really a versatile instrument, really. It was made for chromatography and mass spectrometry. You couldn't do CID with it.

GRAYSON: That was a single…the LKB was a single focusing?

J. MCCLOSKEY: Yes. Yep. **<T: 30 min>** That was it.

GRAYSON: Did you have anything with a higher resolving power than the 110, do you recall, or…

J. MCCLOSKEY: […] The 731 was higher. So while the 110 probably… I don't know. There's what they claim and there's what you get, but if you say that on that instrument, what you get is twenty-five thousand, you know, on the 731 you might get fifty.

Now you could do the heroic things in both cases and move that up, but if you move it up very far, you're in a zone that's not practical, because you have no beam. The beam vanishes, and you can't solve problems. But still, the stepping stone would be to go from 731 to…I'm sorry, from 110—21-110—to the MAT 731 [Mattauch-Herzog].

GRAYSON: With the photo plate detection and all that?

J. MCCLOSKEY: Photo…with the focal plane…The ions arrive at a focal plane, not a point. Put a photographic plate in there, if you've got a way to read the plate. We talked about this earlier. And that…was that the most sophisticated instrument we had?

GRAYSON: Was that resolving power all that useful? You know, a lot of…sometimes resolving power was a horse-race-type thing.

J. MCCLOSKEY: Right. That's a very clever question. [laughter] Because the answer, as you probably know, is no, it's not all that useful. But the fact is that when you really need resolution, you can get it much more easily. So if the max that you can get on it is fifty thousand, whether or not you need fifty thousand all the time, if you're running it at twelve and all of a sudden you need thirty, you can get thirty pretty easily.

So that's the story. But the resolution itself is not…has never been very important. The mass accuracy is what we've found to be crucial, because we worked so hard on converting mass to elemental composition. That was the cornerstone of doing the nucleic acid work.

GRAYSON: So…but that was a fairly tight…you were constrained with a fairly small number of atoms, elements that you had to deal with. I mean, carbon hydrogen, nitrogen, phosphorus.

J. MCCLOSKEY: Yes, but what we did was early on we wrote programs that followed certain rules, and so you'd say that, okay, there is the largest…so the minimum number of nitrogens in any nucleic acid is two. Two per unit cell. So you cannot have a composition delivered by computer with fewer than two.

It has ribose in it, you've got four oxygens. Therefore, you cannot deal with composition with two oxygens, for example. And so you sort through…well, we published that.[17] You sort through certain rules, and that makes it much easier to separate the massive amount of junk that you get, measure exact masses day and night and not know which ones are important.

GRAYSON: So your densitometer would convert all the information on the photo plate into just digital stick mass? Like would it do the centroid…

J. MCCLOSKEY: Numbers. No, just numbers, really. So it'll give you a list of numbers, and you can tell how…you'd have a crude measure of the importance of the ion by its density on the plate.

So you'd get…that's easy to get. Then you make a…but I would say we didn't do very much of that with real mixtures. Very little, actually. We could have done more, but it was always such that we had the wherewithal to purify it or to ask a collaborator to purify it and use it.

GRAYSON: Did you get any collaborations at Utah and in the school there? Were the…most…you were mostly collaborating with people outside of…

J. MCCLOSKEY: Outside the country, mostly.

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[17] S.C. Pomerantz, J.A. Kowalak, and J.A. McCloskey, "Determination of oligonucleotide composition from mass spectrometrically measured molecular weight," *Journal of the American Society for Mass Spectrometry* 4(3) (1993): 204-9.

GRAYSON: Oh, wow.

J. MCCLOSKEY: No. No. In the department, almost never. In the University, almost never. We could go through the… **<T: 35 min>**.

[…] But…so that's kind of curious, that point, and it's been pointed out to me that, wow, you've got a whole career made up of collaborations with people elsewhere, if it was a collaboration. Many papers were not.

GRAYSON: Well, you had the Japanese connection, with a couple of different places, and there was the fellow in Regensburg, Stetter and the thermophiles, and so that's kind of the different approach to things.

J. MCCLOSKEY: Yes. So the story with Regensburg and Stetter was that I learned from him about thermophiles. You can read if you want, but if you're working with somebody who's very enthusiastic and very knowledgeable—he's the number one man for many aspects of thermophily—then when that's…you don't need at some point to continue collaborating. You know what…you learned what to do, and you can take the ball and run with it, and that's what happened with him. We had some things that we could have actually done together [and planned on doing], but we never got to [when I retired].

GRAYSON: So what kind of projects did you take on after you were able to do on your own?

J. MCCLOSKEY: Oh, somewhat more of the same. We were interested in the effects of temperature of cell growth on modifications, which ones and how much modification. See, temperature of cell growth, we're talking above 80 degrees, close to 100, or more than 100 even. And that was an interesting thing, because there were such sharp differences when you get to big, high temperatures. That's a problem. Most large molecules like DNA or proteins dissociate. It's like boiling water, right? That's how you cook an egg.

GRAYSON: Yes. Right. [laughter]

J. MCCLOSKEY: But there are some organisms that are self-protected, and the proteins do just fine at 105 [degrees].

GRAYSON: That's weird.

J. MCCLOSKEY: Nucleic acids that do just fine at 100, 101, 102. So the microbiologists view this as, sort of, phenomenological research. They've learned to do it, right? But as a chemist, you say, well, it's not really a question if they've learned to do. How do they do it? What is the way they do this? And there's a lot of work done over a period of about ten years, not in my lab, but around, trying to figure out how the proteins did it. And they made serious inroads into that problem, but it's not a simple question, and it's not…you know, they've learned to do it. Oh, how nice.

There's science behind this. What are the rules of chemistry? You break bonds at 100 degrees, so how come you have an organism growing, smiling at you?

GRAYSON: Yes. Yes. Well, one of the things I've come to the conclusion is that if there's a little bit of organic and a little bit of energy source, it will create life of some kind or another, you know. I mean, there's all these things that grow in the dark. I think, you know, they get their energy from a totally different place. And it's…it kind of says to me that there's life out there somewhere in the universe.

J. MCCLOSKEY: Oh, yes. […] That conclusion I think is a good one. Plus there's life…the other thing is the oceanography people will tell you that it's proving that there are boundless forms of life in the ocean. All kinds, all kinds, that you don't even know about.

GRAYSON: Yes. That's the scary part.

J. MCCLOSKEY: And so when you start saying, well, this is different and that's different, you're probably also talking not just about how it grows and so forth, but the enzymes that are used to put together all the building blocks. Those can be radically changed by temperature. So you're dealing with many things. So the complexity of the question increases greatly when you get up to 100 degrees, and we hardly know much about that.

GRAYSON: So let's see here. **<T: 40 min>** You didn't have much of an interaction with industry, I suppose. Government was mostly asking for dinero. [laughter] And so I guess your decision to go where you went in your career was just guided by your own interests and the fact that you went into academia was just the convenience of being able to pursue what you wanted to…

J. MCCLOSKEY: That's right, and that…I didn't appreciate that until later in life. It's really something to say that you want to do research and you have enough money to do it. But wait a minute, you work on what you want. Sooner or later, you have to justify it. Right? So at the end

of your grant, if you were supposed to do A but you did B instead, that's okay, so long as you can show that that was a good thing to have done. And you…the strictures tightened up on you pretty much.

GRAYSON: So did you have that occasion for that to happen, where you said, "I want to do A," and then you ended up doing B?

J. MCCLOSKEY: Not such that it would damage the fundability of the grant or something like that.

GRAYSON: So you always kept the grant goal in mind, but you did stray whenever you saw something that looked a little bit interesting?

J. MCCLOSKEY: Yes. Oh, yes. Oh, yes. Oh, yes. And that's how we got into the thermophile business at the start, and that wasn't the thing that we had predicted or planned.

GRAYSON: Were you able to get that funded, then, the thermophile work, when you decided to go into it.

J. MCCLOSKEY: Well, that's one of the amazing things, is that when we really got rolling into the thermophile work, it was funded by NIH. There was no disease connection. None. None. No cancer, no whatever.

GRAYSON: That's interesting. That really didn't hook up with anything that you were…

J. MCCLOSKEY: No, but they recognized…I always thought that, you know, they recognized, A) good science, and B) what we're learning about how molecules stabilize themselves here must also help when they're here. Up here and down here.

GRAYSON: The rules…yes.

J. MCCLOSKEY: And I thought, gosh, that's…that has to be the case. That has to be why they put up with what we did for so long, and we became adept at it, and produced a number of papers, and so forth. So let's see. What else do we need to worry about here?

GRAYSON: I was curious…

J. MCCLOSKEY: We have tomorrow, don't forget.

GRAYSON: Yes. We have tomorrow if you want to…well, that's up to you. You know, I mean, if we want to carry on, it's there to use at least part of the day. I was just curious if you felt…any time in your career where you were particularly challenged, like in the sense that this guy is kind of an outlier, and is he for real? Do we really want to support him, or do we want to really give him some credibility or some support?

J. MCCLOSKEY: There were no major issues along those lines, I don't think. And once I broke loose of having to work on anything health-related, I have a whole grant that almost has no health-relatedness whatsoever, and it got funded happily. Once I get into that situation, you've broken the bonds of whatever, and you can feel good about it.

GRAYSON: Yes. I don't know if that would work in today's environment.

J. MCCLOSKEY: It may not. It works less and less. Put it that way. I've talked to people about it, and just…it's less and less. Now the funding agency will say, "Wait a minute. This is National Cancer Institute. Let's talk about this." You can maybe make the case…there are places in the grant to do it. There are paragraphs that you write talking about the relevance of what you're doing. And…

GRAYSON: Well, yes. You seem to have been in the right spot at the right time in terms of funding, because as a…I think it's getting to be a more and more critical issue with…

J. MCCLOSKEY: Oh, it's bad now. Now it's really bad. Oh, I would hate to be an assistant professor these days because…

GRAYSON: I've got two people who are, and I hear about it.

J. MCCLOSKEY: Yes. Yes. No, there's a real…these are truly bad times for these people, because the rules by which they operate require that they do research, and research **<T: 45 min>** requires money, so getting from here to there is not…

GRAYSON: Yes.

J. MCCLOSKEY: Or you end up doing really mediocre stuff that you don't care about until all this blows over. A lot of people take that attitude.

GRAYSON: Well, or whether it'll blow over is a good…is something that…

J. MCCLOSKEY: Is another issue.

GRAYSON: Because, I mean, if the government's going to be the big funder and it's up to… I mean, regardless of what your political position is, the debt issue has to be resolved somehow. And one way to resolve it is to not spend as much money.

J. MCCLOSKEY: Yes. That's the simple way to do it.

GRAYSON: That's part of resolving it.

J. MCCLOSKEY: Yes. That's the simple way to do it. It's politically easier. But once you start saying we'll fund here but not here, you've opened a real [can of worms].

GRAYSON: So you really didn't do a whole lot of mentoring in your career, but you had some…

J. MCCLOSKEY: Postdocs and graduate students. We can make a list of them.

GRAYSON: Was that… were there any exciting moments in that whole process of mentoring these people, the younger guys? Did you have any issues with some of them, or…

J. MCCLOSKEY: No. I mean, there are a range of success stories in students, a real range of success stories. And some were highly successful, and with…some of the things they did were among the best things that we published. And others, it's the other way around, both for postdocs and for graduate students. When you get a good graduate student, you can do some of the very best work, because if they're smart and they're capable and you've got a good problem

that you've agreed on to work on, they can dig into the details much more effectively than a postdoc, who's trying to get out in a year.

And so the poor graduate student is there for the longer haul, and by and large you hope that this means that the depth that they can reach of understanding is greater. Doesn't have to be.

GRAYSON: Yes. How many people went on to work in that nucleoside/nucleotide business when they left your shop?

J. MCCLOSKEY: That worked for me? Just a handful, probably three or four. And they all ended up in some location where they didn't have that luxury. "I want to work on something to do with DNA. ." "Well, maybe you can, maybe you can't. Let's find out who's paying the bill. Let's find out if the question you want to work on has any real relevance to anything." And so I suspect to a lot of the students who then go on and get other jobs, they are puzzled and astonished by the realization that what they saw in their graduate career was unusual in the paucity of constraints, I would say. Very few constraints.

Let's see. What else can I think of in here that's important? Advisory boards, nothing special. Duh duh duh duh […].

