ORAL HISTORY INTERVIEW WITH RODGER LIDDLE
Duke University Libraries and Archives
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Researcher: Joseph O'Connell and Josephine McRobbie

COLLECTION SUMMARY

This collection features an oral history Joseph O'Connell conducted with Rodger Liddle on February 24, 2021. The 73-minute interview was conducted in Durham, North Carolina. Our conversation explored Liddle's research in measuring CCK levels, his thoughts on connections between enteroendocrine cells and the nervous system, and conducting laboratory research during the COVID-19 pandemic. The themes of these interviews include gastroenterology, academic medical research, the social life of medicine, and medical training.

This document contains the following:

- Short biography of interviewee (pg. 2)
- Timecoded topic log of the interview recordings (pg. 3)
- Transcript of the interview (pg. 4-18)

The materials we are submitting also include the following separate files:

- Audio files of the interview*, **
    - Stereo .WAV file of the original interview audio
    - Mono .MP3 mixdown of the original interview audio for access purposes
- Photograph of the interviewee (credit: Rodger Liddle)
- Scan of a signed consent form

*Due to COVID-19 social distancing protocols and best practices, Joseph recorded the interview remotely via the Zoom web platform.
**Please note that due a technical glitch, several of the interview questions were not audible when recorded. The questions are reconstructed in the transcript with the use of [brackets].

BIOGRAPHY

Rodger Alan Liddle, M.D. is a gastroenterologist with a research focus on GI hormones. He first came to Duke in 1988 as chief of the GI section at the Durham VA Medical Center. During his time at Duke and the VA, Liddle has maintained a focus on conducting and guiding laboratory research, while also serving as an administrator, instructor, and clinician. His lab currently focuses on two topics of research--pancreatitis and enteroendocrine cell biology. This includes breaking ground in the understanding of how gut hormones interact with the nervous system, an area of research that promises new insights into the biological processes that cause Parkinson's Disease.

Liddle grew up in Nashville, Tennessee. His father's career in academic medicine led to an immersion in the social world of Vanderbilt University physicians, researchers, and staff. He recalls that his mother and father would frequently host parties and get-togethers for the endocrinology division. "These would be other doctors, fellows, the staff, the laboratory technicians, the secretaries. Everybody attended those parties," he says. "And those individuals were very nice to me and my siblings … it was like an extended family." Liddle was inspired to remain a member of this "extended family" of academic medicine, and received his M.D. from Vanderbilt University in 1978.

His career-long interest in understanding GI hormones took shape during his time as a fellow at the University of California - San Francisco. At UCSF, Liddle found a hospitable environment for exploring the connections between endocrinology and gastroenterology. Working in the lab of the pancreatic physiologist John Williams, Liddle focused his attention on the gut hormone cholecystokinin (CCK). "At that time there was no good assay for measuring blood levels of CCK," Liddle says. When Liddle developed one, it was a breakthrough. "As a result, we had the only reliable CCK assay in the world," he says. Before he knew it, Liddle had become an expert in CCK, and the direction of his future interests and work was set.

INTERVIEW TOPIC LOG (rodger-liddle-interview-audio.wav)

00:00 Introductions and orientation to current work
01:38 Current responsibilities
03:50 Research freedoms as a physician scientist
05:12 Clinical, academic, and laboratory worklife pre-COVID
07:59 Impact of COVID-19 pandemic on clinical and laboratory work
11:59 Emotional and practical realities of COVID in workplace
13:38 Changes in clinical work; positive outcomes of telehealth model
16:29 Adjustments to routine screening procedures
18:17 Birth in San Francisco and early life in Nashville, TN; birth date
19:15 Father's work as an endocrinologist and plans to write biography about him
22:35 Father's work on what would come to be known as Liddle's Syndrome; anecdote about learning about this name while in medical school at Vanderbilt
27:11 Social life around father's work and family parties with endocrinology division at Vanderbilt
29:43 Differences between Vanderbilt and UCSF in terms of social connections
31:35 Initial impressions of Duke versus UCSF
34:30 Early research interests in clinical and research gastroenterology and endocrinology; fellowship research with John Williams on GI hormones; development of assay measurement of CCK
42:36 Reflections on common priorities and interests of gastroenterologists
45:44 Gender inclusivity efforts at Duke and within medical sub-specialty
51:15 Walk-through of current lab setup and stations; shared equipment resources at Duke
53:50 What a lab shift looks like during current phase of COVID-19 pandemic
00:00 Current research in CCK cells; discoveries with Rashmi Chandra and Diego Bohórquez on foot processes in CCK cells
1:01:47 Discussions with Stan Prusiner about connections between enteroendocrine cells and the nervous system and possible implications for treatment of Mad Cow Disease and Parkinson's Disease
1:10:19 Current research in pancreatitis

TRANSCRIPTION (rodger-liddle-interview-audio.wav)

Joseph O'Connell 0:00
Okay, great. So I will hit record. And I'll give a little ID at the beginning here. So it's February 24, 2021. My name is Joe O'Connell. And I'm interviewing Dr. Rodger Liddle. This interview is for the Department of Medicine, and the Duke University Medical Center Library and Archives. So thanks again, Dr. Liddle, for doing this. I want to start kind of with a broad view of what you do. So I'm curious, when you encounter people who work outside of the field of medicine, how do you describe to them what your job is?

