Alan Peterkofsky, Part 3

June 21, 2023

Higingbotham: Good afternoon. I am Haley Higginbotham, the Assistant Archivist of the Office of NIH History and Stetten Museum. Today is June 21, 2023. This is the third part of our oral history with Dr. Alan Peterkofsky. During this interview, we will discuss more of his career at NIH, along with some of his travel experiences and his wife Beverly's NIH career. Dr. Peterkofsky?

Peterkofsky: Obviously the scientist that I had the most contact with over the course of my career was my wife Beverly, so I thought it would be appropriate to kick off this section by talking about Beverly. While I was a graduate student at the Public Health Research Institute, with my research there being recognized by the biochemistry department at New York University, Beverly was a graduate student in that department of biochemistry at New York University.

I finished my Ph.D. studies and was approved for a Ph.D. in early 1959, at which point we got to work making an arrangement to determine a way for me to bypass getting sent to Vietnam, and we managed to get a commission in the United States Public Health Service. I was therefore ready to go to initiate that commission in the middle of 1959. Beverly was in the middle of her research in the biochemistry department at New York University. She was working with Dr. Charles Gilvarg there on an enzyme that was involved with the biosynthesis of the amino acid lysine and transaminase and doing some very creditable work. But it was not ready for a Ph.D. thesis, so she was interrupted at that point and was granted a Master of Science degree—and therefore was ready to go with me at the time that I was going to go to NIH on this Public Health Service Commission Officer status. The last time we spoke, I went through about dealing with an issue where there was a recurrent series of delays involved with that, so I won't go into that. We eventually came to NIH, and I started this commission.

One of the things that became obvious, as a perk involved with being a Commissioned Officer, was that the family, Beverly and I, were eligible for medical care. One of the aspects of medical care was that Beverly could be provided with obstetric service. I was on this two-year time frame, and it seemed like a really good idea to take advantage of the obstetrical service. We decided to see what's involved in having a baby. We worked at that, and in the latter part of 1959, shortly after we came to NIH, Beverly became pregnant. Eventually we went to deliver a baby at the Naval Hospital in Bethesda, which is right across the street from NIH. In the latter part of 1960, we delivered a baby boy, and she was quite happy about that, and complimented the outstanding care and service that she got as the spouse of a Commissioned Officer in the Public Health Service. We were rather pleased that on exit [from the hospital], the bill that was presented to us was $7.00.

Higingbotham: Wow.

Peterkofsky: That was a pretty astounding kind of a situation that worked out very favorably. That was the story of our first baby. Beverly had the baby, and she had, as I think I mentioned previously, arranged to continue her

graduate studies in the laboratory of Sidney Udenfriend, who was a lab Chief in the Heart Institute at NIH, and had arranged for a cooperative program for his students with George Washington University. My close friend Herbert Weissbach was one of the first students in that program, and recommended that very highly, and was influential in arranging for Dr. Udenfriend to accept Beverly as a student. She started that, and when the baby came, she stayed home for about three weeks and then went right back into the lab to continue her work. We got a housekeeper who would come every day and spend all day in our house. We were extraordinarily fortunate, because this housekeeper stayed with us for 12 years and never missed a day. It was pretty, pretty incredible in terms of where it was.

Beverly was working in the Udenfriend Lab, which was a lab that was very much interested in the process of hydroxylation of different kinds of molecules. The area that she was assigned to work on dealt with this protein called collagen, which is the most abundant protein in your body. And it turns out that the initial form of collagen that's made is called pro-collagen, which has some repeating sequences in it that contain proline residues, which are eventually converted to hydroxyproline residues. The formation of hydroxyproline in collagen appears to be essential for the collagen to form the appropriate structure that is really a triple helix capable of forming fibers that constitute connective tissue. She was working on that and looking for an understanding of the mechanism by which the proline residues and pro-collagen were converted to hydroxyproline residues in the final collagen. She was screening all kinds of molecules to see what the requirements for that conversion were in a system that involved embryonic chickens. She made this discovery that ascorbic acid, vitamin C, was essential for this conversion, and that discovery provided a scientific basis for the long-standing observation dealing with the disease called scurvy. The story was that in the old days, sailors going on long voyages would eventually run out of their stockpile of citrus fruit and then develop scurvy. This put together a puzzle of understanding precisely what it was that linked citrus fruits with scurvy. It was that vitamin C requirement, so that was pretty important.