Living in Japan was an exciting thing, actually, and we were there for six months.

GRAYSON: And what period of your career? Was that fairly early? Middle?

J. MCCLOSKEY: It was in 1972. […] It was [early in my career]. I had already…I was already a full professor, but I wasn't self-sustained. Put it that way. So…

K. MCCLOSKEY: Sabbatical.

J. MCCLOSKEY: Sabbatical. I didn't take enough sabbatical leaves. That's always a problem for some people. They don't want to take sabbatical leaves, because either they can't go away and manage what's at home…that's my big complaint. You lose track of managing what's happening. And the other thing is that it just simply puts you too far away from things you're supposed to be dealing with.

GRAYSON: Yes. It would seem that it would, kind of…I mean, in a way I can see where it's a nice perk, but then…

J. MCCLOSKEY: Well, it can be a nice break. **<T: 50 min>** Put it that way. That's okay. And sometimes it's in fact very helpful. But I was discouraged to see some of my colleagues that I know, they took sabbatical leaves for trivial reasons. What they did turned out to be nothing they could point to, really, on their curriculum vitae. Holy smoke. It's up to them.

GRAYSON: Now did you take a sabbatical leave to Japan, or did you just say, I…do that on your…

J. MCCLOSKEY: […] It was officially a sabbatical, but on the other hand […] I was having trouble getting Baylor College of Medicine to pay for it. They didn't want to pay for me.

GRAYSON: So this was back when you were in Baylor?

J. MCCLOSKEY: Yes. Starting there, that's when I was going to Japan the first times. And then that's when I went on sabbatical to Japan, was at the tail end of the Baylor experience. And so…hmm. I was also very naïve and I didn't pay attention to the problems of the world, right? "You're going on sabbatical leave? Fine. Who's paying for it?" You say, "Well, wait. What do you mean, who's paying for it?" "Well, do you want a salary? You want to eat? Who's paying for it? Let's visit this very carefully."

So people who worked for state universities and had their salary paid with state money, so-called hard money, have a better time of it, because whether they're paid here or they're paid there, if it's the same pay, roughly, and there's no big problem. But when they're grant-supported, that's the difficulty.

GRAYSON: I see.

J. MCCLOSKEY: Because when they're going away to some other place, the granting agency has to concur.

GRAYSON: Buy in. Yes. Yes. So you were… when you were at Baylor, Baylor was an independent school, or was it part of a…

J. MCCLOSKEY: It's a private medical school.

GRAYSON: Private medical school.

J. MCCLOSKEY: And when I arrived, they had loose connections with Baylor University, which is a private university, and didn't change anything. But they realized after a while that—being told by Baylor University that federal money was bad, get rid of it, we don't like that—boy, to run a medical school, whoa, federal money is the heart of how you get things done. And so finally Baylor College of Medicine had to say to the other University, "I think we're on different paths here." And they separated. That was while I was there. And the name didn't change, but you saw some changes in the advisory boards and things, way upper level University administration. So it was a private medical school, one of, I think, three or four in the United States, and had no undergraduate affiliation.

GRAYSON: Yes. That's kind of weird.

J. MCCLOSKEY: It is, it is. And that's why we felt so fortunate to be across the street from Rice. And you had University of Houston not far away. And those were essential.

GRAYSON: So there was enough recognition to the Baylor name that they wanted to keep that in the medical school? Even after they split, they wanted to keep Baylor as part of the…

J. MCCLOSKEY: Oh, yes. Yes. I think they…yes. I think so. The medical school had and has a considerable reputation, and so the last thing they wanted to do was start over…

GRAYSON: Come up with a new name. Yes.

J. MCCLOSKEY: Oh, that creates all kinds of problems. So they said, well, let's just quietly drop out of the Waco story.

GRAYSON: Yes. So I guess the outsider doesn't realize that they're independent organizations even today.

J. MCCLOSKEY: You mean medical school and so forth?

GRAYSON: Yes, the medical school, because of the Baylor name, they just assume…

J. MCCLOSKEY: There are a few, and of course, the medical…Baylor, most people would assume that Baylor College of Medicine is related to Baylor University. And it ain't…it ain't no more […].

GRAYSON: Okay. I want to review my notes here.

J. MCCLOSKEY: Just to get that done. And see what else…I can undoubtedly think of some things, that we haven't talked about.

GRAYSON: Well, I was just curious about the 731…did you have another instrument beyond that MAT 731?

J. MCCLOSKEY: No. What did we end up with? We shut down the 731. Oh, yes, what did we end up with? We ended up with a…ah, stop. A VG instrument.

GRAYSON: Well, they have ZABs and…

J. MCCLOSKEY: This is a lesser…

GRAYSON: I'm trying to remember the…but that was the vacuum generators?

J. MCCLOSKEY: I'll have to look at a grant. I've got a grant here I can go look at. Isn't that awful? I can't remember. Jeez. It was a…you'll know what it is the minute I mention it to you. Let me find the grant here somewhere […].

There's some things I want to show you, and that might be where I do those tomorrow, but it'll take me a few minutes to find what I want.

GRAYSON: You know, what we could do is make a list of things that you can research between now and tomorrow, and then…

J. MCCLOSKEY: Then do it.

GRAYSON: And then that'll give you a chance to catch up on some of these details, and likewise for me.

K. MCCLOSKEY: Here's one from 2003.

J. MCCLOSKEY: Oh, that's pretty up to date, isn't it? If it has a list of equipment, that's what I need. […] So the largest molecule we worked with was probably the **<T: 60 min>** ribosomal RNAs and one from *E. coli*.

GRAYSON: Ribosomal RNA?

J. MCCLOSKEY: Ribosomal RNA. That's different than transfer. tRNA means transfer RNA, and ribosomal RNA is a different RNA, and in many ways less is known about it, certainly about modifications. And so we got into that because we had, finally, the tools to work with something that big.

GRAYSON: How big was it?

J. MCCLOSKEY: Well, fourteen hundred and some odd nucleotides, [and perhaps double that size].

GRAYSON: That's getting up there.

J. MCCLOSKEY: Here you go. Here's a picture of it. Pictures are cute.

GRAYSON: Ouch.

J. MCCLOSKEY: Biologists love these. They love them.

GRAYSON: It looks like a chemical engineering.

J. MCCLOSKEY: Looks like an airport to me. Lost and found. Delta.

GRAYSON: Fourteen hundred nucleosides, you say?

J. MCCLOSKEY: […] There are ion tracks that you get with LCMS, with that…whoa, the whole thing is a mess.

GRAYSON: Oh, yes.

J. MCCLOSKEY: Three and four pieces underneath these. Lord knows how many under there. Right? But you can separate out the tracks and assign meaning to them, usually, often.

GRAYSON: So that ribosomal RNA, did you end up working with some kind of enzyme to break that…

J. MCCLOSKEY: Cut it down.

GRAYSON: Yes. Cut it up into pieces. Yes.

J. MCCLOSKEY: You have to. You have to. And it has to be a very reliable enzyme. You say, "I'm going to cut it. I want to know the rules, and I don't want it disobeying the rules," because you make a lot of hay out of that. [Rustling]. Ah, I forgot, we also had a Sciex API III.

GRAYSON: Now that's a time-of-flight, isn't it? Sciex?

J. MCCLOSKEY: Yes. That was 1993. The Quattro…we had a Quattro in 1995, and the [other] one I'm trying to think of is the VG 70-SEQ.

GRAYSON: 70-SEQ?

J. MCCLOSKEY: 70 dash SEQ. That was retired…I bought in 1986, retired in 1997.

GRAYSON: So these were kind of like sequential instruments and…

J. MCCLOSKEY: Yes, pretty much. You can tell by looking on the…

GRAYSON: You didn't…you didn't have one of these shops where you got, you know, one of each laying around, like Mike Gross has, I don't know…they buy mass spectrometers like we buy candy bars, you know, in the med school there.

J. MCCLOSKEY: [Yes, yes]. No, I mean, this is from an R01. That's a personal grant. And so the API III we acquired in 1993, buying the source, ESI. The Micromass Quattro II, 1995.

GRAYSON: That Quattro, was that a sector a…

J. MCCLOSKEY: No, that's the…

GRAYSON: Quad, metrical quad?

J. MCCLOSKEY: Quattro, Micromass Quattro. That was a triple quad.

GRAYSON: Okay.

J. MCCLOSKEY: Yes. Purchased under this grant. That was purchased under a different grant in the same…two years apart. So I had two grants going, kind of leapfrogging each other. One was a cancer grant, and the other one was a non-cancer grant. So finally they looked at them and said, "Wait a minute."

GRAYSON: What's that?

J. MCCLOSKEY: Then finally they looked at the two and said, "Wait a minute. I think we're…There's a shell here. I'm not sure where the pea is, but McCloskey…" [laughter]

GRAYSON: There's a shell, but you're not sure where the pea is. Okay. Well, you know, I mean, you were doing science with the stuff. It wasn't like you were…

J. MCCLOSKEY: […] I wasn't running a scam; no Ponzi schemes. **<T: 65 min>** So those are the instruments….

This is post…this is after the big instrument lab [in Utah with lots of people, big instruments, lots of space], MAT 731.

GRAYSON: And the 731 had been put to sleep by then?

J. MCCLOSKEY: Yes.

GRAYSON: Well, so what happened to those old instruments? Did you give them away, or did they just get…

J. MCCLOSKEY: We had a lot of trouble when I got ready to [retire] because I didn't want to just [junk] any of them. I had to give them away, and I went out of my way to find recipients for them, and I did, as far as I can tell. Nobody reneged. I said, "Look, you want this instrument? Here is an active Vestec," or whatever, "LCMS machine. If you want it, come get it. Here is the address. Let me know when you're coming. And then you sign something and it's yours. It's yours."

GRAYSON: So the school and the grant was okay with giving those away? There was…

J. MCCLOSKEY: Oh, yes. Yes. That…

GRAYSON: …you purchased them with grant funds.

J. MCCLOSKEY: At that point, yes, the end of its lifetime, at the end of its lifetime, and they know that's the case, and I just…so [rustling] I'm still looking for stuff in here. Specific aims, Okay.

GRAYSON: Sounds vaguely familiar.

J. MCCLOSKEY: The specific aims?

GRAYSON: Yes.

J. MCCLOSKEY: [Rustling] There was a protocol that we'd use, probably starting with RNA and going this way…

GRAYSON: Hyperthermophile.

J. MCCLOSKEY: Yes. That's hot, hot. [laughter]

GRAYSON: I like this.

J. MCCLOSKEY: Thermophile is 60 centigrade, and by agreement, that'll take you up to about 80 or 85. And then it's 85 to 100 [for so called hyperthermophiles]. That's a different world.

GRAYSON: *Pyrococcus furiosus*.

J. MCCLOSKEY: *Furiosus*. You like that?

GRAYSON: I like that name.

J. MCCLOSKEY: Love it. Stetter was naming things. Oh, he loved naming these things. [Rustling] So on and so on and so forth and so on.

GRAYSON: Did you ever have any of your grants rejected?

J. MCCLOSKEY: Yes. Never rejected. The question was whether you had a fundable priority score. I never had one that they said, "No, we're not going to grant it."

GRAYSON: Okay. So…

J. MCCLOSKEY: No, I had one that…I had one one time I think that didn't rank high enough to get paid, and so I resubmitted it, bent over backwards, and got it fixed.

GRAYSON: But they never said, "This is garbage?"

J. MCCLOSKEY: No. That didn't happen.

Oh, a few cases. That would chip away at the priority score. You'd get people looking at this, and they'd say, "Wow, is this guy…what? He says he's…he says…"

GRAYSON: Yes.

J. MCCLOSKEY: "And so I'm not going to give him my very best."

[…] Oh, so this is the one that was put back in, original proposal submitted July 1st, 1998, refused Fall 1998, by the Metallobiochemistry Study Section. Priority score of 254, percentile 36.1, was assigned. **<T: 70 min>** And 36.1 doesn't cut it. You need to be in the top 15 or 20 percent.