Rodger Liddle 0:43
[laughs] Yeah, that's a good point. What's really important is what you talk about in a cocktail conversation, right? So I first tell them I'm a physician and I work at Duke, and I also do research. So I spend part of my time doing laboratory-based research. And part of my time seeing patients, [and] working with fellows and residents and students. And then a conversation usually evolves to "Well, what kind of either patients do you see, with what kind of clinical problems?" Or, "What type of research do you do?" And then, depending upon how interested they are, in that particular topic, I describe what we do in our research laboratory.

JO 1:38
And so your position right now is Professor of Medicine. And are there other pieces associated with your current role?

RL 1:52
Well, I'm in a position right now where it's really perfect. Because I came to Duke in 1988. And my first position was chief of the GI section, at the Durham VA Medical Center. And so that entailed clinical and administrative work, as well as running my research lab. And then five years later, when the person who recruited me -- Ian Taylor -- left, I took over running the GI division at Duke. And I did that until 2002. And I took a sabbatical at that point, and worked for a company in RTP, as well as sort of reinvigorating my lab activities. And when that year was over, I came back and worked again at the VA and running my lab. And I've since at various times over the last 19 years I've continued to do some administrative work at the VA. But three years ago, I stepped down from all of that. And so now I continue to do clinical work, I still run my lab. When people ask me what I do now and I tell them those things they say "Wow, sounds like you're a professor." And I step back and think, yeah, that's exactly right. So I'm able to do things in the lab that we really enjoy doing, and hopefully we're good at.

JO 3:50
So you kind of chuckle when you reflect on the fact that you're a professor. I'm curious what you're thinking when it strikes you that way.

RL 4:02
Because you're able to do things that you want to do. I mean, as a physician scientist, I think it's the greatest career I could possibly have. Because basically I can choose to work on whatever I want to work on. Now, the key is to get funding to support that research. But there aren't many

jobs where nobody tells you what work you're to do. You just have to be, you know, creative enough to assure that you fund that work, so that you still have a job. So you have tremendous freedom. And I think that's a unique situation. And it's a lot like what university faculty members do, right? I mean, it's sort of common across all spectrums of the university where people are doing research that they think is important and worthwhile. And it's an avenue for creativity. So, it's fantastic.

JO 5:12
That's so interesting that you put it in terms of creativity, I can see that. Because it does rely on your ability to generate ideas. I'm wondering, so at this phase of your career, when you are in that professorial mode, what's an average day of work like for you?

RL 5:42
Pre COVID or post COVID [laughs]?

JO 5:45
Wow. [laughs] Let's do pre.

RL 5:52
So I have assigned clinical duties, which used to entail doing clinical work at Duke and the VA. But most recently, it's been concentrated at the VA, where I would work with fellows in clinic on the consult service, I would supervise them doing endoscopies. But most of my time was devoted to doing research. And my research has been supported through the VA, as well as the NIH. So I would attend laboratory meetings that we have, regularly, as well as participate in ongoing activities like reviewing grants, writing grant applications, writing manuscripts, and so forth. And so it'd be a combination of those activities, depending upon what I was assigned to do on what days from a clinical perspective. So if I wasn't in the clinic, then I could devote all of my time to working in my research lab. Now, when I talk about working in my research lab, that has evolved over the years too, because I am no longer doing hands on experiments myself. The people who do that work are probably glad that I am not physically in the lab doing the experiments myself [laughs]. Because I don't think I could do them as well as they can. But it's supervising students, fellows who may rotate through the lab or are postdocs who've been with me for a good while now. So, since COVID… [laughs].

JO 7:59
That's my next question, is how does that change things?

RL 8:03
Well, when COVID happened, we ended up having to close down all laboratory activities. There was a lot of concern on the part of the administration that they did not want anybody to become infected, working at Duke. And so they basically shut down our labs from March until June, and everybody had to basically work from home. So everything that we would otherwise do in the lab had to be either terminated -- so all of our animal studies and laboratory-based experiments had to be terminated. And then, as a result, people ended up spending their time writing results that they had been working on. So it gave them time to sort of divert some of those activities so

that they were able to write rather than to do experiments. So opportunity to focus more on grant writing, for instance, as well as producing some manuscripts. And then in June, we were able to open up some lab activities, probably to about 70% capacity of what we were doing pre-COVID. But we were doing lab work with experimental animals, namely mice. And so we had to decrease our breeding, and decrease our animal use. And so that took a little while, to get that back up to speed. So we are still under guidelines for social distancing in the lab, so we can't have as many people working in the lab at any given time. We have had to stagger work schedules. So that some people will work in the morning and afternoon, some people would come in later in the evening. So we have had to make some accommodations like that. And all of our laboratory meetings are held by Zoom, rather than in-person meetings. But I'm able to come into my office, we are able to work in our research buildings. Everyone has to complete a daily health assessment in order to have access to the building. So there aren't as many people, at any given time in the building. But we're able to keep things going.