It turns out that years later, when Sidney Udenfriend was on the verge of retirement, he was asked to write a memoir, and in that memoir, he said, “Beverly was the best thing that ever happened to me.” That was just an indication of how important she was in terms of that. Beverly had this incubator in the lab, which was a really beautiful piece of furniture that had little shelves in it that she would put chickens’ embryonic eggs on. That kept them at a precise temperature. The nature of her experiments was that she would cut a little hole in the shell of an embryonic chicken and add certain things to it, and then take out the tissue and see how it affected the development. It turns out that every now and then she would come to the lab in the morning, and first thing as she came into the lab she would hear [would be], “Cheep, cheep, cheep.”

Higingbotham: Oh no, they hatched.

Peterkofsky: … which meant that some of these eggs had actually gone too far and hatched. They were not good experimental samples anymore. But she had these cute little chicks, so she would put them in a box and bring them home for the kids to play with. We had a little chicken farm in our basement, and what we quickly realized is the little “cheep, cheep, cheep” chickens would grow very fast, at which point they turned out to be not that much fun for the kids to play with anymore. Well, it turned out that a very short distance from where we lived

there was a chicken farm, and we had developed an arrangement with this chicken farmer that when we had chicks that had grown to a certain stage, we would deliver them there. We had sort of a pipeline of supplying some chickens secretly to this farmer. That was sort of an interesting thing.

It turns out that Beverly got her Ph.D. degree in 1965, and then it was the question of where she would go for some postdoctoral experience. Now, when I first wanted to come to NIH even as a student, the person that had been recommended to me as the most exciting person to be associated with was Gordon Tompkins. Unfortunately, it did not work out for me to go to Gordon Tompkins because he was a young person and didn't have space in his lab. But by 1965 Gordon Tompkins had sufficiently been well recognized that he was given the opportunity to establish a new laboratory in the Arthritis Institute [now the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS]. That was the first Laboratory of Molecular Biology. He populated that laboratory with a bunch of really great collaborative scientists. Beverly made contact with him, and he remembered the Peterkofsky name and fulfilled a long-term promise to have an association with a Peterkofsky, but now it was not Alan, it was Beverly. He took Beverly into the lab to work with him.

I might mention that some other people in that Laboratory of Molecular Biology became close friends. There was this very talented bacterial geneticist, Bruce N. Ames, who became quite famous and eventually left NIH to go to University of California at Berkeley. While he was at NIH, he developed a test that became known as the Ames test to diagnose whether certain compounds were carcinogenic. Well, we do remember that in the Laboratory of Molecular Biology, they had a little coffee room, and people would go in there to drink coffee and sometimes have snacks. Bruce Ames had put up a very prominent sign in the laboratory that said, “Eat and die.” It was sort of a fun thing but indicative that he was proposing that almost anything you ate was going to give you cancer. I know that one of my other friends used a test to determine that some of the coloration that you found in dyes was carcinogenic, and that was an important, troublesome contribution to the beauty care industry. The other person that's noteworthy in that laboratory was David Davies, who was an X-ray crystallographer. Later on, when I became interested in structural biology, I collaborated with him. I spent time frequently visiting my wife, as well as other people in that laboratory, located in Building 2—very frequently—and got friendly with them.

When Beverly was in the lab with Gordon Tompkins, she was supported by this postdoctoral fellowship that was called a Helen Hay Whitney Fellowship. She would have to go once a year to Princeton for the annual meeting of the Helen Hay Whitney group and present her work. The kind of research that Gordon was interested in was on how hormones affected the process of protein synthesis. The research that she did was based on the knowledge that hydrocortisone stimulated the synthesis of various enzymes. The one that they paid attention to was the enzyme called tyrosine aminotransferase. Well, Beverly used her background in mechanistic studies to discover that the messenger RNA for tyrosine transaminase didn't actually require the synthesis of protein. It played an important role in diagnosing what the mechanism of this hormone effect was. They published that work by getting Marshall Nirenberg to communicate the results of that study to the Proceedings of the National Academy of Science. It got a lot of recognition. Gordon was a very voluble individual, and he spent a lot of time going to give talks about this, and he always referred to the work as the “Beverly experiment,” so that was useful to know.