GRAYSON: Yes. I think that percentage requirement now has gotten a lot skimpier. Yes. This was one of the points with Fenn. A lot of his grants got rejected because they were a little bit off the wall, and he was an outsider, you know. He was trying to convince people to do these things, or fund this stuff, and he didn't have name recognition in the community, you know. And he was a…

J. MCCLOSKEY: Well, I was involved in one of those reviews. And his grants, though, were very…applications were really…you know, he'd have a piece of…something where he had done…it was a pen and ink recorder, and marked on it, and sent it in. And it's not sophisticated. And so that kind of begins to…it wasn't just the idea. It seemed like the idea…of course, later on, people said, "Well, the idea was gold." [laughter]

"The idea was gold. How come you didn't give him any money?"

GRAYSON: I would like to conduct a study of all the papers and grants that are rejected that ended up being…you know, like the Munson…Field and Munson paper on CI, you know, that scotched by somebody who's reviewing it, and…for *JACS* [*Journal of the American Chemical*

Society.]. Fenn's research had a hard time getting accepted. All these things that, you know, are real paradigm shifters and changed the way the world views science and how it gets done.

J. MCCLOSKEY: Yes. […] Yes, indeed […].

GRAYSON: Did you have a pretty good rapport with your instrument vendors? I noticed you had a little bit of everything.

J. MCCLOSKEY: Yes. Good rapport. And, of course, they all wanted to sell me more.

GRAYSON: Yes.

J. MCCLOSKEY: No, we were never involved in any disputes […].

GRAYSON: Did you have any interactions with [Austin L.] Wahrhaftig when you were…or was he already gone?

J. MCCLOSKEY: A little bit, just to say hi and…

GRAYSON: So he was still on the faculty then at that time?

J. MCCLOSKEY: Yes, he was in chemistry.

GRAYSON: […] A famous name. Well, he did a lot of fundamentals and, I guess, theoretical stuff, in the early days.

J. MCCLOSKEY: Yes. And I…what's fun is to listen to him on a student thesis [defense]. In many of these cases, he wouldn't understand really what the point was of the student, decades younger, and so forth. But he would ask questions that had great substance to them, you know. [laughter] **<T: 75 min>** I thought…I always thought that…

GRAYSON: Give the student a little bit of a run for their money?

J. MCCLOSKEY: That is fun.

J. MCCLOSKEY: [He'd say], "I see what you're doing here. What do you think is the energy spread of the beam coming out right over here"? [laughter] Whoa. Let's talk about what determines the spread. Can you guess about what that would be?

Well, let's see. So making a list for tomorrow. I'd like to show you a picture of the evolutionary tree that we worked on.

GRAYSON: And I don't know if there's a website for those nucleosides…

J. MCCLOSKEY: Yes, I can see about getting you the URL for that.

GRAYSON: There's a publication that has that in it?

J. MCCLOSKEY: The one I had… the URL when I ran it, when it was principally mine…got taken down, got taken down, when I gave it away. I gave the whole website away. And a whole bunch of people took it over. They added people to it and so forth and so on, and I just threw my hands up and said, "Guys, I'm getting ready to retire. I'm not going to mess with this stuff anymore" […].

GRAYSON: Did you ever have any patents?

J. MCCLOSKEY: None that worked. My name is on a couple of them from people in other departments. **<T: 80 min>** One of them, in fact, I don't even know existed until last week, I asked somebody, "Hey, what do you know about this?" And they said, "Well, it didn't go anywhere. That's why I know about it."

There you go. That's the current version. [http://mods.rna.albany.edu]

GRAYSON: Oh, wow.

J. MCCLOSKEY: The colors were from my era, made up by Jef [Jozef] Rozenski, and so forth and so on. It's a shadow of its former self. I may be crazy for giving it up, but I didn't want to mess with it any more. It gets many hits. Many hits.

GRAYSON: None of your work ever involved getting…with industrial operations or collaborations or…

J. MCCLOSKEY: No. No, no, no.

GRAYSON: No pharmaceutical houses?

J. MCCLOSKEY: No. I would…the only thing was I would go there occasionally to some of those guys and give talks or something, but that's not a [collaboration].

GRAYSON: […] Okay. So this…my understanding is the higher the score, the less likely it is to get funded.

J. MCCLOSKEY: Yes. But the percentile is all-encompassing.

GRAYSON: That tells you pretty much, yes.

J. MCCLOSKEY: That tells you where you are in the world. So 13.8 is pretty good. I don't…even today I think that would get funded. Well, I don't know.

GRAYSON: Yes. Things are tough.

J. MCCLOSKEY: […] That's the one that then got funded after I sent it back in, you see. It had 34th percentile, and went back in and came up to 13, was it, or something like that.

GRAYSON: So there's a lot of microchemistry in your approach to these things.

J. MCCLOSKEY: Microchemistry?

GRAYSON: Yes.

J. MCCLOSKEY: Yes. Yes. The samples you're dealing with are all small, even before you cut them into smaller pieces.

GRAYSON: Yes. Overall, that proposal must be much improved compared to the version previously submitted.

J. MCCLOSKEY: Does it say "it is much improved?"

GRAYSON: No, it says, "Overall, it must be much improved compared to the version previously submitted." So it kind of suggests it still needs further improvement.

J. MCCLOSKEY: Hmm. They paid it, though.

GRAYSON: Yes. This is one of the critiques from one…one…

J. MCCLOSKEY: One reviewer said**, "**You're on the right track," keep going, in other words.

GRAYSON: […] If he's willing and the oral history will go up on the internet, on the **<T: 85 min>** ASMS website, it would be also available from the CHF website. So from that…and […] a PDF file could be supplied, like, you know, you've got a copy of Biemann's PDF file in the transcript, so…but, I mean, it's a lot…another thing would be to have…there is a hard copy bound book that will be the transcript and all the supporting documentation that goes into it, so, I mean, you'll get a copy, and ASMS gets a copy, and the CHF library gets a copy, because they've got a collection of these transcripts, and various people, scientists from all kinds of fields of chemistry, and other mass spec partners, our little, you know…

J. MCCLOSKEY: Corner of the world.

GRAYSON: …together. Yes. But I think it'd be nice for the library to have a copy to put on the shelf, and then, you know, people who can find it that way, if they're…I guess everyone is going to be web-wise in the future, but, you know, who knows? Maybe…

J. MCCLOSKEY: They should be.

GRAYSON: Should be.

K. MCCLOSKEY: Well, here…this should go to Joan Stoddard, Deputy Director [Spencer S. Eccles Health Sciences Library, University of Utah].

GRAYSON: Okay.

K. MCCLOSKEY: And then here's the address down here…

GRAYSON: Yes. Let me make a note here, then we can make sure that that happens […].

So by revising that proposal that's kind of rejected, but not… you were kind of encouraged to resubmit it, I guess, is what I got from you.

J. MCCLOSKEY: Yes. Yes.

GRAYSON: And then, so that…

J. MCCLOSKEY: The review of the one that didn't get funded was kind of interesting to read. The minute they start saying anything negative, the priority score starts going down. And if you start your review with, "This guy is a terrific scientist, but…" [laughter] you've sealed his fate.

GRAYSON: But. [laughter]

J. MCCLOSKEY: You've sealed his fate. Golly.

GRAYSON: Well, you were able to work that game pretty well over your career, so if you get one resubmission, that's not exactly a, you know…

J. MCCLOSKEY: Not too bad. No. It's not too bad.

GRAYSON: So there's not a lot of people doing this kind of mass spec in this nucleoside/nucleotide arena today? Is it down to a handful, or…

J. MCCLOSKEY: No, it's a handful, and they're usually spread out, and you can't tell them what…they're not focused like this is. This is focused on…

GRAYSON: Yes. I mean, everybody seems to be in the proteomics or some kind of -omics, you know, proteomics or glycomics or whatever -omics. And not a lot of interest, I guess, and I don't know why is it…maybe it's too difficult to mess with.

J. MCCLOSKEY: Well, the -omics thing is that it's become famous.

GRAYSON: Yes.

J. MCCLOSKEY: And…let's see, does this go somewhere?

GRAYSON: No, I don't…do we want to carry on with some of these other issues now, or you want to try and find something in particular, or…it's up to you.

J. MCCLOSKEY: Yes. I wanted to find you some things that would be about…really recent reprints […].

[END OF AUDIO, FILE 1.3]

[END OF INTERVIEW]

INTERVIEWEE: **James A. McCloskey**

ALSO PRESENT: **Kathleen (Kay) McCloskey**

INTERVIEWER: **Michael A. Grayson**

LOCATION: **the McCloskeys' Home**
Helotes, Texas

DATE: **20 March 2012**

GRAYSON: […] So I'm just going to comment that we're starting again on the 20th of March, back again at the abode of Professor McCloskey and his wife, and we are going to finish off what we started yesterday, and hopefully get all the details that we need sorted out. So I guess first I'll ask if you if there's some particular items that we didn't cover yesterday that you'd like to talk about, you know. You've had a chance to sort some things…so what did you…

J. MCCLOSKEY: […] You ready? One to start was I was trying to show you this tree of life.[18] Oh, this came from Wikipedia, did it not, Kay?

GRAYSON: Okay.

J. MCCLOSKEY: So this was our guiding map. This is entitled "Phylogenetic tree of life," and this was our guiding map for years, even though it turns out to have had some cracks in the lines and so forth and so on, you know. It became famous because it was a very logical way to relate organisms to their ancestry, and the man who developed this—the tree was known, it's a really old idea—but the man who set this in place is named Woese, Carl [R.] Woese, […] at the University of Illinois. And this is a computer-constructed tree showing you where the origins were of bacteria, archaea, and eukarya, and the relatedness to each other. So you'd say this group is not closely related to this group, but…and so forth and so on. We could say this group is more closely related to this group than to this group, but it was individual things on the tree that are intriguing. Some are very closely related and some are not.

And the thermophiles all turned out to be mostly over here, and there are bacterial thermophiles as well. They're not nearly as hot as this. They run 90 or 92 [degrees] or something like that. And we examined a couple of those in some detail, actually. So the way this was reasoned by Carl Woese, his reasoning still is commanding to me—although people have

[18] Available at: http://en.wikipedia.org/wiki/File:PhylogeneticTree,_Woese_1990.PNG (accessed 7 June 2012).

found ways to complain about it—because it was extremely successful, and it's a fundamental concept in biology, relatedness of everything, where did they come from. So there is an RNA in all organisms that is called ribosomal RNA. There are two ribosomal **<T: 5 min>** RNAs usually, or maybe more, but usually two, and the smaller one is pretty much invariant across everything. It has an important function, but it has just enough changes over evolutionary time that you can compare sequence one to sequence two and find out how close they are. And so you can extend that to the notion of looking at comparative sequences like this and create the tree, and when a new organism was discovered, is discovered, that kind of RNA is sequenced. Actually, they never sequence the RNA, just like you never sequence a protein. You sequence the gene, because the gene is a template precisely for the RNA.

So you sequence the RNA and say, "Oh, it belongs over here. It belongs over here. Or to our surprise, we didn't know where it would go, it turns out to be related to something over here." So that created kind of a scientific sensation when it was first made, but it drew its detractors, and one of the most serious ones I think turned out to be the fact that there are exceptions to this tree that you see based on the fact that genes themselves can move from one place to another and kind of infect the wrong side of the branch and make it—excuse me—give you false readings. And you find out that genes have jumped around in the past, and if that is the case, to the extent that is the case, it weakens the precise nature of the tree. And there are people who hooked onto that immediately, saying, "Oh, well, you know, we've missed the importance of the big tree. Now we can hack away it and claim a little sliver of fame." And that's still going on, although the tree is recognized as important.

So what one finds out—and this was not discovered by us, actually, it was discovered by Carl Woese—but what one finds out is that if you look at RNA modification (what he looked at first was transfer RNA modification, one of the RNAs) you find that they're very distinct for each group. The archaea are distinct, bacteria are distinct, eukarya are distinct.

Now they have a huge overlap. In other words, they've all got AUGC in them, and they even have common sequences in them, because it was related to the historical ancient tree, two million years ago or whatever. But in many cases they have changed evolutionarily, and that's what permit them to place them on the tree, but more importantly, he found that there were a few modifications that seem to be only in the archaea. So we seized upon that idea and made a foray…this was done to a large extent by Charlie [Charles G.] Edmonds, who was in my group for some time, to sort out is it true that certain modifications are unique to archaea?

And in order to ask that question and answer it, you have to have a number of these organisms. I mean, [just] one won't work.