JO 10:48
So in that period through June, when the research activity at the lab was completely postponed, did that mean that nobody was coming into the lab space at all?

RL 11:00
Yeah, with rare exceptions. So there was an effort to determine what work was absolutely essential. So if it was something that could not be replicated, so for example, should I have a particular genetic strain of mice that could not be maintained and that work cannot go forward there were exceptions made, with very careful monitoring of who was in the building at any given time. So that we were not exposing people to anything that was perhaps unnecessary or avoidable. So there were a few exceptions, but for the most part activities were pretty much shut down.

JO 11:59
And what was the mood like among the people who worked in the lab when that happened? What were people thinking or talking about?

RL 12:13
Well I think there was a sense of anxiety, just because we didn't know what to expect. And the reports that you were hearing on the news, we didn't have much more information than what everybody else had. So there was a lot of apprehension about what could happen. But I think Duke did a tremendous job in how they were able to both manage the activities that were allowed, as well as reducing exposure in the workplace. So I don't know the statistics, but there have been very few [cases], I don't know of anyone who has contracted COVID at work. My understanding is that staff who have been infected, it either might have been contracted outside of the workplace, or I'd heard about people eating together where they then have to remove their masks. But I think overall, Duke has done a very good job in managing staff safety. But initially, people just didn't know. So there was a lot of apprehension and staying home was thought to be the safest thing that you can do.

JO 13:38

And how has the onset of COVID affected your clinical practice?

RL 13:46
So the biggest change there -- so I'm not doing endoscopy, myself, but all of my GI colleagues have been -- and so those procedures were reduced, so that all elective procedures were canceled, and only emergency procedures were being done because of the risk of transmission during the during the endoscopic procedure. Those have gradually been ramped back up now. Patients are getting tested before their procedures. And now that the vaccine is being distributed, virtually all of the health care workers at the VA and maybe now at Duke also have been vaccinated. So I think people feel much more comfortable about what they're doing. But we also reduced the clinic visits, and only essential clinic visits were being held initially, and a lot of that was converted to either telephone or telehealth visits. And at the VA that has actually been very well received, because a lot of patients come to the Durham VA from all over North Carolina. So a lot of them drive fairly long distances in order to be seen for a clinic visit. Some of them come from the coast, so that it would not be unusual for somebody to drive three or four hours to come to the VA for a clinic visit. And once we converted to telephone or telehealth visits, we could do a lot of what we would otherwise do in person remotely. So that it's actually been well received. And the VA has embraced this. In fact, they were even encouraging us to do these types of visits before the pandemic. It's been the only way that we could maintain continuity of care for a lot of our patients. And I think a lot of patients like it. So we may never go back to doing things the way we were before the pandemic, where virtually everything was being done in person. So I think telehealth will be part of ongoing medical care in the future.

JO 16:29
I want to ask you a little bit more about the effects of the pandemic, since I think that's an important thing to document. Can you think of a specific example, maybe something that was going on in the lab or a specific clinical activity, that postponing it or reducing it has had a big effect?

RL 17:02
Well, one thing that has been a stress for VA has been part of a backlog of patients who need routine screening procedures. So we were doing a pretty good job in getting all of those sort of up-to-date. And once we were unable to do procedures again, all of those things become backlogged. And so that's putting a stress on the system again. So I think that emergency things get taken care of, because they're the very nature of doing emergency care. You just make accommodations to accomplish those things. But things that are more elective, [like] screening, by definition, is elective. It's important, we need to do it, but doesn't necessarily have to be done urgently. So that puts a stress on the system.

JO 18:17
Thank you. I want to back up and talk about your early life a little bit. So I believe I read that you grew up in Nashville, Tennessee. Were you born in Nashville?

RL 18:35

No, I was born in San Francisco. And we lived there until I was three. And my father, who was a physician, went to the NIH, we went to Bethesda for three years. But I lived in Nashville from the time I was six years old all the way through high school and ended up going to Vanderbilt to medical school and so forth. So Nashville is really my home.

JO 19:03
And I'm documenting people's birth dates and places as well. So what date were you born?

RL 19:11
I was born on August 17, 1950.

JO 19:15
And you mentioned that your father was a physician, and in academic medicine. I wonder if you could tell me a little bit about him and what influence being around his profession had on you at a young age?

RL 19:38
Oh, it had a great effect. My sister has asked me to write a biography on my father. So I have a brother and three siblings, and I'm the only one in medicine. And so my sister was going to write a biography on our mother, and she asked me to write a biography on our father. And I found it -- I'm still in the process of doing that -- actually quite stressful [laughs]. Because I'm not a biographer. And my father is no longer living, so I'm trying to gather information about him from whatever sources I can. I've interviewed some people who've known him but a lot of his colleagues are no longer living. So I've had an opportunity to think about that a lot. And it's been interesting to think back on the influence that he had, because a lot of this was really not something that was on my mind as I was going through it and living through it. But I wish I had the opportunity to talk to him about these things now. Because my questions now would be a lot different than things that we talked about when I was growing up and going into medicine and so forth.