Then Beverly finished her work on this fellowship and was ready to go look for a real job where she could become an independent investigator. One of the first people that she was interviewed by who had a job opening was a scientist in the Cancer Institute [National Cancer Institute] by the name of Herbert Sober. She came with her credentials, and he looked at her CV, and he was very impressed with that, and then asked her, "Do you plan to have any more children?" And that was the end of that interview. Beverly went on to elsewhere, and she eventually got a job at the Laboratory of Physiology at the National Cancer Institute. She began to go back to her long-standing interest in collagen and research that she had done for her Ph.D. degree. [It's] interesting to note that while she was in that lab, she met a very young guy who had come to learn about science, whose name was Robert Gallo, who eventually became the guy who became famous for his studies on the HIV virus. We got to know people as they were growing. Eventually, Beverly transferred to a brand-new laboratory in the Cancer Institute, titled the Laboratory of Biochemistry, that was being formed by Robert Goldberger, who was a very important figure that originally had come from Chris[tian] Anfinsen's laboratory. And she spent the remainder of her career in that laboratory working on collagen.

Beverly's reputation, on the basis of the work that she did, mainly on connective tissue, was pretty well-established, and like an established scientist, she began to travel to conferences. There was one conference that was held reproducibly every summer in New Hampshire that was called the Gordon Research Conference. There was one specific Gordon Conference on connective tissue that she would go to, almost every year, and present the ongoing results of her research. One year, she actually served as the organizer of that conference. Things were going pretty well. She had some postdoctoral fellows while she was there that turned out to become important. It was one fellow, whose name was Robert Diegelmann, who came to her lab as a postdoctoral after getting his Ph.D. at Georgetown University. He eventually took a position at Virginia Commonwealth University and developed a treatment for wound healing that was used very frequently in the Armed Forces for wounded soldiers and made a significant impact and became well known for that. She had some postdoctoral fellows from Poland. There was one occasion I remember where there was a symposium organized in one of the cities in Poland, where Beverly was invited as a major contributor, and I went along to accompany her as a spouse of the speaker but not a participant in that symposium. That was a very nice experience. Eventually, in the year 2000, Beverly retired from her studies at the NIH and began to concentrate on playing the violin. She became the first violin in a quartet that she formed. They named that the Dupre Quartet after this famous woman cellist. That's sort of a summary of her life.

Higingbotham: I had heard somewhere that she was part of the NIH Orchestra when she was at NIH. Is that true?

Peterkofsky: Yeah. There was this interesting incident I remember where she was playing the violin in the NIH Orchestra. That orchestra was composed primarily of NIH scientists, some of whom were there for short periods of time. During that period of time, there was a guy who was the tympanist in the orchestra, and he left, and there was this orchestra with no tympanist. They were getting a bit frantic about how they could play serious music without a tympanist. At one point in time during an interview, Beverly pointed out that she had a 12-year-old son who could play drums, and they eagerly accepted her offer to bring her 12-year-old son as the tympanist

for the NIH Orchestra—which he served with distinction for a while. That was sort of a nice kind of thing to happen to her as well.

Higingbotham: She seems like a really interesting woman—great at science.

Peterkofsky: She was very, very talented in many ways. Let me go back to where I was the last time.

Higingbotham: You were talking about your transfer to the [Marshall] Nirenberg Lab.

Peterkofsky: Yeah, well before that, I wanted to just point out that I had started out with the stuff on transfer RNA modification. I was studying the role of methylated bases and transfer RNA. As I grew in terms of size of my laboratory and had more people coming in, I was able to initiate studies on what was becoming known about other aspects of tRNA structure—that there were not only methylated bases in tRNA, but other modified bases as well. There was a scientist that I got to know in the Heppel laboratory that I would go and visit frequently, whose name was Marie Lipsett. She was the wife of Mortimer Lipsett, who at one time was the Scientific Director in the Arthritis Institute. She had been collaborating with another scientist at the Walter Reed [Army] Institute [of Research]. His name was Dr. [Bhupendra P.] Doctor, and they had discovered that there was another kind of base in transfer RNA that was called thiouracil. Both of them were more biophysically oriented and didn't really know too much about approaches to tracking down biochemistry, so they asked me if I would help them to understand how the thiouracil in transfer RNA is formed. I began this collaboration with Marie Lipsett and discovered that the origin of the sulfur in the thiouracil came from the amino acid cysteine, which is a sulfur containing amino acid. There was also some peculiar requirement for another compound called beta mercaptopyruvate that was also necessary. Eventually what we did was propose that there was some kind of a complex between cysteine and beta mercaptopyruvate that eventually resulted in the transfer of sulfur to a uracil base in transfer RNA, and that was the story with that.