GRAYSON: Oh, yes. No, but…

J. MCCLOSKEY: You've got to…ten will work. And so I…the people like Karl Stetter would grow them for us on our request, and other people as well. And we would take out the RNA, and

it's a tailor-made question for LCMS, because when you take out the RNA and you hydrolyze it, you'll have many, many pieces, depending on how you hydrolyze it. There'll be many, many pieces. And to deal with those is very difficult, but LCMS saves the day, because it tells you which pieces you have by looking at the masses or by looking at the actual mass spectra from collision-induced dissociation, or whatever. And so that was…lets us look deep down **<T: 10 min>** into these…and these occasionally led to discovery of new nucleosides. I mean, completely new, never mapped before. I guess, we discovered more than half a dozen that way, and of course, you have these terrific parameters of LC position, elution position, and mass spectra, the same old for many…in many fields. But it's very powerful, as you know. And we also had the standard nucleosides for almost anything you needed, and quite a collection, probably the largest collection in existence. And that's helpful, because you'd say, "Well, I think this is this." Let's now…without breathing hard on the column, let's run it with the standard and see if it comes in the same [elution] position. Things like that. Those are old techniques.

GRAYSON: Did you need to use special columns for the nucleoside work compared to what other people were…

J. MCCLOSKEY: Yes. Yes. No, they're not so different from other people. We got it out of the literature, refined it slightly, and reversed phase columns.

GRAYSON: So did you—excuse me—have these synthesized, these standard nucleosides that you kept in a… could you synthesize these, or did you have to collect them from your…

J. MCCLOSKEY: Well, many of them it turned out were known synthetically.

GRAYSON: Oh, okay.

J. MCCLOSKEY: Just not known naturally. So you'd say, "Well, I think this is the structure. Now let's get into the literature and find out if it's floating around somewhere, someone has made it, and get a sample." Or in other cases where it's never been made before, we could attempt to make it, or we could lure one of our collaborators into making it…

GRAYSON: I like that. Lure.

J. MCCLOSKEY: Well, I mean, it's… [laughter] you know, some of these are not Saturday afternoon projects.

GRAYSON: Right. So it seems to me you're more a biologist than a mass spectroscopist.

J. MCCLOSKEY: Well, this is what led us, you see. The path was defined by questions like I'm describing for you, and then the questions of, well, if it grows at one hundred degrees in the same tree as something that grows much, much lower, are these modifications different? And the answer turns out to be yes, and you get that only by getting the clean RNAs from each one, or the cells, wherever you want to start, and doing the LCMS thing, which scrapes the bottom of the barrel, and you can find really trace materials that way. And perhaps the most interesting case of this that I can think of was the nucleoside called—we named—it was a new molecule, and we named it archaeosine or G+, and its claim to fame initially is one of the nitrogens in this smaller ring is replaced by carbon, and it has a charged side chain, which is asking…chemists would look at that and say it's asking to interact with somebody's phosphate docket or something like that.

So this was not so simple, because at first we didn't recognize…we didn't know that it wasn't a normal base, and we knew, however, it came from G, but the evidence we had didn't quite fit G. Some of it did; some of it didn't. And my graduate student, John [M.] Gregson, finally, after a long time—and we worked on this for several years, groups of people worked on it for several years—called me up one Sunday and said, "I have it. I know what it is." And he told me, and it sounded okay to me. It's a member of this family, like Q. We talked yesterday about Q.

He says, "It's missing the nitrogen, and the only way to deal with this is to make it…" so he concocted a way, an eleven-step synthesis, and not terribly complicated, but enough to make sure you're on the right path. And he made it, and he was…then I said, "Well, this is it for your thesis." But no, he wanted to stay. So he stayed [for a month] after that [in order] to make it.

GRAYSON: And who was this gentleman?

J. MCCLOSKEY: This is John Gregson. And so…

GRAYSON: So the significance…

J. MCCLOSKEY: So that's a case where we identified…we proposed a structure that hasn't been made before, so we have to make it or get someone else to make it. There are **<T: 15 min>** others who…I had friends in the synthesis community that made members of that family, and I could go to them and say, "Whoa, we got something really in your pocket right here. Look at this structure. Can you make this for us?" Or they'd say, "Well, you know, we made it ten years

ago, and it's in the refrigerator." I'd say, "Okay, let's roll." So anyway, that's just a sideline, telling you how those things worked.

GRAYSON: So this probably occupied the majority of your career, at least at Utah.

J. MCCLOSKEY: Well, you know, it did. This approach and what one did to…and, of course, the technology behind that, we spent a considerable amount of time on mainly how to sequence these oligonucleotides by CID, [collision-induced dissociation]. That wasn't our…the chemistry was known from work mainly by [Scott A.] McLuckey.

GRAYSON: Scott?

J. MCCLOSKEY: Scott McLuckey. But really nitty-gritty, when you put it into action and try and sequence these pieces coming from here that have modifications in them, that was…so it was pointed out to me that at the time I retired, my collection of rare nucleosides, many of these are…was unique, just plain unique. And there are very few people doing work like we were doing. So it wasn't…people weren't knocking on the door to get them, but they were going to be hard to reproduce. And so I made a lot of trouble to get samples of them separated out and labeled and gave them away to different friends of mine. Colleagues, I would say is a better word. Colleagues whom I knew who could make use of them, or agreed to offer to become the repository, so there's somebody who says, "Oh, I need some archaeosine. Where am I going to get it?" I can say, "Well, I'm retired. It doesn't come from me, but it comes from Professor So-and-So, who has a cache of these…"

GRAYSON: Yes. Well, it's good that all those…all that science was spread around to where it can be used by those people and by other investigators in the future, so…

J. MCCLOSKEY: Yes, it wasn't…that hasn't been an explosively popular thing, and I think the technology behind using it, like an LCMS, is sufficiently complex that not many biochemists or biologists or microbiologists can get into it, or want to get into it. So we had carved a path that was fairly unique, but ended up in not being heavily traveled. I mean, other people did pieces of it, and…but, you know, we showed them how to do it, especially the sequencing. And I had a colleague in my group who went back and forth to Belgium named Jef Rozenski […].

And he expanded the logic for the software and made this a do-it-yourself sort of program, where you could put the CID data in from an oligonucleotide and learn how to creep along the ends from both sides to get the sequence, not unlike the way people do it for proteins, only the rules are different. You have exceptions and this and that. So that worked well. Okay.

GRAYSON: So you've got a…it's kind of like J.J. Thompson when he said, you know, showed that positive rays could be used for chemical analysis, and everybody says, "Okay, that's great, but I don't want to do it, because it's…" you know, equipment at the time was too horrendous, so…

J. MCCLOSKEY: This is true. People look at like LCMS, even the ones who want…desperately want to get into protein measurements, proteomics, so to speak, and they look at it and say, "Wow, I've got to find a postdoc who knows how to do this, and that's all he's going to do, because it's not something I can tell a technician to just hook into it."

GRAYSON: Yes. Yes.

J. MCCLOSKEY: So many of these are similar in that respect. So there are a number of targets on here that we never got to, especially in the eukaryotes. There were many I wanted to get to over there, but they were less exciting, because the archaea was where the action was at, because so little was known when we began, and **<T: 20 min>** we then discovered this temperature dependence that was quite striking. And we also…there are organisms, by the way, they're mostly bacteria, that grow below zero centigrade. They'll grow at minus five centigrade. And so that forced us over to that branch to take a look at those and see if they really do look like bacteria—and the answer is yes—and then do exhibit [structural] changes one would expect based on what we had learned from high temperature organisms over here. And so that was what I was doing about the time I retired, was making comparisons like that.

GRAYSON: So the organization of the tree, the way its branches represent, like, from early prehistoric or pre-biological times, going…as you go up, you get into more…this is a time-wise evolutionary thing…

J. MCCLOSKEY: That's right. And so the question is, where is the root? That's always the question. Where is the root of the tree, and how long ago was it? And a cottage industry developed, which people were throwing rocks at the tree. It became, you know, something that you'd say, "Oh, I know an exception to this, an exception to that." And so forth. And so a lot of those concerns have quieted down lately. People believed in the tree, but they don't believe that it's perfect in every case. You may have an organism that isn't quite right here and isn't quite right there, but…so they don't know what to do with it. If they care. If they care. I was intrigued by the fact that this is so basic, this is such basic biology, evolution and what came to be, and so I was intrigued by it. Okay.

K. MCCLOSKEY: Here's a little thing that says, "Before 1977 and Dr. Carl Woese, the domain archaea didn't exist."

J. MCCLOSKEY: Is that from *Science*...

K. MCCLOSKEY: No, it's a kind of a student contest essay winner thing. It's talking about the advent of the phylogenetic tree, so…it was there, but it hadn't been discovered.

J. MCCLOSKEY: It hadn't…yes, that's right. It was always there, the archaea had always been there, but to make them, to put them into that context, was Woese's deal, and they're right there. And some are…some may…well, some are thermophiles, some are not. Some make methane. So in other words, all the bacteria in cows that crank out tons of methane.

GRAYSON: Yes. And other greenhouse gases.

J. MCCLOSKEY: It turns out…yes. It turns out those are in the tree here. All those organisms can be found in the tree. Okay. Let's see.

GRAYSON: Very good. Did you have anything else that you wanted to cover that…from…that we passed over yesterday?

J. MCCLOSKEY: Well, I was thinking when I was reading some of these other interviews that it's very hard to give credit to everybody. It's also kind of unfair. The minute you start going down, saying, well, the top people who worked on this were so-and-so and so-and-so, thereby leaving out somebody. , it could be that I would be guilty of false reasoning, or just plain everyday not a very…what am I trying to say?

Not a very polite thing to do. So I haven't done that, except I mentioned a few. And the other…the guiding person behind much of this [work] was Pam Crain, whom you've met before, and she retired at the time I did, because the grant was coming to its final close. But I recruited…she worked at Baylor College of Medicine when I was there, and worked partly with me, but mostly for Marjorie Horning. But she had a number of skills that I thought were extremely valuable, and so when I moved, I induced her to move with me, and so she stayed all those years, and many times, she's behind the scenes. So you'd see P.F. Crain as a name on a paper, but the sum total of those efforts, you know, a little bit here, a little bit there, whoa, pretty soon, you do that on <**T: 25 min**> fifty papers, and […], in the end, the contribution here [was] considerable.

So she…she's the exception to the rule that you're better off just not making lists of who did what.

GRAYSON: Yes. Well, I noticed…I did an analysis of your publication output, and it's kind of interesting in that I think her name appears on probably… most of the stuff that you've…a large amount of the stuff that you've published […].

And I had a count of like eighty-three papers that…I mean, of all the people you've collaborated with, she's the one with the most…you know, co-authors, she's the most, Pamela Crain.

J. MCCLOSKEY: Yes. I believe that has to be true.

GRAYSON: Now did she get a Ph.D. degree, or was she…

J. MCCLOSKEY: She did. She decided to go to graduate school. after she moved and became a biochemistry graduate student, and got a Ph.D. in biochemistry [from the University of Utah].

GRAYSON: […] So she started out as a lab tech at Baylor?

J. MCCLOSKEY: Yes, and was a chemist. She had a degree in chemistry. And…

GRAYSON: Then ended up getting her Ph.D. in biochemistry. Wow. That's pretty neat.

J. MCCLOSKEY: That's right. Yes. So she had an understanding of both the biochemistry behind many of the things we were dealing with here, as well as the measurements, she was very good at.

GRAYSON: Yes. That's something…an art that's still important, is being able to make the machine…the equipment do what it is you want it to do.

J. MCCLOSKEY: Yes, for sure.

GRAYSON: The next most…well, I don't know if we want to go to this particular point. Before I get into some of these personal interactions, I was…I know you had plenty of financial support. I was just wondering if you had good moral support in your local…like, the local environment you were in at Utah. Was…did people accept the fact that you were really kind of an oddball?

J. MCCLOSKEY: Yes. They did.

GRAYSON: You didn't get too much grief for the fact that you were…

J. MCCLOSKEY: No, no. That I wasn't working on drugs or something? I think it became evident to them, though, pretty fast, that I was…although I was primarily in a department of medicinal chemistry, I wasn't working on therapeutics in any fashion.

That was rare. Occasionally there would be a foray into something, but by and large, it didn't drive what we did at all. What drove it is what I'm describing here.