JO 21:14
What kinds of things do you want to know that you would ask him now?

RL 21:21
So he was in academic medicine. So we never really talked about research because he died a year after I moved to Duke. And he had suffered a stroke six years before he died. So he had to retire and was aphasic and paralyzed on his right side after his stroke so he was completely incapacitated. So we were not able to really discuss my professional career, and the things that I'm working on and thinking about now. So I think he would be a tremendous resource, an appropriate critic, if you will, for the things that I'm doing. So I've learned to appreciate a lot of the things that he went through as he was going through his career as I've tried to recapture these in the biography that I'm writing.

JO 22:33
Was he in gastroenterology?

RL 22:35
No, he was an endocrinologist. I'll tell you an interesting story. There is a syndrome that is named after him. People don't really necessarily confuse it with me, because it is referred to as Liddle's Syndrome. And it's a genetic syndrome in which individuals have high blood pressure, and it looks like they have elevated levels of aldosterone. My father as an endocrinologist studied the pituitary gland and the adrenal gland, and the relationship between the pituitary and the adrenal. And one of the hormones that the adrenal produces is called aldosterone. And that regulates blood pressure by controlling the amount of salt that the kidney excretes. And so there was a woman who was referred to him at Vanderbilt who was thought to have high levels of aldosterone. And my father had a laboratory that was able to measure all of these hormones and he developed assays for them and so forth. And he found out that her levels of aldosterone were actually not elevated. But she had all of the biochemical and phenotypic features of high aldosterone levels. So he wrote this and described it as pseudo, meaning false, hyperaldosteronism. Pseudohyperaldosteronism. And he published a paper on this. And after this was published subsequent authors talked about this pseudohyperaldosteronism as described by Grant Liddle. And then people started calling that Liddle's Syndrome. So when I was a first year medical student at Vanderbilt, a classmate of mine came to me and said "What is Liddle's Syndrome?" Well, I had never heard of Liddle's Syndrome before. And of course, I was embarrassed. And I went and asked my father. I said. "Did you know there's something called Liddle's Syndrome?" And I'm sure he thought I was a complete idiot. He said, 'Well, it is, yes, it's pseudohyperaldosteronism." But nobody at Vanderbilt referred to it as Liddle's Syndrome. That would have been too presumptuous. They all called it pseudohyperaldosteronism. So, I took away from that story -- I mean, I was terribly embarrassed that I didn't know what Liddle's Syndrome was, right? -- but I knew what pseudohyperaldosteronism was. So the moral of that story is when you're sitting around the dinner table, once in a while tell your children what you do. And it will save them a lot of embarrassment later in their lives [laughs].

JO 26:32
That's such an amazing story. When he explained to you what Liddle's Syndrome was, did he also explained to you that he had done the research on it?

RL 26:44
Well, I knew that that's what it was. But I didn't know that it was referred to as Liddle's Syndrome.

JO 26:51
I see.

RL 26:52
But he was a very quiet person. And he was not the type of person who was going to be talking about what he did. He never talked about his work or what he did. You'd really have to pull it out of him.

JO 27:11

And that's why people didn't didn't call it Liddle's Syndrome at Vanderbilt, because they didn't want to embarrass him or shine the spotlight on him. Wow, that's amazing. It sounds like he was pretty quiet about it, but do you have memories about your dad's job or what his life was like as an academic physician?

RL 27:44
As a child growing up, the most meaningful things to me were that.. this was in Nashville, and so a lot of people entertained in their homes. So we would have endocrinology division parties in our home, where my mother and father would host the entire division. And everybody in the division would attend those parties. These would be other doctors, fellows, the staff, the laboratory technicians, the secretaries, everybody attended those parties. And those individuals were very nice to me and my siblings. And it was like an extended family. And I thought that's the way it was everywhere [laughs]. I mean, I thought that's the way academic medicine was, it was just a very congenial, cordial, working environment. And so that was the most impressive thing that I took away from what he did. He would harbor those types of activities. So I remember Christmas parties that they would have at the hospital where it would be sort of a joyous occasion.

JO 29:21
So you're kind of immersed in this culture of his workplace, and the social life of it?

RL 29:29
I don't know how much of that was due to the fact that we were living in this house. It was just the way it was. I just assumed that that's why academic medicine was.

JO 29:43
And it seems like you found out that that's not the norm [laughs]. What kinds of experiences did you have in your professional development when you started to see that the experience can vary?

RL 30:02
Well, after medical school I did my internship and residency and fellowship at UCSF in San Francisco. And that was very different. It was a wonderful place and I loved being there. It may be the most formative period in my academic career, actually, was being at UCSF. But it didn't have that sense of cohesiveness that I sensed at Vanderbilt. And I think part of it is due to just the nature of the city. In San Francisco after work people would go off in three different directions. It's very dispersed, people live in different places. There wasn't so much socializing in people's homes, the group activities and departmental parties were held at a restaurant or hotel. And so it was just different. I mean, I loved the people, they were bright and hardworking. But it was just a different feeling. And when I came back to Duke, it was more like Vanderbilt, actually. So I thought Vanderbilt and Duke were very similar in a lot of respects.