Now, Robert W. Holley, who shared a Nobel Prize with Marshall Nirenberg, was responsible for outlining what the typical structure of a transfer RNA is, and it was sort of like a cloverleaf structure. That's the way it was referred to, as three arms on a stem, with one of those arms being a portion of a transfer RNA that was involved in deciphering the code for that particular transfer RNA for that particular amino acid. There was another modification of trans RNA that had been described, which had this complicated name of isopentenyl adenosine. We wanted to try to understand how that was formed. The speculation was that that structure of isopentenyl looked a little bit like the one of the precursors for cholesterol. It turned out that there was a bacterium that was called lactobacillus acidophilus that had a requirement for this precursor of cholesterol called mevalonic acid. It seemed like a really good way to study that isopentenyl adenosine formation on transfer RNA. And we did that and showed that, in fact, that mevalonic acid was an essential precursor for that modification and transfer RNA. It turns out that modification was in that region of the tRNA that was called the anticodon region, and only observed certain species of transfer RNA for certain amino acids. That was useful to know.

Then, finally, there was this other one that we worked on, which was even more complicated in terms of its name, that was called purinylcarbamoyl threonine, where we found that was a precursor, and the location of

the modification was always in the anticodon region. This pattern was established with these various transfer RNAs that could affect the recognition of the tRNA in the process of translation. It's useful to point out that years later, people began to talk about this phenomenon that is commonly referred to as epigenetics. "Epigenetics" means genetic transformations that really are not encoded in the DNA. Then, thinking about it, it became obvious that these post-translational modifications of transfer RNA were a very, very good example of what happens epigenetically. We were doing these studies before the term "epigenetics" was ever invented. Now we realize that this kind of change was really a good example of epigenetics.

Higingbotham: That's really interesting. Epigenetics is so fascinating to me.

Peterkofsky: Now I think it's appropriate, just in terms of generating a perspective, to reflect a bit on what was going on in this new field of molecular biology and how it all started. It really all started in 1953 when [James] Watson and [Fracis] Crick discovered or outlined the structure of the DNA helix. The idea of this double stranded form of DNA helix formed the basis for all these ideas that then stimulated people to think about how the information in DNA encoded what eventually became proteins—how the four nucleotides that are found in DNA would eventually provide the information for the formation of proteins that contain 20 different amino acids. This was the major puzzle that was occupying the attention of people once the structure of DNA, and the idea that DNA was the reception of heredity, was found. There was a scientist who was more of a biophysicist, whose name was George Gamow, who, at the time of interest, was a professor at George Washington University. But more important than his being a professor at George Washington University, he had the reputation of carrying the nickname "Prankster." He was always carrying out funny stuff with people, and people loved to interact with him because he had this spectacular sense of humor. Shortly thereafter, after the structure of DNA was worked on by Watson and Crick, Gamow had a meeting with James Watson, where they started talking about how DNA could form proteins. The notion that this was such an important aspect of molecular biology was tossed around by them to where they thought that they ought to form an association. In his humorous way, Gamow came up with the idea that they should get some really spectacularly intelligent people to form a club, and the club that they formed was called the RNA Tie Club. In his humorous way, he said that this club will have 20 members, one member for each of the 20 amino acids. What they decided to do was to go to some haberdashery place and convince the haberdasher to make 20 different ties—one tie for each amino acid—and they would present the unique tie to each of the 20 members. And each of those members was assigned one of the 20 amino acids as his name. They would hold conferences of this Tie Club. It was really the first example of a society that would communicate scientific ideas and information without publishing papers.