GRAYSON: Sure. Yes. I mean, you were a self-directed individual…

J. MCCLOSKEY: The biochemistry…

GRAYSON: …in the biochemistry business. Let's see. You had a lot of interactions outside of the organization. As a matter of fact, as you pointed out, most of your collaborations were with people outside of your immediate vicinity, you know, where you were…those all apparently worked pretty well. You had a lot of interactions with the Japanese.

J. MCCLOSKEY: Yes. That's right. More than one lab. It wasn't just Nishimura, but several [others as well].

GRAYSON: And that was all in this area of the RNA…transfer RNA…

J. MCCLOSKEY: Well, no. Some of it was and a lot of it wasn't. There were antibiotic…we got involved in antibiotic work with Kiyoshi Isono. I mentioned him yesterday […]. And some of that had nucleoside relationships, and some of it didn't, but we worked easily with each other. And he came and spent a little time with me, and I visited him several times.

GRAYSON: Was he in Tokyo as well?

J. MCCLOSKEY: Close by, very close by. So you would take a train, commuter train from Tokyo to get to his place. So he also retired, is retired.

GRAYSON: So you really weren't involved in the development of any products or equipment or…I mean, like developing chemical ionization or […] developing instrumentation or doing anything along those lines?

J. MCCLOSKEY: We tried to use it as best we could. We made changes in existing hardware and so forth, but many people do that. There's nothing truly novel about what we did. The closest thing probably was writing this suite of programs that let us sequence oligonucleotides by collision-induced dissociation, and even those ideas were not ours, but other people's. But putting them together to **<T: 30 min>** make it work…

GRAYSON: For the nucleosides.

J. MCCLOSKEY: Yes. Well, oligonucleotides sequence.

GRAYSON: Yes. The oligos. Yes. Sure. Okay. So yes, and we really covered a lot of this professional networking with peers inside and outside of your immediate environment. You had a lot of that, and a lot of collaborations that are very fruitful and very interesting. And so do you have any particular interest currently in any specific kind of work? Are you just in the retirement, pretty much?

J. MCCLOSKEY: I slid into deep retirement. [laughter] It's great. But I quit reviewing papers, I quit, you know, accepting invitations to do this and that. And it was just easier for me to close it down. Now the problem in doing that, however, turned out to be…I didn't realize how difficult it was about a year out to say, "Well, I'm living…my lab lives on grant money. Here's this grant. How do I partially close the faucet, so that on the last day it's empty?" You don't want to leave huge amounts of money there unspent. That's not tasteful. , but on the other hand, if you get out of whack and you overspend, that's embarrassing. You'd have to go find the money somewhere.

But we did it. We managed to just take it right down, and when I left, Pam was still working, and when I physically left Salt Lake City, was still working, and could clean up an

awful lot of stuff that we had there. And then we had, of course, to get rid of mass spectrometers.

GRAYSON: Right.

J. MCCLOSKEY: And you close a lab that's been active for many years, and you find all kinds of stuff in there to get rid of. , some of which no one wants or cares about.

GRAYSON: No one even remembers what it was there for.

J. MCCLOSKEY: And other things, you know, you call someone up and say, "Now, look, I've got this labeled reagent, so and so and so and so, and it's got one ^{15}N and two ^{18}O…"

GRAYSON: Oh, wow.

J. MCCLOSKEY: And they say, "Whoa. But I can't use it." [laughter] In other words, verifiably exotic and interesting, and we had a number of things like that. , but we managed to get rid of all of them.

GRAYSON: Yes. Yes. I can imagine over the time period, the accumulation of chemicals, and in particular, like you say, very exotic ones that could be valuable to someone, but whoever that person is is another story.

J. MCCLOSKEY: Yes. Yes. Of course, all these things that we got rid of and so forth had to pass hazardous waste.

GRAYSON: Oh, yes. Yes.

J. MCCLOSKEY: And that became another pain. And so forth.

GRAYSON: Yes. When I was at Wash U, they really got serious about these stockpiles of chemicals that all the individuals have. And, of course, Gross came from Nebraska, it was a ton of, you know, two milligrams of this and five grams of that and four milliliters of this compound, and whatever, these strange exotic things that somebody ordered to do a…you

know, a study in whatnot, and they'd left it in his lab decades earlier. But he brought all that stuff with him, so it all had to be inventoried and sorted out and put into the system and kept track of, and that was…

J. MCCLOSKEY: It's difficult.

GRAYSON: That's difficult. That's difficult. It's hard enough to do for a handful of common chemicals, but then when you have all these exotic and small quantity things, and some of these things are seriously hazardous.

J. MCCLOSKEY: Yes. It's difficult. And you're torn between why don't we just dump them, and doing the right thing.

GRAYSON: Well, I think it's all getting a little bit more…I don't know if you want to say stringent, but more controlled with regard to the handling of chemicals than it used to be, that's for sure.

J. MCCLOSKEY: Yes.

GRAYSON: So you are basically, like you say, you quit reviewing papers, you quit…

J. MCCLOSKEY: Well, my decision was—I made it consciously, and it turned out to have been an important one, because it…I made the decision at some point,—was to really kind of retire. Now a number of friends of mine would retire, and that meant that they came in to work two days a week, and then came in one day a week, and still had a little office over here, and there's some real merit in that. But when you leave, when you physically leave, you know, and sell everything you own, like your house and all that, close your **<T: 35 min>** lab forever, and get rid of all the mass spectrometers and samples, wow, that's a…really a shocking terminal thing. You're used to working a certain number of hours a day and a week, and all of a sudden you're gone. You've got other concerns about keeping things going in your life, and it was just, I thought, easier to just…sharp cutoff thing […].

My age was 71? […] Because I thought, "That's enough." Enough is enough. Yes.

GRAYSON: Was there any movement or interest in the department of trying to get someone to come in and take that…your shop over, and…

J. MCCLOSKEY: Yes, I think they thought about it, but decided not to pursue it. For one thing, my instruments were getting on in age, some of them, and so that wasn't so attractive to say I had a brand new lab and I have to go give it to him, so forth. And of course, this is the Department of Medicinal Chemistry, and you've got all kinds of other things going on in their scientific world, just all kinds of topics. And the same thing for my biochemistry…part of me was in the biochemistry department. And so on. And I was…even though I was doing something that was under the fence or through the fence biochemistry, this was pretty radically different from them.

GRAYSON: Yes.

J. MCCLOSKEY: But they always…and I appreciate the fact, they always enjoyed, I think, listening to me when I spoke about it in the department, about what I [was] doing […].

GRAYSON: Okay. Well, I mean, it's…it happens frequently. I know Klaus' shop shut down after he left MIT. I'm not sure what all the details of that were, but, you know, I was kind of surprised that they decided to close it, but I guess they decided they didn't want to stay in the mass spec game.

J. MCCLOSKEY: Yes. And, I mean, a place like MIT has such a reputation, and is so powerful in the world of science, that they would say, "Gosh, we can get people from, you know, a dozen fields. Why keep this one going?" And that was the problem, because Klaus had at least one person working with him who wanted to stay on, and it didn't work out. It was…

GRAYSON: Yes.

J. MCCLOSKEY: That was a problem.

GRAYSON: Well, I mean, these are decisions that schools have to make, and that, you know, involve major…

J. MCCLOSKEY: Yes. So I was kind of surprised that they didn't…you know, well, and I watch and I see this happening routinely, the person retires, I mean, drop dead retires, right? And you turn out the lights, and they don't have much interest in continuing it. And many times the professor has made their way in the world, if they have been successful, such that there may not be anybody who can step right in, and that sort of thing.

GRAYSON: Yep. I remember when I interviewed Al [Alfred O.C.] Nier, he was the kind of guy that actually he went into the lab every day, even on weekends, after he'd retired. And he said his wife commented to him, she says, "The only thing you retired from is your paycheck."

J. MCCLOSKEY: Yes. Yes. It's…this is very true. But if you leave, if you retire and leave the city…

GRAYSON: That's a different story.

J. MCCLOSKEY: …it's a different story, and you have a hard way of getting partly retired in a case like that. It seemed difficult. It was easier for me to say, "This is it." And you write all kinds of grant reports and so forth. But…

GRAYSON: Yes. So you're basically kind of a gentleman farmer right now, **<T: 40 min>** I guess, or just a gentleman countryman.

J. MCCLOSKEY: Yes. Taking care of…

GRAYSON: A couple of odd animals, and…

J. MCCLOSKEY: Strange animals. And so forth.

K. MCCLOSKEY: Picking up grandchildren and …

GRAYSON: Oh, yes. Well, that's true. Grandchildren are…

J. MCCLOSKEY: Ferrying grandchildren around.

GRAYSON: So my sense is that there is a dynamic going on worldwide in science in that American science may be overtaken by say the Chinese or, I'm not sure, the Japanese have been at it for quite some time, but the quote/unquote developing countries are becoming much more involved in science…

J. MCCLOSKEY: Sure.

GRAYSON: I mean, over the span of your career, I think you've seen a lot of American science and a lot of science in both Europe and Japan. I was wondering how you see those scientific endeavors changing, evolving, over the life…over the span of your scientific career. Has it…

J. MCCLOSKEY: Of course, part of what one sees in this is related to going to the ASMS meetings, and you say, "Gosh, it keeps getting bigger." And this is a sign, of course, of good health. And it could be driven by A, B, or C, but it's certainly not going to die out, you know what I mean? Because no interest and so forth. So that has been a comfort to me, to watch the society of which I was once closely related in what I was doing continue to just grow explosively in some directions. And at the same time, to see that it is indeed true that the United States no longer can claim a unique or semi-unique…make a semi-unique claim to ideas and publications. Boy, there's some terrific stuff going on in Europe.

And I don't…China's hard to judge, but it's coming along nicely outside the United States, and there doesn't seem to be any real rankle over that. You know what I mean?

GRAYSON: I think the scientific community as a whole tends to be not terribly…I don't know what you want to call it, nationalistic. You know…

J. MCCLOSKEY: Yes. No, no, no.

GRAYSON: It's more of an international thing.

J. MCCLOSKEY: That's right. There's people who come suspicious when a totally new unit comes on the scene, right? All Chinese, or a Japanese group that gets a lot of money and so forth, is more skeptical.

GRAYSON: Mike Gross just got back from a trip to Brazil, where he was invited to give a talk, and he says he was just amazed at, you know, how the mass spec is being used in Brazil, and how much energy and excitement there is in that country, as it's burgeoning with people who are doing good work there. And…

J. MCCLOSKEY: That's probably I think an example of a case where that is true, but nobody knows it.

GRAYSON: Yes. Yes. [laughter]

J. MCCLOSKEY: Their physical proximity, their geographic proximity to everything else that's going on, I think, hinders them to a considerable extent.

GRAYSON: Sort of like they're in the shadow of the United States.

J. MCCLOSKEY: Yes. And then they have good problems to work on, and I certainly think they have money to buy equipment and so forth. Wow.

K. MCCLOSKEY: Getting to the US to attend meetings and present papers.

J. MCCLOSKEY: Yes. Yes. It's difficult for them.

GRAYSON: So one of the things I found a little bit disturbing when I was visiting with Keith [R.] Jennings in the U.K. was that they're actually shutting down some chemistry departments in the universities there.

J. MCCLOSKEY: Yes. That's right. I mean, all the way down.

GRAYSON: Yes. And I guess that apparently relates to the fact that they don't have enough students taking chemistry. Is that something that has any potential probability to happen in this country, or…

J. MCCLOSKEY: I don't think so. One…the problem…we have one problem that we share with them, and that is that they don't have enough money. So some of these shutdowns are not just because they don't have jobs for organic chemists coming from thus and such. , but to educate them is so expensive, and then you have all the machinery that goes with it. Professors have to publish papers to get promoted and do all that, and in the end, **<T: 45 min>** that superstructure of moving the whole thing forward is so expensive. And these days, especially in science, you know, it's not the same in many other fields, maybe even almost most other fields.

GRAYSON: The problem is once that infrastructure is taken apart, then it's not likely that…it's even more difficult to rebuild, and not likely that that'll happen, if it…

J. MCCLOSKEY: Well, that's what makes them…they're probably quite sad about that fact. They're seeing it…they're not putting it to sleep for a while. They're killing the animal, right?

GRAYSON: Yes. Yes.

J. MCCLOSKEY: And wow. And some of these places, I don't…I've never seen a list of all of them, but some of them have, you know, quite historic roles they played.