JO 31:35
That's really interesting. So at Duke there is that kind of social connection with your co-workers, it sounds like. Can you tell me a little bit more about what that looks like? When people get together and what those communities do together?

RL 32:01
So Duke had a reputation of being a difficult place, sort of a malignant atmosphere where there was a lot of one upsmanship. That was sort of the impression I got. And I think part of that was due to how hard people were expected to work. So when I was a medical student at Vanderbilt, we were on call every other night. When I went out to San Francisco, the call schedule is every third night, or every fourth night. And I thought, "Wow, this is great, this is like being on vacation" [laughs]. But at that time the only place in the country that was worse was Duke, because they were on call five out of seven nights. So So Duke had this history of, "You go to Duke, you'll get great training, but you'll work really, really hard." You know, you live in the hospital. And so when I came from San Francisco to Durham, I was expecting there to be a lot of competitiveness amongst the house staff and fellows and faculty and so forth. And I was surprised that there was none of that. That did not exist. Now the call schedule had changed, but I don't think it was just that. I think that there was a sense of community that I didn't appreciate before moving here. Now, maybe it's because Durham is a small town and so you can't really be a jerk to somebody because you might see him at a restaurant that night [laughs]. It's got that small town feel to it. So I have loved it here. And I think that that same sense of community that I felt at Vanderbilt, I share here at Duke also.

JO 34:30
I want to ask you a little bit about how your interests took shape in both your specialization and your research. What drew you to gastroenterology in particular? Were there specific experiences that you had kind of confirmed that that was your passion?

RL 34:55
When I was in medical school, I had worked in a biochemistry lab during the summers, and it was a lab that actually worked on reproductive hormones. So again, it was sort of endocrinology, if you will. And I knew that I wanted to do research. And for some reason when I was in the latter part of medical school I was drawn to clinical gastroenterology. And this was reaffirmed when I was doing my house staff training in San Francisco. Maybe it's because of the association I had with the GI fellows there, I just sort of meshed with them. I liked the work that they did. I like the clinical discipline. I like the personality of gastroenterologists for some reason [laughs]. So I thought it was a good fit. But I knew I wanted to do research. And so when I applied for fellowship, basically I ended up staying at UCSF. They had a great GI program, and so I stayed there. But I was interested in combining my research interests in endocrinology. Maybe it's because [with] endocrine systems there are these feedback mechanisms where these organs communicate with one another by hormones, and I just thought about the things in those terms. And at the time there was a field that was just getting started in GI endocrinology, so hormones that were being discovered in the gut, the GI tract. And so it was a brand new field for study. And it was facilitated by the ability to measure levels of these hormones. So there were two places in the country that were doing really good work in the area of GI hormones. One was the NIH. And the other was UCLA, where Mort Grossman and John Walsh were. And so I went to our division chief, I was now a GI fellow and I was in my first year of fellowship, and I said, "I think I need to transfer to another program where I can study GI hormones. And I either need to go to the NIH or I need to go to UCLA." And our division chief was Rudi Schmid, who was a

liver expert, and he was very authoritarian. He was Swiss. But he was Germanic Swiss [laughs]. So he would tell you what to do. So he said, "Come back and see me tomorrow." So of course, I came back the next day. And he said, "I want you to go work with John Williams." Well, I didn't know who John Williams was. I'd never heard of John Williams. So John Williams was the vice chair of the physiology department at UCSF, and he was a pancreatic physiologist. And so I go talk to John Williams, and I tell him my interest in GI hormones. And John said, "You know, I work on the pancreas, and the pancreas has receptors --abundant receptors -- for the gut hormone cholecystokinin, abbreviated CCK." At that time there was no good assay for measuring blood levels of CCK. So he said, "If you can figure out a way to exploit the receptors on these pancreatic acinar cells, you might be able to develop a bioassay for measuring CCK." So I thought, "Well, okay, that sounds like a good project. It's GI hormones, and there's no good assay, maybe if I could develop an assay, that would be a good thing to do." So I went and I followed Rudi Schmid's advice. I went to work in John Williams lab. And I spent two years remaining in my fellowship, working on trying to develop an assay, using pancreas tissue, for measuring blood levels of CCK. Well, fortunately, I was able to develop a method for extracting CCK from blood and I could incubate those extracts with isolated rat pancreatic acinar cells. And if CCK was there it would stimulate amylase release the pancreas normally produces. And you could measure amylase using a fluorometric method. And so the amount of CCK in the blood was proportional to the amount of amylase that was released. And you could calculate off of a standard curve, how much CCK was there. Well, fortunately, it worked. And every day, I would make pancreatic acini from a rat, and do these blood extractions, and do these incubations. It would take about eight hours to do the assay. And I would have the results of 20 samples at the end of the day. So I could measure 20 samples a day, 100 samples a week, spending eight hours a day making pancreatic acini from rats. Well, it worked. And as a result, we had the only reliable CCK assay in the world. But we could measure CCK in the blood of rats, and mice, and dogs, and baboons, and humans. And we could determine what CCK did, what stimulated its release. And what it does on different target tissues, how it stimulates pancreatic secretion, and gallbladder contraction, and regulates satiety, or food intake. So as a result of that I became an expert in CCK.