During the course of this, Gamow did some mathematical calculations where he decided that the four bases in DNA, if you took three of them at a time, had enough combinations to code for the 20 amino acids. That was actually the precursor of the concept that a codon that coded for an amino acid was composed of three nucleotides. Eventually Francis Crick, who was one of the members of the Tie Club, came up with the idea that there must be some kind of a so-called adapter that would utilize the three base units to communicate the information in DNA to make proteins, and the three base units became known as codons. And so, they worked out this kind of a strategy for understanding the whole basis for converting the information in DNA into protein. In order to do this, Crick came up with the idea that there was this adapter, which was eventually identified by

Robert Holley as a small RNA. It was actually the transfer RNA, which was the thing that I spent so much time working on. Holley, of course, was the co-recipient of a Nobel Prize with Marshall Nirenberg. It's interesting to note that of all the members of that RNA Tie club that were so influential in determining the ideas about how molecular biology works, none of them were at NIH. And it didn't include Marshall Nirenberg, who was actually the one who eventually worked out the code. Interesting aspects of life, in that sense.

Let me go on to talk a little bit about some aspects of travel.

Higingbotham: You've been to a lot of conferences.

Peterkofsky: As time went on and I became more recognized, I was invited to meetings. The first thing I'd like to mention is that I had met Marianne Grunberg-Manago, who originally had been a postdoctoral fellow from France in Severo Ochoa's laboratory. She discovered the enzyme called polynucleotide phosphorylase—which originally was actually used to make this polynucleotide, poly-U, that Marshall Nirenberg used for his famous experiment that showed that poly-U coded for polyphenolalanine. That was the first codon that was worked out. In 1996, Marianne Grunberg-Manago decided that she wanted to stimulate meetings of scientists who were making great contributions to molecular biology. In order to encourage these people to come to such meetings, it was always a good idea to have the meeting in a very attractive place. She set up this meeting that was called "The First Summer School on Molecular Biology" that was going to be held on this beautiful Greek island called Spetses. I was invited to participate in that meeting, and I spoke there. The interesting thing that I remember from that meeting was that we would have our scientific discussions in the morning and in the evening, with afternoons off—and very frequently the participants in the meeting would get together in the evening at a little club up on a hill. This was actually at the time that the Beatles were very popular, and they named that club Blueberry Hill. We would go up to this place and talk and maybe drink a little bit as well.

One evening, a bunch of scientists, including me, were there. It turned out that James Watson and Francis Crick were at the meeting. All of a sudden, this absolutely beautiful woman, who was this great actress called Melina Mercouri, came to this club to hang out with her husband, who was a movie producer. His name was Jules Dassin. And of course, she attracted a lot of attention because she was a well-known actress and also quite beautiful. James Watson ambled over to them, introduced himself, and told them that he was in the process of writing a book about the discovery of the structure of DNA, and began to tell them their story. The movie producer Dassin was sort of, tongue in cheek, stringing Watson along and saying to him, "That's a great story for a movie!" One of the aspects that Watson was pointing out in this book is that there was a bit of a scandal in the determination of that structure—there was some data that had been produced by some X-ray pictures taken by a woman scientist by the name of Rosalind Franklin. It turned out that she would have shared in the Nobel Prize that was given to Watson and Crick and Wilkins, except that she died of cancer before the prize was given out. In any event, Dassin says to Watson, "Why don't we make a movie of this story, and you will play yourself in the movie, and Melina Mercouri will play the role of Rosalind Franklin?" Watson, of course, was bowled over by this idea that he could be a costar in a movie with Melina Mercouri and created a lot of attention. The standpoint of any conversation that he had with anybody for the remainder of the meeting was that he was not only going to become a famous scientist, but also a movie star. That was sort of a funny kind of thing, wasn't it?

In 1996, there was a symposium that was held at Cold Spring Harbor. Cold Spring Harbor was a place where they frequently held summer meetings that they call “Symposia on Molecular Biology” on one thing or another. That particular year, it was, of course, a lot of focus on the advances that had been made in molecular biology. I was invited to give a presentation there, which I did, and James Watson was at the meeting, and Francis Crick was at the meeting. Every now and then, in the afternoon, a lawn party was given for entertainment. One of those afternoons, Francis Crick came out of a building dragging a big dolly with a huge box on it that had a ribbon on it. He announced to the people on the lawn that this was James Watson’s birthday, and this was going to be his present. At that point, out of the box jumped this nude model. Everybody of course went “hahaha.” Then of course, the model came out and embraced James Watson, which was quite a spectacle to see. Francis Crick, the real gentleman, then came out with a cloak to cover up the model and escorted her away. That was quite a thing to remember.