GRAYSON: Right. It's, kind of…well, it is sad. Like you say, they have historic roles in the development of the science, and they're being shut down.

J. MCCLOSKEY: Yes. Well, we're heading for more trouble in that respect, I think. , so we'll see what happens. , but I'm not part of the group that says US is out of it. , we're no longer anything. But it's clear that we have slipped, and part of it is real slippage, and part of it is that other people are getting ahead. You know, it's a relative, sort of, thing.

GRAYSON: One of the things that we do here, at least from my experience at Washington University, is we're actively recruiting people from other countries to come to our schools.

J. MCCLOSKEY: Yes. Yes.

GRAYSON: I know at Washington U, there's a gentleman on the faculty there who probably is…just got back from China. He goes to China every year to look for…you know, drum up support for graduate students to come to Washington University. Now I'm not sure how…if that's done in other departments, chemistry departments around the country, but…

J. MCCLOSKEY: A few, I think, but not many.

GRAYSON: And I mean, it's one way of keeping this system going. I think it's apparent that not a lot of typical Americans are all that excited about going into chemistry. There's not a lot of

desire. , so they're actually, you know, padding the students by bringing in, you know, people from outside the country who are interested in chemistry. So we…I think Mike Gross' group had…at least half of his graduate students were Chinese, you know. And that's…you know, we had…we were actually lucky to have a number that were just regular American, white Anglo-Saxon Protestant, WASP types.

J. MCCLOSKEY: A few WASPs in there.

GRAYSON: Yes.

J. MCCLOSKEY: Well, there used to be, in the world of pharmaceutical sciences, talk about sending emissaries to one or two universities where people knew somebody, and to try and work that into a way to get promising students. , but I never saw it work out very well. Around us, it was tried once or twice, and some students came, but there was always a fear on the American side that if you open this pipeline and…you have to shut it, because things are, you know, not what they used to be, and so forth. So it never really got going in our case. Of course, many institutions are so well-known that they capture students by virtue of…

GRAYSON: Yes. There was… I guess they maybe get a reputation back in the home country. I…when I was at University of Missouri Rolla, which is really the old Missouri School of Mines, they had a huge enrollment of Indian students doing engineering, you know, getting engineering degrees there, and a real significant fraction, you know, of the student body was from India, so it…

J. MCCLOSKEY: That was a case where there was truly a pipeline that has been opened.

GRAYSON: Yes. Yes. It was very interesting and surprising when I first got there to find out how many from India had come there.

So let's…I want to save a couple of these for a little bit later on in the…when we do the little videotape segment.

J. MCCLOSKEY: Oh.

GRAYSON: So did you just kind of <**T: 50 min**> segue into this business with biological applications and the oligos, was that just something that you fell into, pretty much? Or you didn't have any…did you have a conscious desire to do this? Or you just kind of…

J. MCCLOSKEY: Yes. Yes. I did have a conscious desire. It turns out that originally when I was a graduate student, it was recognized that the polarity problem was very important, and there were classes of compounds of biological importance that could not be worked on. , and that to me is always intriguing. And so once I found that you would overcome some of the real difficulties to work on those things, and with a little ingenuity you could create methodology that would be truly useful and so forth, then that was its own reward, I think.

GRAYSON: So you were challenged by the fact that this was a hard thing to do?

J. MCCLOSKEY: Yes. Yes. That's largely true. And then of course I became infatuated with the issue about high temperature organisms and their relationships to other organisms and whether modifications in the RNA were being used to stabilize things. And the answer turned out to be yes, and so that was a big positive push.

GRAYSON: Okay. And so once you were onto that, you…did fast-atom bombardment offer a significant move forward in your ability to look at these different…

J. MCCLOSKEY: You know, it did for a while, but it became evident that chromatography was still needed, because of the mixture problem. So it overcame a lot of the polarity problems, and you could run mixtures of oligos, and you could probably mass select certain ones for this and that. , but in the end I recognized that it was very hard to beat chromatography-mass spectrometry, as it has fundamental properties that just…you know, and you can, of course, intermarry these things. You can do MSMS and then chromatography at the same time, and that's a winning strategy.

GRAYSON: So what do you think the impact of your work has been on the field of biology as a whole?

J. MCCLOSKEY: Oh, I don't think it's been that great. I don't think it's been that great, because we work on just a corner of these things, and, of course, there are other whole giant areas of the endeavor relating to transcription and translation and the genetic code and how it's used. And now, of course, you have issues of very fast, cheap sequencing of genomes, and that is revolutionizing the whole world.

And so…but we were good enough at it when I quit that we could do things other people couldn't do, and we answered some questions that were very difficult otherwise to answer. But I never saw that the people hitched onto that very much. The bedfellows were too unequal.

GRAYSON: Yes. I thought…I don't know if this is…I put this together. This is a graph that shows your output in terms of papers per year.

J. MCCLOSKEY: Mine?

GRAYSON: Yours. So I thought it was kind of interesting to see the highs and lows.

J. MCCLOSKEY: Yes. Really moved around there, didn't it? […] So there probably would be clear reasons one could dope out for this max and this min.

[…] Still, you have a shape that looks like this. […] And 2005, 2008, toward 2010. Well, it's clear that the productivity angle was going down by 2000 or so.

GRAYSON: So then you're looking at like an average of ten papers a year, is what I am seeing, for a period of about twenty-some-odd-plus years.

J. MCCLOSKEY: Yes. So that's a pretty good stream.

GRAYSON: That's a lot of work.

J. MCCLOSKEY: **<T: 55 min>** Oh, yes. It's a lot of work, and you don't want to think about what it cost. In all honesty, people don't realize in the end the cost of doing these…

GRAYSON: A couple of Ph.D.'s there, and, you know…so I'll you, if you let me have this sheet, I'll give you that sheet. [laughter]

So according to what I was able to find out when I looked through your publication record, you've got…Al Burlingame is a fellow with whom you had…had the next most number of papers. Does that seem right to you?

J. MCCLOSKEY: No, it isn't right.

GRAYSON: Okay. Then something must be wrong in my analysis.

J. MCCLOSKEY: Not papers. I mean, we…he was an editor and I was an editor, and we'd get papers in the books that way, but that doesn't that doesn't mean collaboration.

GRAYSON: Okay.

J. MCCLOSKEY: There, the…the retrieval of information is not all…

GRAYSON: Incorrect.

J. MCCLOSKEY: Yes.

GRAYSON: What about that *Methods in Enzymology* book?[19] When did that…

J. MCCLOSKEY: Wow, that was a huge endeavor.

GRAYSON: Oh, yes. Nine hundred pages or whatever, 700.

J. MCCLOSKEY: Yes, because I had no co-editor. I did the whole thing, and I decided it would be more enjoyable for me to design it and do it and everything. And of course, as you…as anybody could figure out, it was more work than one knew. People would promise this, and it never happened. [laughter] So that was…yes, let's see, that was 1990. So that may be…

GRAYSON: That may be why you…why you didn't do so much…get so much done that year. So this was one of these deals where you were the editor, and you went to ask people for contributions on different subjects?

J. MCCLOSKEY: Yes. So I designed the book. I designed the chapters and what was going to be in them, my own ideas. I had some advice from different people, but mostly it was what I

[19] James A. McCloskey (ed.), *Methods in Enzymology. Vol. 193: Mass spectrometry* (New York: Academic Press, 1990).

thought was the way to go. And some people came back later and sniped a little bit, "What is this supposed to be? Is this a textbook or isn't it?" And so on and so on.

GRAYSON: Yes. No matter what you do, somebody's going to say that wasn't what I…

J. MCCLOSKEY: […] But I don't know how many copies they sold, but a lot, it turns out.

GRAYSON: Well, I mean, it also seems to me a significant honor to have been requested to…

J. MCCLOSKEY: To do it.

GRAYSON: …to do it. In addition to a lot of work.

J. MCCLOSKEY: Yes. They came to me and asked me. I wasn't the instigator of that. , so I guess they had their own way of determining whether I had the skills needed to do that.

GRAYSON: So what's with the enzymology? I mean, that's…did you…

J. MCCLOSKEY: Oh, that's a series. That's all. […] It's a series. It's well-known, and has whole sets of it. Had nothing to do with enzymology. […] It became a methods thing where you could do really simple biological…

GRAYSON: Yes. When I looked on the web there's like one hundred ninety-three volumes or something of this thing. And it's just like an encyclopedia. A superencyclopedia.

J. MCCLOSKEY: And now it's gotten bigger, and it's very difficult to deal with it, because it is…volume two hundred forty-three. But they'll get to a certain point and there'll be a field that they will define, and then they'll add sub-volumes that run off on another plane. And trying to find out where that paper is and how to get it and so forth, it's a problem.

GRAYSON: That would be a problem. Yes. So who's…or there's some organization that's behind this thing, keeping it alive?

J. MCCLOSKEY: Academic Press.

GRAYSON: Oh, okay. It's their thing?

K. MCCLOSKEY: It's a serial publication.

J. MCCLOSKEY: Yes. But, I mean, they make money from the whole series.

GRAYSON: Sure. Oh, yes. I'm sure they do.

J. MCCLOSKEY: It's a for-profit organization. , and they have their own boards of whatever telling them what…where to go and where…and so forth.

GRAYSON: So I'd just like to work through a couple of names here that…where I've got a lot of what look like collaborations. Obviously Al was not one, but then I've got Hashizume…Takeshi Hashizume?

J. MCCLOSKEY: Yes. He was a professor in Japan whom I met **<T: 60 min>** while he was still there, and he retired from the Japanese system—boy, they have a rigorous deal—and came to work with me. So he spent the last decade of his life, I guess, in my lab.

GRAYSON: So this is…in their system there, are you, like, pushed out the door at a certain period in your…

J. MCCLOSKEY: Yes. Yes. It's age-related. They take great pride in being able to find something after that, where they can point to the fact that they have now something to do. You know what I'm saying? There's that element of it. Now in his case, he was, of course, delighted that…I don't know how old he was. I can find out. But he was delighted to have a paid position. He worked on my science. In other words, they weren't his ideas. And that's, of course, why I was able to support him.

GRAYSON: Yes. And he actually emigrated, or did he just go come on a green card, or…but he was at…

J. MCCLOSKEY: No. It was a green card story, and his wife came with him, and he contracted, initially, lung cancer. […] He smoked lifelong. Lung cancer while he was here, died here…no, sorry, he died in Salt Lake City. […] And that was a painful episode.

GRAYSON: […] So he was a serious collaborator. I've got like twenty-nine papers that you guys published together.

J. MCCLOSKEY: Yes. He had synthetic talents.

GRAYSON: Oh, okay.

J. MCCLOSKEY: So that is a whole area that can support somebody doing structure work, right? And he had worked with a class of nucleosides called cytokinins.

GRAYSON: Cyto…

J. MCCLOSKEY: Kinins […]. Many of which are nucleosides. And he had expertise in that, and that's how we got to know each other. , so translating that over to my work was not difficult for him, I don't think.

GRAYSON: So he came to you. Did you have any interactions prior to the time that he came to work for you?

J. MCCLOSKEY: Only when he…we collaborated on some things while he was in Japan. and initially with no thought of him retiring. And then all of a sudden I realized, whoa, he's on it. And when the date comes, my gosh, it's really something to see. I was in Susumu Nishimura's lab visiting on the last day of his work there.

GRAYSON: Oh, really?

J. MCCLOSKEY: Yes. And that is just something to see. I mean, there's a day for this, right? The last day is serious stuff. And they have a lab party, and you've got the staff members in there cleaning off the shelves, and he's sitting there writing, I remember, a review for *Nature* on something, and people were out there, you know, it's, like, a big party for him and so on. , and

then it was all over. I mean, he was out of that building. He had no…when they say retire, […] they mean it. And he of course immediately found several positions after that one was a pharmaceutical company, and another university, and so forth.

GRAYSON: So is this, like, sixty-five or sixty or is there some kind of typical…

J. MCCLOSKEY: Oh, yes. I used to know what it was exactly. I think it's more like sixty.

GRAYSON: Really? That's kind of young.

J. MCCLOSKEY: Yes. But I'm not sure. But it's a fixed date. It's pretty much uniform. In universities, it is slightly different than industrial.

GRAYSON: Yes. But when the time comes, then that's it?