JO 41:40
Because you essentially invented a process for measuring it.

RL 41:46
Right.

JO 41:48
And so measuring the presence of the hormone CCK, to understand what it was up to, you needed to have some way of finding out how much of it was present in a particular area at a particular time?

RL 42:04
Yep. Most gastrointestinal hormones are stimulated by eating a meal. And so different proteins, or fats, or carbohydrates, may stimulate. So we determined what stimulates CCK cells, and what

causes levels to go up in blood, how long they're elevated, and what they do, and what CCK does. I'm still measuring CCK today [laughs].

JO 42:36
I read a bit about some of the more contemporary research, which sounds completely fascinating. I want to back up to something you said about gastroenterologists having maybe a particular personality. What is that personality [laughs]?

RL 42:58
Well, I don't want to say everybody's the same [laughs]. That would be an oversimplification. Nobody's ever asked me that before [laughs]. I think there's a spectrum. If you know any gastroenterologist, you probably have your own opinion. The people that I was working with, and I enjoyed working with, they were trained in internal medicine. And I think internists have a certain personality, but they also like doing things with their hands. So GI had become a procedural specialty, right? We do endoscopy, and that changed the specialty a lot. And so there were people who love doing endoscopy, love working with their hands. They have a little bit of a surgical mentality where they want instant gratification and get things done. But there is obviously a side of that where it's very disciplined, having to be very thoughtful in the way somebody approaches these diagnostic problems. So it's a good question. I don't know that I have a great answer for that personality.

[JO: Maybe another way to frame the questions is what character traits did you notice that drew you to gastroenterology?]

RL 44:38
I think they were outgoing. They were expressive. They enjoyed social activities.

[JO: I understand that you had a part in addressing gender inclusivity when you were division chief. Can you tell me about that effort?]

RL 45:44
I wish I could take more credit for having devised a fantastic plan and strategy. It seemed like a natural thing to do. The person who recruited me, Ian Taylor, had also recruited Joanne Wilson to our division. And Joanne had been a Duke student, and was then at the University of Michigan on their faculty, and she and her husband were recruited back to Duke. And so Joanne has been a very prominent physician in our division, since 1986 I believe is when she came. And I think she's been a beacon for attracting a lot of bright young trainees. And so as we expanded the division in the late 80s and early-to-mid 90s, we had fantastic applicants, many of them from Duke. And at that time there were more and more women who were being trained in internal medicine. So the pool actually was large. So we were able to select the best and the brightest. And among those were the best and brightest women around. So it just seemed like the right thing to do. We didn't have quotas, we didn't say we need to expand the number of women on our faculty. It was that we selected the best people. It's like football recruits, right? You select the best player, or the best player for a position. And we selected the best players. And we were fortunate that they were women. I don't know the exact statistics. But we may have had the most

women per capita of any GI division in the country. From traveling around and visiting other divisions, that's been sort of my impression. I don't have the exact numbers on that to prove it, but I wouldn't be surprised if that's the truth.

[JO: What kinds of conversations are going on currently about equity in the division?]

RL 49:00
So Anna Mae Diehl followed me as the division chief, and she's now been succeeded by Andrew Muir, and they have both done a wonderful job in advocating for diversity within the division. Andrew, some of his very first papers in the GI division at Duke have been on health quality and equity. Now it's a very topical thing to discuss. But he's been in this area for almost two decades now. And he has been very involved, as have a number of our other faculty, in bringing health disparities to the attention of the GI community. So it's clearly very important. But again, it's been sort of a natural extension of those individuals' individual work. So I think it's been, at Duke I think the GI division has done an excellent job, and has sort of led the way in some of these areas.

[JO: I know that laboratory research has been very important to you. I've never actually been to a medical research lab. If I walk into your lab, what do I see? Can you describe the space?]

RL 51:15
So if you walk into the lab, there are benches that are basically work benches that have a variety of things including chemicals, equipment like centrifuges, pipettes for dispensing liquid from one tube to another, test tubes. At one end of each bench, there's a workstation where an individual has a computer at the end of the desk where they can sit and write, where they have telephones available, although now everybody carries phones in their pockets. So that's on sort of one half of the room, and in another half of the room, there will be individual work rooms that may contain large pieces of equipment like centrifuges, refrigerators, freezers. If you take another step down the hallway, there'll be a work room off to the right that will house microscopes for doing imaging of largely cells and tissue material. We have a small animal surgery room where we can actually do operations on animals under anesthesia. And we'll have a series of work benches for different investigators, so that each student or fellow will have their own work area where they can do individual experiments. We use common equipment that is too large to house in any given lab, or too expensive, that are shared resources on the campus. And so we may have to actually go into another building where they'll have special microscopes, electron microscopes, and so forth that we share with other members of the research community here at Duke.

[JO: So what would I see people doing in the lab?]