In 1984, there was a symposium that was called the “Symposium on Gene Manipulation” that was scheduled to be held in Czechoslovakia. It was going to be in a beautiful mountain resort in Czechoslovakia that was, I think, something like 50 miles away from the capital city, Prague. The instructions were to come to Prague and register for the meeting, and then there would be a bus that would transport the participants in the meeting to this mountain resort. I came to Prague a day before the registration and met up with a colleague of mine by the name of Jesse Rabinowitz, who was also going to participate in the meeting. We were wandering around Prague looking for interesting sites to photograph. At one point, a gentleman approached us and asked if we would like to transfer our American dollars to Czechoslovakian currency, and he would offer an exchange rate that was much more favorable than the official exchange rate. This seemed to be an opportunity that was too good to be true, and we gave him significant amounts of money, and he exchanged it for a bundle of Czechoslovakian currency. Later on, we proceeded to go to this hotel where it was required to register for the meeting, and there was a registration fee in Czechoslovakian currency. I came with my bundle of Czechoslovakian money and gave it to the person, who then said to me, “Where did you get this money?” And I told him this story about how this gentleman had exchanged currency. The registrar said, “You know that was not legal. You couldn't get Czechoslovakian currency unless it was officially exchanged and recorded in your passport—and your passport does not show any record of having made an official exchange of currency,” and [he said] that this was very bad. A bunch of officials at this conference began to huddle and have a serious discussion of what consequence should be made of my having done an illegitimate conversion of currency. Eventually they said it was okay, and they took the money. A little while later, one of the participants in the meeting told me that it was very lucky for me that I had an American official passport. It was that red passport that saved me from being put in jail, so there was a bit of luck there. A friend of mine decided that instead of my having to take the bus up to this mountain resort, he would drive me there, and so I got there in a more comfortable way than using that bus and got there before most of the other participants. Because of that, I was able to tour the accommodations in this facility, and I saw that there was one room that was really very large and elegant compared to the other rooms and said, “Well, if that's available, I'll select that room to sleep in.” Why not? I actually did that with another participant in the conference. During the course of that meeting, it was revealed to me that during the occupation by the Nazi Germans, that facility had been occupied by the German army, and the room that I

stayed in was the one that was occupied by the Commandant of that Nazi group—so that was pretty distinguished. That gives you an idea of some of that travel that I was doing.

In 1967, I moved over to the Nirenberg lab, and I was continuing these studies with transfer RNA, going on with my stuff. The activity in the Nirenberg lab was on determining which kind of codons corresponded to which amino acid. This was tedious work that was very labor intensive, and a whole bunch of postdocs in the Nirenberg lab were involved with that. By that time, it was getting pretty close to having all the assignments of the genetic code made. One of the people who was a postdoc at that time was Philip Leder, and he made a major contribution to that effort by inventing this little device that was called the Leder multi-plater, which I believe is in the NIH [Stetten] Museum of artifacts. And I believe that in the Nirenberg exhibit in the Clinical Center, there is an example of Leder's multi-plater. That was interesting to know. There was also another very active post doc there. His name was Tom Caskey, and he made a major contribution.

What eventually happened is that, as the number of codon assignments were made, eminent scientists, like a lot of the people who were in that RNA Tie Club, said the whole business with molecular biology was over—and if you wanted to be ahead of the science at that point in time, you shouldn't be doing molecular biology anymore, you should be doing neuroscience. People like Francis Crick decided to move into the field of neuroscience, and a number of other people did that as well. And Marshall Nirenberg sort of began to feel like he did not want to be left behind, so he made the decision that he too wanted to become a neuroscientist. He began to spend a lot of time at home, out of the lab, trying to learn background in neuroscience so he could think of approaches to do neuroscience. The main administrator function in the laboratory became mine, and shortly thereafter, I was identified as the Deputy Chief of the laboratory. I had to do that kind of stuff as well, but I was there every day and managed to do that. We were in Building 10, and shortly thereafter, there was this brand-new building open. It was number 36. Marshall was given the opportunity to move to this Building 36 that was going to have a focus on neuroscience. The move was made, and he was given space on both the first floor and the third floor. He designated the space on the first floor to be the neuroscience space, and the space on the third floor to be space for other investigators in his lab, like me. I moved to the third floor. Tom Caskey, at that point, had become a section head in the lab, and he was concentrating on studying the enzymes that were involved in the termination of protein synthesis. It was a nice group of people. They had an electron microscopist named Mathew Daniels, who was there on the third floor. One of the newer people who came was named Bill Catterall, who eventually became well known for his studies on calcium channels. We had a nice group of people.