J. MCCLOSKEY: The time comes. And they view it as a way to generate jobs. I mean, they're very frank about it. This is the way the young people wait and wait for the big man to go, because they can move up. They all get to move…

GRAYSON: The whole thing ratchets… [laughter]

J. MCCLOSKEY: Yes. Yes. There's a ratchet of sorts. It goes on, and…yes. But it's something to watch this happen. And that happened to Isono while we were collaborating, and he shut down his operation in <**T: 65 min**> Tokyo and went to another university for a few years. But…

GRAYSON: So they make it into, quote, a kind of an honorific happy occasion, but on the other hand, it's also an out the door…

J. MCCLOSKEY: Yes. Absolutely.

GRAYSON: Clean out.

J. MCCLOSKEY: Absolutely. Yes. And it's viewed as a real badge of honor to find something, and it's widely displayed at the time that they retire, that this is what…I have another job and I'm going over here to do this and do that.

GRAYSON: You can push me out of here, but I got a place to go.

J. MCCLOSKEY: That's right. Absolutely. And of course, the better known they are as a scientist, the easier it is for them to make those arrangements. But the, you know, severity of the cutoff is notable when you're up close seeing it.

GRAYSON: I noticed one of your other frequent collaborators or someone with whom you've published a lot of papers is this fellow [Steven C.] Pomerantz, Steve Pomerantz.

J. MCCLOSKEY: Pomerantz. Yes. He was…in the end, he was a graduate student. He started out as a technician. And so he was just my lab member.

GRAYSON: Was this at Utah primarily?

J. MCCLOSKEY: Yes. Yes. University of Utah. And he decided to get a Ph.D. in medicinal chemistry, and so he became a graduate student. And then he finished that and left for an industrial position. But for years before he became a student, he was a lab member doing all kinds of things, so…

GRAYSON: Okay. So he was…and so he probably had a pretty good feel for the equipment, and…

J. MCCLOSKEY: Oh, absolutely. He could write software, write programs, and things…

GRAYSON: Okay.

J. MCCLOSKEY: He was a good guy to have, and…

GRAYSON: Yes. Made serious contributions to the lab.

J. MCCLOSKEY: Yes. Absolutely he did. Yes.

GRAYSON: I think we've mentioned Charles Edmonds before.

J. MCCLOSKEY: Yes.

GRAYSON: Yes. So he was another frequent collaborator, 21 co-authored publications, it looks like I got here. [laughter]

J. MCCLOSKEY: You're counting…Yes, that's right, and he came as a postdoc, and he left [ultimately] to go to NIH, I guess. He's now [an administrator for NIGMS, actually].

For mass spectrometry related things. So he worked very extensively in the early days when we had a thermospray instrument, and it was an instrument that had been owned by Marvin Vestal. We had a joint grant, and the understanding was that…the grant was that he was going to build it and make it work, and then give it to us, and then we would do things with it. And that in the end is what happened, and the machine was shipped over to us, lock, stock, and barrel.

GRAYSON: This is something that Marvin did it in Houston, put this instrument together?

J. MCCLOSKEY: Yes. Yes.

GRAYSON: Yes. I vaguely remember something about that in his oral history interview, that he had had this…there was something to do with equipment, I guess, that needed to be…

J. MCCLOSKEY: Yes. Transferred out of ownership from University of Houston, I guess it was, over to us. And of course, having him close by was helpful, because that was an instrument that required lots of…

GRAYSON: Yes. So how did thermospray work for you?

J. MCCLOSKEY: It worked very well. It worked very well. And we got a number of very good research papers out of that.

GRAYSON: Yes. Because it looked like that was going to be the ionization method of choice for a whole lot of things. But…

J. MCCLOSKEY: Yes. So it worked fine. I mean, it had its own faults and so forth, and even it has polarity limits. It wasn't until you got into desorption ionization that the polarity limits began to fade. Right? And FAB and electrospray, all of a sudden you're in a new world.

But with thermospray, it worked well enough that you could do pretty reasonable LCMS. Had all of the attendant advantages.

GRAYSON: So that would have been one of the earliest thermospray machines that was available, right?

J. MCCLOSKEY: Yes.

GRAYSON: And so you were kind of on the cutting edge in the use of that equipment.

J. MCCLOSKEY: Yes. It can be said, although **<T: 70 min>** once again, we weren't a lab that had broad interests, and we made it work to suit what we were doing. And also, the instrument that we got was not a commercial instrument. , it was pieces put together. , and later on we got a Vestec, as I recall. That's much better, because…

GRAYSON: Yes. Yes. Marvin's an interesting fellow.

J. MCCLOSKEY: That's an understatement. [laughter]

GRAYSON: Understatement.

J. MCCLOSKEY: He's also very talented.

GRAYSON: Oh, yes. Yes.

J. MCCLOSKEY: And that was recognized at the time he was at the University of Utah, and became a graduate student of Jean Futrell's, and that was an interesting time.

GRAYSON: It looks like there's an Indian name here, Satinder [K. Sethi]?

J. MCCLOSKEY: Yes. He was a postdoc. He originally had been a graduate student of Don [Donald F.] Hunt's, and so he came as a postdoc and worked for several years. I can't remember what the time frames were. , but in the end then he left to go into industry, and the last time I saw was moving up very fast. It was a thing that all of a sudden he found his niche. , although scientifically he was very good, as a chemist, so there's no problem there.

GRAYSON: Yes. Leemans, R.A.J.M. Leemans. .

J. MCCLOSKEY: F.A.J.M. Yes. Frank Leemans was a…

GRAYSON: Frank?

J. MCCLOSKEY: Frank. Yes. Was a visitor, I guess you'd say, in the Baylor laboratories, and was sort of a visiting scientist person. And he did not have a Ph.D., but he was very…he came from a lab in the Netherlands—Belgium?—the Netherlands that was well-known for instrumentation and chromatography. And so he fit in like a glove, and…

GRAYSON: […] You know, with all those initials, I figured he must have been from Europe somewhere. You know, it's not a common…

J. MCCLOSKEY: No, no. F. A. J. M. Leemans. Wow, that was…those were early days.

GRAYSON: Yes. So this was back in Baylor?

J. MCCLOSKEY: Yes.

GRAYSON: I've got one or two other guys here that were pretty productive with you. Prochaska ?

J. MCCLOSKEY: Oh, that's an interesting story, and I'll tell you what I know about it, but it maybe ought to be forgotten about, and that was that recently…oh, you sent me a list of retrievals from SciFinder with my name. And there are maybe fourteen or fifteen papers of Prochaska. Prochaska is nobody that I know or ever heard of, ever […].

I spent some time […] trying to find this person, and my final conclusion was that he…this was a deal concocted by Frank Leemans, and that he found a way while in the Netherlands to take mass spectra from here and there, mostly ours, I guess, from collections. I mean, we had quite a few. And make papers for this Archives of Mass Spectrometry thing, which was a McLafferty thing that existed just for so long.[20]

GRAYSON: Mass Spectra Database…

J. MCCLOSKEY: Yes, a database type thing. And these papers all came into existence in…it was a continuous thing. But that they had…I was the senior author, I guess, but I had no knowledge of them till you sent me that list. I never heard of this person [and didn't authorize it].

So in the end, I think it was a scam of sorts to patent a publication list. without coming to me. It is…

GRAYSON: Yes.

J. MCCLOSKEY: …things, strip them off and list them as the paper. Leemans was the other author, and…

GRAYSON: So in other words, they were both always on, the two of them were always <**T: 75 min**> on the same paper?

J. MCCLOSKEY: Yes.

[20] Wiley Registry of Mass Spectral Data. Available at: http://onlinelibrary.wiley.com/book/10.1002/9780470175217 (accessed on 21 January 2014).

GRAYSON: Huh. That is strange.

J. MCCLOSKEY: Yes, it is strange, and I came one inch from calling him. I think…because probably I could find him. But then I thought, well, what…since I've already concluded that it's a fraudulent publication with my name on it, what good does it do?

GRAYSON: Yes.

J. MCCLOSKEY: So I just gave it…I've got other worries […].

I taught a series of short courses at meetings based on notes that I created for my course, and I never did anything with those notes, nor did the course…it had a finite lifetime. And did not become like a cottage industry of…

GRAYSON: Yes. Well, that's something that people can do quite a bit of and actually earn a living at in certain areas, and, you know, so that's a…

J. MCCLOSKEY: Yes, I just wasn't interested in that. But I was interested in the fact that at one point it seemed to me that biochemists—this was in the seventies, I guess—were so unknowledgeable about mass spectrometry that it would go a long way to get about fifty of them or a hundred of them in a room and tell them about it. Have them work problems and so forth. So that was fun, and I thought it was useful.

GRAYSON: Yes. It's unfortunate that more people aren't willing to get involved in…I mean, from other disciplines. I think now, today in the biological community mass spec is pretty well known as a tool that's got a lot of uses, but at the time you were doing these courses, they probably, you know…

J. MCCLOSKEY: It was up and coming. They've heard of it.

GRAYSON: Yes. But it wasn't useful…

J. MCCLOSKEY: And that's the basis on which I think I sold the American Society for

Biochemistry and Microbio…is that it? Biochemistry…gosh, I've thrown all that stuff out. And those were successful. It may have had a separate parallel lifetime in Japan.

GRAYSON: Oh, yes. Sure.

J. MCCLOSKEY: See, that I didn't even know about.

GRAYSON: That you wouldn't know about. [laughter]

J. MCCLOSKEY: I only found out when I saw this book, [that I was asked to review] and [it] was packed with stuff that's mine.

GRAYSON: It's just right out of…your own stuff got back to you.

J. MCCLOSKEY: Yes. **<T: 80 min>**

GRAYSON: […] David [L.] Smith. I know there's a bunch of Smiths in the business, but that's not the one that's related to the Smith up in University of Washington labs? There's a Smith up there that does a lot of proteomics stuff, but…this is Richard [D.] Smith I'm…

J. MCCLOSKEY: Oh, that's Dick.

GRAYSON: Dick Smith. Yes.

J. MCCLOSKEY: Dick Smith who does instrumentation and stuff like that.

GRAYSON: Okay. But this is a guy that worked with you, David.

J. MCCLOSKEY: This is a guy that…David worked with me. And came in as a postdoc. He had worked for Jean Futrell, and stayed a few years, and moved into the faculty ranks. In other words, visiting assistant professor or something like that. Adjunct. Adjunct ranks. And he became an adjunct faculty member, and…

GRAYSON: This was at…

J. MCCLOSKEY: At Utah. Yes. And then he left and went to…I thought…

[…] He had an eye […] grant, that came up through his wife, and he worked on stuff. He was a very physical chemistry guy, though. He wasn't a biological…

GRAYSON: Yes.

J. MCCLOSKEY: But had worked with Jean Futrell, and had a number of talents as a result of that.

GRAYSON: Ed [Edward] White [V]. I remember…I know Ed personally. He was…was he a graduate student with you, or…

J. MCCLOSKEY: No, he was a postdoc.

GRAYSON: Postdoc. Okay. So…

J. MCCLOSKEY: The fifth.

GRAYSON: The fifth. Yes.

J. MCCLOSKEY: […] Leading to a whole raft of…as you could tell by my corrections. Those are real corrections. I think they have to stand. That's not a letter of his name, and it's treated differently with regard to having no period and a common after it, as in junior. And his son is the sixth.

GRAYSON: Oh, God. [laughter] So what did the first Ed White do that was so important that they're all the other Ed Whites are named after him?

J. MCCLOSKEY: Dynasty. And so I don't know where all that went. His son, in fact, worked in Salt Lake City for…

K. MCCLOSKEY: I think he's still there, for Overstock.com.

J. MCCLOSKEY: Overstock. Yes.

GRAYSON: […] So how long did you have…the postdocs' normal tenure in your shop? A couple of years standard, or…

J. MCCLOSKEY: […] Rarely a year, but sometimes a year, because they then wanted to go to a job, permanent job, somewhere. And some of them got comfortable to the extent that they were getting things done, they felt like, and I agreed with the notion that they were contributing, and so they'd stay for two or three years. There were a couple of them were longer than that, and it wasn't that…they became special people then. They weren't just a postdoc who came in and left, and they…

GRAYSON: Yes. That seems to be in a lot of the areas today a common problem. You know, people who are [rustling] having postdoctoral positions extended for a long time.