RL 53:50
[Laughs] Hopefully, it would be full of people doing work. They would have to be socially distanced. So we've had to disperse people among the space that we have for that purpose. But what you would see would be people in various phases of research. Some people may be sitting at a desk, or they'd be doing writing, or recording results. Some people would be standing at the bench where they would be doing pipetting. Earlier in the morning, we would have somebody in

there who would be actually washing dishes, because we generate glassware that gets dirty that has to be washed. So that's an important position as well. We'd have some people who would be over at a microscope looking at samples under a microscope. And there may be somebody who was actually doing an operation on a mouse. And then at certain times, everybody stops their work and we all meet together to discuss the progress of what they're doing. That wouldn't be done in person anymore, even though we may have individual conversations, but we would have a group Zoom meeting where people would present their results and discuss ideas and so forth.

[JO: And where is the lab on campus?]

RL 55:17
We are now in Genome Science Research Building One, also known as the Snyderman Building, which is on the southwest part of the medical center campus. Our address is actually on Lasalle Street, which is kitty corner to Nosh, the restaurant, when people used to go there, when people used to go out to restaurants [laughs], actually very close to that restaurant.

[JO: What aspects of the research are you currently most excited about?]

RL 56:11
My lab's a little bit unusual, in that we work on two different areas that seem to be quite diverse. One is that we still work on GI hormones [that] are produced by what are called enteroendocrine cells. So those are cells in the gut that produce hormones. And so that work that I described, where we measured CCK, has really evolved into characterizing these cells. And we wanted to know everything about CCK cells. And so one of the experiments that we did a number of years ago was we had a mouse that expressed green fluorescent protein in CCK cells. So you could look at them under the microscope, you could look at the intestine under the microscope, and the CCK cells would fluoresce green. So we took an image of intestine and looked at it. And folks in the lab, actually it was Rashmi Chandra working in the lab, noticed these cells, which are normally triangular shaped, actually had a little foot process coming off the bottom of the cell. And she showed that to me and I said, "That's not supposed to be there, that little foot process is not supposed to be there, all the textbooks draw these cells as triangular shaped cells." But because she could look at these things with confocal microscopy, which means that you can see it in three dimensions, you could see what normally might be cut off because it'd be outside the plane of two dimensions. You can see these little foot processes. And at about that time Diego Bohórquez joined the lab, and Diego's job was to determine what that foot process was. What is it, and where does it go, what does it do? And he performed three important experiments. One was he did, the first time I think this was ever done, three-dimensional electron microscopy in the gut, where he developed a technique to find one particular cell of interest. Because of expressed green fluorescent protein we could see it by combining confocal electron microscopy in three dimensions, which is a new technique that was just being developed. He could look at this enteroendocrine cell in 3D. And he discovered that foot process contained many features like neurons. It contained vesicles, neurofilament proteins, abundant mitochondria. The second experiment that he did was to show that these cells would grow together. We had the impression that they were going to connect to nerves because they contain synaptic proteins, pre- and post-synaptic proteins and they had neurofilament. These enteroendocrine cells were like little nerve

cells, little neurons. They looked to be coming in close contact with nerves. To prove that they contacted nerves he did two things. One was he grew them in culture. He put an enteroendocrine cell in culture with a nerve. And the nerve grows towards the enteroendocrine cell. They grow together, they form a connection, which is pretty astounding when you look at the timelapse photography. And then he put rabies virus in the lumen of the gut. Now, rabies only infects nerves. But he showed that rabies in the lumen of the gut would infect enteroendocrine cells, and it would spread to the nervous system. Now, rabies only spreads through synapses. So with that, we were able to prove that these hormone cells are not just hormone cells, that they connect to the nervous system. And it provides a direct link from the lumen of the gut to the brain. So now you have a connection, whereby foods that you eat, bacteria in the gut, potential toxins, could be exposed to the nervous system through enteroendocrine cells. So we call this the gut connectome. And we're interested in what that does, and what that means for health and disease. Diego has done a great job, and has set up his own lab, and is studying how these cells sense nutrients and communicate those to the brain.