Just across the street from building 36 was this building that had a little cafeteria, and it was Building 35. I would frequently go to lunch in that cafeteria and had an opportunity to interact with people there. I would see Julius Axelrod in that building, who eventually won a Nobel Prize for his work on neurotransmitters, and that was nice. One of the people who would frequently come to lunch with me was an Italian scientist named Ettore Appella, who we knew pretty well because he had been a postdoc with Gordon Tompkins at the same time that Beverly was in the Tompkins lab, so we became close friends with him. Ettore Appella was, at that point, working in Building 37 with a scientist named Michael Potter, who was well known for his study of plasma cell tumors in mice, and he had collected a big supply of these different mice that made these different plasma cell tumors. One of the things that had been observed about the structure of the plasma cell tumors, which were producing

these fragments that were called “light chains of antibodies,” was that instead of having the normal amino terminal amino acid—which on all proteins was methionine—it was not methionine, but a blocked form of an amino acid that was called pyroglutamic acid. They approached me, a biochemist—they were immunologists—to help them to understand how this pyroglutamic acid was formed. I entered into a collaboration with that group, where Potter would supply plasma cell tumors to me, and I would study extracts of them to try to understand what the precursor of this pyroglutamic acid was, assuming that it was involved directly in the translation of that protein—which turned out actually to be a misconception. Not long thereafter, it was revealed that the gene for these tumors was one that gave a precursor protein that had a leader peptide on it; it was called a signal peptide. In fact, the protein had this initiation by the normal methionine, as you would have expected, and there was a sequence of something like 19 amino acids that was eventually processed and clipped off to reveal this amino acid, which eventually became pyroglutamic acid. When it was possible, as advances were made in molecular biology, to determine the DNA sequence of these precursor proteins, the amino acid and the sequence of the precursor protein that eventually became pyroglutamic acid was actually glutamine. That sort of solved that problem, and it never became clear exactly how that process of the formation of pyroglutamic acid in those light chains was formed, although it was clear that it was glutamine as the precursor.

Because my interest in pyroglutamic acid was stimulated, we decided to look at a model peptide, and it turned out that there was this three-amino acid peptide that was well known in terms of neuroscience as a peptide called thyrotropin-releasing hormone. And the structure of thyrotropin-releasing hormone was that the first amino acid was pyroglutamic acid, followed by histidine, followed by protein proline, which was blocked to form proline amide. It seemed like a really interesting, simple model system to study the significance of that blocked amino acid. We began to look at systems that process that. In brain extracts, we exposed purified thyrotropin releasing hormone and discovered that there was an enzyme, which we named pyroglutamic acid peptidase, that clipped off the pyroglutamic acid from that thyrotropin-releasing hormone, and also an enzyme that clipped off the amide group from the proline. Once the pyroglutamic acid was clipped off this tripeptide, the consequence of that was that we were left with a dipeptide.

And that peptide cyclizes, interestingly, to form a cyclic dipeptide which we named histidyl-proline diketopiperazine. We began to study the significance of this histidyl-proline diketopiperazine, and it turned out that in some studies we did in rats—which you could feed alcohol to make them drunk, and therefore display what we called narcosis—that if you gave these histidyl-proline diketopiperazine, the narcosis was blocked. We published the results of those studies in Nature, and that created quite a bit of attention with the possibility that this could be a drug that could treat alcoholism. We were encouraged by some Patent Officer at NIH that we could apply for a patent for this, but if we did, that would probably suppress further research on it, because a pharmaceutical company wouldn't be able to get some profits from this. We basically dropped our interest in it and let it float out. But over the years, we showed that this diketopiperazine had some very interesting effects, in terms of having an effect on cyclic GMP, and also effects on ATPase and brain. It, in fact, is an important brain peptide that we discovered.

I think that maybe that’s enough time for me to stop and call a quits to this. I’ve exhausted my session.