J. MCCLOSKEY: [Yes. Yes].

[So post docs of mine]… Dave Smith. Joachim [G.] Liehr was a postdoc from Germany. Chad [C.] Nelson was a graduate student who now runs the mass spectrometry **<T: 85 min>** laboratory at the University of Utah, so-called. And Karl [H.] Schram, if you know Karl. Was a graduate student [of Leroy Townsend's at Utah and my postdoc], and ended up finally at Arizona, right? Arizona State? ? Arizona, I think it was. And we didn't have too many interactions after he left, but he was a hardcore nucleoside synthesis person.

GRAYSON: Hardcore nucleoside synthesis?

J. MCCLOSKEY: Yes. So he could make all kinds of things, and that was very helpful. And he got interested in stable isotopes, and so we had methods to get O18 into things and so forth that was useful. And then Jeffrey [A.] Kowalak is another very special case. You know him, yes? You've met him?

GRAYSON: Kowalak?

J. MCCLOSKEY: Yes. Maybe not. Maybe you never met him.

GRAYSON: That name's not familiar to me.

J. MCCLOSKEY: Well, anyway, he was a graduate student. He was from Wyoming and got a Ph.D. under me in biochemistry. His choice was biochemistry, not medicinal chemistry. So his was a Ph.D. in biochemistry. , and he was a go-get-'em…go-get-'em person […].

GRAYSON: […] Well, I've kind of gone down through people you have at least ten, a dozen publications…

J. MCCLOSKEY: No, that's a good list. Is this the same list…

GRAYSON: […] I've got some names on here that I don't understand. Mike Gross is on there. You didn't do too many collaborations with Mike, did you?

J. MCCLOSKEY: No. We had a couple of papers together.

GRAYSON: Yes. Nothing significant?

J. MCCLOSKEY: FAB of nucleosides.[21]

GRAYSON: And John [B.] Fenn, I think, is on there, but I don't know what that was about.

J. MCCLOSKEY: We never published a paper together. I don't know how that happened.

GRAYSON: I'm not sure how that came about. Maybe that list is not…I don't have it on this list, so maybe my list has been refined from when I created that one. Let's see.

[21] Frank W. Crow, Kenneth B. Tomer, Michael L. Gross, James A. McCloskey, and Donald E. Bergstrom, "Fast Atom Bombardment Combined with Tandem Mass Spectrometry for the Determination of Nucleosides," *Analytical Biochemistry* 139(1) (1984): 243-62.

J. MCCLOSKEY: Some of these people, like [Masakazu] Uramoto, belonged to one of the Japanese labs, so he was not a direct collaborator in the sense that he worked for me. He worked for someone else. And [Gareth A.] Brenton…I do not know who that is.

[…] Ron [Ronald D.] Macfarlane. Yes. We did publish a paper together.[22] We did. That is correct. We both worked on the [same] structure problem, not knowing the other one was working on it.

GRAYSON: Not what?

J. MCCLOSKEY: Not knowing the other of us was working on it. We did relatively little, but it was quite important. What he did and what I did was quite important. , and we came up with the same answer.

GRAYSON: No way.

J. MCCLOSKEY: And he told me later, "I was sure…" he worked usually with californium. […] He says, "I sure was happy to see your results, because I wasn't sure about mine."

GRAYSON: Yes.

J. MCCLOSKEY: And it was the same answer, so we both published a *JACS* paper.

GRAYSON: There you go. [laughter]

J. MCCLOSKEY: […] Dick Smith, [R. Thomas] Solsten. And [Kenneth B.] Tomer, it may have been a paper I published with Mike that had…the Tomer […] <**T: 90 min**>.[23] [John R.] Yates and Hsu, Fong-Fu Hsu.

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[22] H. Kasai, K. Nakanishi, R.D. Macfarlane, D.F. Torgerson, Z. Ohashi, J.A. McCloskey, H.J. Gross, and S. Nishimura, "The Structure of Q* Nucleoside Isolated from Rabbit Liver Transfer Ribonucleic Acid," *Journal of the American Chemical Society* 98(16) (1976): 5044-6.

[23] Frank W. Crow, Kenneth B. Tomer, Michael L. Gross, James A. McCloskey, and Donald E. Bergstrom, "Fast Atom Bombardment Combined with Tandem Mass Spectrometry for the Determination of Nucleosides," *Analytical Biochemistry* 139(1) (1984): 243-62.

GRAYSON: You said he was a postdoc for you, or…

J. MCCLOSKEY: […] He was a graduate student. , yes.

GRAYSON: Graduate student. Okay. So I guess he…I know he was trying to get on at Wash U at one time, which he obviously did, but I guess I…did he go there?

J. MCCLOSKEY: He was working with a thermospray business, trying to make it work, and we had the machine that we inherited from Marvin.

Ian Jardine? No, I've never published anything with him.

GRAYSON: Okay. My apologies for screwing up the list. I don't…

J. MCCLOSKEY: I wish I could get on some papers with some of these guys. [laughter]

GRAYSON: Some of them are good company.

[…] I think we talked about the *Methods in Enzymology*. That must have been a heck of a project, and obviously it made an impact on your publication.

J. MCCLOSKEY: It did, and it took a…well, you've seen it? Have you seen the book?

GRAYSON: No, I haven't.

J. MCCLOSKEY: [Here's a copy]. It really…wow, that was a…you're right. That was an undertaking.

GRAYSON: Yes. When you sign up for these things, you don't realize until after the fact that you've taken a tiger by the tail and…

J. MCCLOSKEY: What are you doing… I was never worried about doing it wrong. It was only to find out how much work it was to get it aligned.

[…] The list of people who wrote chapters is, I think, pretty nice, really. I didn't even know all those people, but they were recommended to me as somebody who worked on…on glycans or something, you know, that I had no interest in, but we needed a chapter. The topic was one that should be covered. And so…

GRAYSON: Wow. Yes. I recognize a lot of the names in here.

J. MCCLOSKEY: Oh, yes.

GRAYSON: Interesting. So this is the kind of thing that people in the biological community would tend to turn towards to get a sense of what's going on in mass spectrometry, what it can do, what they need to do if they want to…

J. MCCLOSKEY: Yes. I think it's a big seller for libraries, because it covers so many topics.

GRAYSON: Yes. Deuterium exchange, chemical derivatives. Did you write any of these chapters yourself?

J. MCCLOSKEY: Yes, maybe three or four.

GRAYSON: Some because nobody else would…oh, here's one by James A. McCloskey.

J. MCCLOSKEY: That's me.

GRAYSON: Deuterium exchange.[24]

J. MCCLOSKEY: Yep. Deuterium exchange, because we got good at that, and we knew a lot about it, and I had done a lot of work while I was a graduate student on that.

[24] James A. McCloskey, "Introduction of Deuterium by Exchange for Measurement by Mass Spectrometry," in James A. McCloskey (ed.), *Methods in Enzymology, Volume 193: Mass Spectrometry* (New York: Academic Press, 1990): 329-38.

GRAYSON: So what was the use… what did you use deuterium exchange for?

J. MCCLOSKEY: You use it for two reasons. One is to find out something about the molecule, because you've now identified the number of exchangeable hydrogens. Hydroxyls and amino groups, carboxyl groups, right? You just count them.

GRAYSON: Yes.

J. MCCLOSKEY: And the second would be to label the molecule so that you understand its mass spectrum better.

GRAYSON: Yes. Wow.

J. MCCLOSKEY: There are different ways to do it, but, you know, you could…you know, loose deuteriums to put in, or you have the firmly bound ones, which would be a different story. Bound to carbon, for example, that are non-exchangeable.

GRAYSON: Right. Very interesting. Yes. So it's really like a primer on mass spectrometry, up to the point in time where you are publishing it. So methods of ionization doesn't have anything to do with some of the more recent methods, but it's…

J. MCCLOSKEY: Hmm, no, no.

GRAYSON: …that you worked at one time.

J. MCCLOSKEY: The point at…1990, that was what made it rock.

GRAYSON: Yes.

J. MCCLOSKEY: It has even californium in there.

GRAYSON: Yes. I can see Macfarlane's paper.[25] Biemann actually made a contribution **<T: 95 min>** on exact mass measurements.[26]

J. MCCLOSKEY: Yes.

GRAYSON: Richard Milberg. That name's familiar.

J. MCCLOSKEY: Oh, he was at […] Illinois. [Yes. Kenneth L.] Rinehart's place, I guess.

GRAYSON: Yes. I think so. Klaus has another one here.[27] Very nice. Wow. Well, that kept you off the streets for a while.

J. MCCLOSKEY: Yes, it did, indeed.

GRAYSON: So I'm curious. This is just a total aside that I'm curious about, and that is there's one paper that I saw on your publication record that talked about the wobble rule.[28]

J. MCCLOSKEY: […] Wobble rule. Yes. That's about…it's hardcore biology.

GRAYSON: That's hardcore biology. What's that about?

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[25] Ronald D. Macfarlane, "Principles of Californium-252 Plasma Desorption Mass Spectrometry Applied to Protein Analysis," in James A. McCloskey (ed.), *Methods in Enzymology, Volume 193: Mass Spectrometry*, (New York: Academic Press, 1990): 263-80.

[26] Klaus Biemann, "Utility of Exact Mass Measurements," in James A. McCloskey (ed.), *Methods in Enzymology, Volume 193: Mass Spectrometry* (New York: Academic Press, 1990): 295-305.

[27] Klaus Biemann, "Peptides and Proteins: Overview and Strategy," in James A. McCloskey (ed.), *Methods in Enzymology, Volume 193: Mass Spectrometry* (New York: Academic Press, 1990): 351-60.

[28] Satoshi Matsuyama, Takuya Ueda, Pamela F. Crain, James A. McCloskey, and Kimitsuna Watanabe, "A Novel Wobble Rule Found in Starfish Mitochondria Presence of 7-Methylguanosine at the Anticodon Wobble Position Expands Decoding Capability of tRNA," *Journal of Biological Chemistry* 273(6) (1998): 3363-8; and Kozo Tomita, Takuya Ueda, Sadao Ishiwa, Pamela F. Crain, James A. McCloskey, and Kimitsuna Watanabe, "Codon Reading Patterns in Drosophila melanogaster Mitochondria Based on their tRNA Sequences: A Unique Wobble Rule in Animal Mitochondria," *Nucleic Acids Research* 27(21) (1999): 4291-7.

J. MCCLOSKEY: That's about certain modified residues in transfer RNA cloverleaf. tRNA is a cloverleaf.

GRAYSON: tRNA is a cloverleaf.

J. MCCLOSKEY: Yes. It's a secondary structure, if you write it on a piece of paper, flat, it looks like this.

GRAYSON: Oh, okay.

J. MCCLOSKEY: And so there's certain modifications in the anticodon that are…they're in the so-called wobble position, because the base pairing is not the same as for the others. But it's a central part of reading the genetic code. The tRNA has to dock, docks with the message. Right? When it docks with the message, it is being told to leave here whatever amino acid you have hooked onto the other end of the molecule. So phenylalanine, phenylalanyl tRNA would in that case deposit at that moment—that brief moment in time—would deposit a phenylalanine to the growing peptide chain.

GRAYSON: I see.

J. MCCLOSKEY: And all that's under control of tRNA. . tRNA is full of modified nucleosides, so that's how we got into it.

The wobble rule…the wobble position and so forth is related to the triplicate region in the DNA, or vice versa. Whichever…

GRAYSON: So that is hardcore.

J. MCCLOSKEY: It's pretty hard…yes. Protein synthesis is what that is, and RNA runs the show, actually.

GRAYSON: Well, some of these others, I think, we've touched on the idea that you were kind of an outsider on the biological applications of mass spectrometry but that didn't seem to bother you at all. Everybody else was hopping on proteomics. It seems like that's what the big buzz thing is.

J. MCCLOSKEY: Yes. It still is, in the sense that it's now being…those are now applications that are red hot, and they work, and they sell mass spectrometers to do it. I can't tell you how many companies do it, but…because protein is so important.

GRAYSON: Yes. Yes. Well, unless you have any specific things that you want to cover, I think we can wrap up this portion, and then…

[…] Okay. Why don't we put the lid on this portion of our interview, and then we can do a little short video interview so we can get a picture of you for posterity, and then I think we can wrap it up and call it a day.

[END OF AUDIO, FILE 2.1]

[END OF INTERVIEW]

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