RL 1:01:47
We now are working on, I was interested in what this means for disease. And I thought this was how you got Mad Cow Disease. So, Mad Cow Disease is a prion disease. Prions were discovered by Stan Prusiner, who won the Nobel Prize in 1997 for prions, so those are infectious proteins. So you may remember there was an outbreak of Mad Cow Disease in the U.K., around 1999, 2000. Right around there, there was this outbreak. And so they had to kill off all the beef supply in the UK because people were getting this prion disease, Mad Cow Disease. And it was from eating infected meat. Through the infected meat these infectious proteins would get into the body, into the nervous system, spread to the brain, and people would die of that. So I said "Well, this is obviously how you get Mad Cow Disease." Because you would eat a prion-infected meat, it would get into an enteroendocrine cell and then through this connection the nervous system go right to the nervous system and into the brain. So I said I need to talk to Stan Prusiner about this. Stan Prusiner had discovered prions. And Stan was at UCSF, and I knew you know what was going on when I was out there with his stuff on prions. It was actually very controversial. So I think I can't just call him and say "Hey, I think this is how you get Mad Cow Disease." He'll think I'm a nut. So this is another reason why you work at Duke, I guess, because you have these opportunities. So I was thinking about this, and thinking about this. And I didn't know whether to call him. I said, "I need to talk to him about this." And then I'm walking by and I see this notice on the bulletin board that Stan Prusiner's coming to Duke. He's coming to give a talk at Duke. So I called Jim McNamara and I said, "Hey, Jim, I need to talk to Stan Prusiner when he's here." He said, "What do you need to talk to him about?" I said, "Well, I just need to talk to him." So Stan comes and gives his talk. And then I meet with him afterwards. And I tell him this story about how we discovered this connection between enteroendocrine cells and the nervous system, and that this provides a connection between the lumen of the gut and the nervous system. And I show him this video, where we've got the timelapse photography of enteroendocrine cell and nerve coming in culture together. They come together, they're connected by what we can now call a neuropod. And it's a dramatic video because you see this stuff happening, the cells moving and connecting. And Stan goes, his eyes get real big, and he goes "Wow." And I said, "Stan, I think this is how you get Mad Cow Disease." And he says, "I think you might be right." And with that, I'm feeling pretty good about myself, right? You know, I stick my chest out and I said, "You want

to work on this together?" And he goes, "No." I go, "What? What do you mean?" [laughs]. I said, "You won the Nobel Prize for prions, this might be how you get mad cow disease. You sure you don't want to work on this together?" And he goes, "No." And I go, "Why?" And he says, "When was the last time you saw a patient with Mad Cow Disease?" And I go, "Well, I've never seen a patient with Mad Cow Disease." He goes, "See? That's why nobody cares about this anymore." He says, "You want to work on Parkinson's disease." And I go "Parkinson's Disease? I'm a gastroenterologist. What do I know about Parkinson's Disease? And what does it have to do with this connection?" And he says, "No, no, no, no. There's evidence that Parkinson's Disease is a prion disease. And maybe it starts in the gut." So we started to work on that. And, it's kind of a long story. But we've discovered that the prion is actually a neuronal protein called synuclein. And these enteroendocrine cells have synuclein. And we've just discovered that they can pass synuclein on from an enteroendocrine cell onto a nerve. And it looks like it spreads onto the vagus nerve. So it's kind of crazy. Here I go from working on GI hormones to now working on a nerve connection, and Parkinson's Disease. So it's an hypothesis that we're working on, and we'll see whether that turns out to be true or not.

[JO: So what would be the goal of testing that hypothesis?]

RL 1:07:45
So our hypothesis is that there is an event that takes place within a neuron that causes synuclein to misfold. And it goes from a normal, safe form to a misfolded form that then can spread from nerve to nerve. So then it becomes a prion once it misfolds. And once it enters a cell, it serves as a template, so that the synuclein in that cell will then also misfold through this templating event. And the disease can spread that way. So our hypothesis is that perhaps the enteroendocrine cell is the cell of origin, that might be the cell where the initial misfolding event takes place. And there's a lot of evidence that certain environmental toxins can cause synuclein misfolding. And you can be exposed to toxins that you ate. There's evidence that the microbiome in the gut is abnormal, you have a dysbiosis, if you will, and that that microbiome can affect the pathogenesis of Parkinson's Disease. So maybe that microbiome interacts with enteroendocrine cells and affects misfolding. So that's our goal, is to determine whether the enteroendocrine cell is the cell of origin. And if it is, one can imagine that perhaps those events can be affected by diet, for instance. Changing the environment within the lumen of the gut, or determining how the microbiota in the gut affect those cells, and how that might affect that process. So there's a lot to be done. It's taken me out of my comfort zone because I'm not just measuring, you know, CCK levels in the blood anymore. I'm learning neurobiology. I'm having to learn microbiology. A lot of things that I never thought I'd be doing before.

[JO: I guess that's the nature of studying how different systems of the body interface.]

RL 1:10:19
So that's what one half of our lab does. The other half, we're working on pancreatitis. And that work came about because I thought that our work on CCK cells was not as immediately clinically relevant. So I said I need to work on a disease that my colleagues will care about. And well, every day we make pancreatic acinar cells, right? Why don't we work on the pancreas? We're pretty familiar with the pancreas. And there are basically two diseases of the pancreas. One

is pancreatic cancer, and the other is pancreatitis. So we decided to work on pancreatitis. So unfortunately, there's no specific treatment for pancreatitis. And so we're working on ways in which we can affect pancreatitis, and hopefully we'll be able to translate that to human studies before too long.

[JO: Is there anything else that you want to be sure to add to this record?]

RL 1:11:39
Well, we've covered a lot. I hope I didn't go into too much detail about the research that might not be as interesting to others. But it's nice being surrounded by bright, hardworking people who are enthusiastic about the ideas that you're working on. So that's what's made it all possible, and made it as enjoyable as it has been. But I think we've covered a lot. I do appreciate it. I think this is great. I hope that you do more of this, because I think having an oral history like this is a wonderful, wonderful resource.

[JO: Thank you so much for your time.]