

Harvey R. Colten
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Oral history interview in Chicago, Illinois. Harvey Colten served as a research associate at the National Cancer Institute and later joined the first section of the biology branch as head of the Molecular Separation unit. Interview conducted by Dr. Tibor Borsos.

Colten: You're not going to ask me any more questions.

Borsos: At the moment.

Colten: All right. I studied zoology and philosophy at Cornell, and went from there to Western Reserve. Cornell was in Ithaca. My undergraduate was in Ithaca. I went to Western Reserve, which was in Cleveland, and was asked during my interview for that a very important question that stuck with me forever. The dean of admissions, who was the sole determinant of who got in, was interviewing me. It was supposed to be a half-hour interview. It extended over an hour and a half, and I'll tell you why in a moment.

Borsos: What year was that, by the way?

Colten: I graduated from Cornell in 1959, so I was interviewing in the fall of 1958 for this position in the medical school. And he asked me during the course of that hour-and-a-half interview, was I trained or educated at Cornell, and I understood instantly. It was the first time I thought about the question--I was a young pisher--the first time I thought about the question, and I realized, for the most part, I had been trained. But then in a few courses, I had really gotten an education, and one of the courses that I took, an advanced zoology course, was very exciting to me because it was shortly after that time, and I was very... That course was one in which I really felt I got an education. It was shortly after the Hershey and Chase experiments that defined DNA as carrying genetic information, and the Watson and Crick model and all of this. It sounded very exciting to me. And the other area that I was educated in was in my philosophy courses, which I loved.

It was a fabulous philosophy department, with many of the famous Cambridge philosophers having come over to Cornell, but for the most part, trained. The reason it was an hour and a half instead of an hour is, they were undergoing an experiment in medical education, the first since the Flexner report, and it had been in place for about six years at that time. And I said, "So, how is it working?" And he said, "How would you measure it?" And then, as Socratic dialogue ensued where every time I suggested something, he would knock it down, and I would suggest something else, and he must have liked me because my record wasn't that good. I had failed German. The only course I had ever failed in my life, but I had not done well in that. It brought down my average. And this was an elite school, very difficult to get into at that time. At the end of the conversation, he said, "I've been a little bit unfair, because many of the things you mentioned we actually use, but we don't know what we're measuring. We don't know what we want out of this medical school, its heterogeneous product. We don't know how to measure success, but we try because we think we don't want to make changes without evaluating. So I went to Western Reserve, and that was a terrific time at that school. They had several Nobel laureates. The whole business with cyclic A&P was discovered at that time, second messengers, so they had outstanding science. They had this experiment in education going. And initially I went there thinking I was going to be a psychiatrist. They were strict Freudians. First lecture, Freud is the word, the word is Freud, and I said if I wanted to go to theological school, I would have done this, so I switched out of that. I decided I wasn't going to be a pediatrician because they have a program where you were assigned to a woman in their last month of pregnancy, and then you followed the baby for well-baby care, and I figured if you can take people as ignorant as we are at this stage, put them in the setting, there can't be much content to this field, and I switched.

Every course I took was, I was excited about, and actually did a little bit of research at that time, but nothing very serious. I encountered Lepow at that time, and he was in the Pathology Department and in the Department of Medicine and was a brilliant teacher, clear, became an advisor to me during medical school because what happened, as I moved along, it became obvious that I wanted to do something that combined clinical and experimental, science and medicine. I knew I wasn't going to be satisfied just being a physician. Intellectually, it wouldn't be satisfying. On the other hand, I didn't think that I wanted to go exclusively in the lab. I thought it would be a waste of my medical education to turn my back on that. And I didn't even consider at that time an M.D. - Ph.D. I might have done that later but didn't even think about it. They had a program there, but it wasn't in my consciousness. Moreover, Lee, who was my advisor by this time--informal advisor--didn't recommend it, so I didn't even have my mentors proposing that. The thing that really made me believe that I should have a serious time at the lab was reading the work of Charles Janeway. He was doing something...

Borsos:

Janeway?

Colten:

Yeah, senior, who was then the chairman of the Department of Pediatrics at Harvard, and in fact remained so for some 27 years. Later on I went to work for him. He became my academic medical hero from those papers. He was using the leading tools of protein chemistry. I mean, it wasn't so long before that electrophoretic separation of proteins had been accomplished. He used those in his early work to separate the plasma proteins and to analyze them afterwards, once those tools became available, and he got interested in immunoglobulins. And as a result of having access to these leading-edge technologies of the day, he was able to go into the clinic and essentially describe the compartmentalization of the immune system by virtue of analyzing these kids with primary

immunodeficiency. The observations in the kids which he and Robert Good's group went kind of back and forth describing also stimulated fundamental research because they began to define, by virtue of natural knockouts, so to speak, what the lesions were, and that began to provide a framework for additional studies. And it was that shuttling back and forth that I found so interesting and wanted to pursue myself. I didn't know what area I wanted to do it in. And, in fact, at that time, when I looked at the *Journal of Immunology*, I actually found it a very dull journal. It was dull, to tell the truth, for a long time afterwards, too. It was an archival journal that had a lot of stuff that needed to be published but wasn't really the most exciting stuff. That was appearing in other journals. But that was my principal exposure to fundamental immunology.

So, I had entered the Berry plan. Oh, I decided to do pediatrics because of this and got very excited about it, and actually antedated DiGeorge in identifying a child with a primary T-cell defect. This was not a child who had hypoparathyroidism. It was a child who, it's pretty clear, lacked T-cell immunity, and there was no clinical immunologist in Cleveland at the time. In fact, outside of Minnesota and Boston, there were very few anywhere. So I began to work this kid up based on the literature and Lee's advice to me and actually defined it. But the surgeon who was going to do--in those days, you had to do a skin graft from somebody to prove, something we couldn't do today knowing what we know, from somebody to the child to prove the child will accept the skin graft and not have T-cell immunity. The surgeon who was supposed to do that absolutely went crazy, literally went crazy, didn't show up for the procedure. The mother got angry. We never saw the child again. So I missed out completing what I thought needed to be done to do that study. But it was that that got me really interested in this. And I decided also to do pediatrics because,

although I was initially not interested in pediatrics, it was very exciting to me now because it had two things. One is, it allowed me to look at primary genetic disorders--I didn't know in what area--and to work them out with tools that were coming online at that time. I thought that was an interesting area. Second, it was kind of almost pure-culture medicine. These were kids usually with a single set of problems or a single disease state, and acute medicine didn't involve the kind of complexity, and therefore you could both have some positive impact if you could resolve the problem. You had lots of life ahead and productive life ahead, but you also had something that could be intellectually teased apart in the way that a simple experiment could be dealt with. And the final thing is, I liked the kind of direct honesty of these children. By and large, they had not learned to cover up all the things that adults learn, and in a medical setting, this made it a much more satisfying thing to me to do. So I decided on peds. And I signed up for the Berry plan. The Berry plan at that time was a system whereby you could assure completion of your residency to get your specialty training, and then you would go into the military for a period of time as a medical officer, but now as a specialist, not as a general medical officer. And the draft was deferred for that period of time that you were training and you paid them back year for year. So if you had a three-year residency, you had three years' military service, and then you were finished except for reserve status. In 1963, when I signed up for this, the military accepted me, no problem. They wanted pediatricians at the time. By the time of 1964, when I was applying for the NIH, a position at the NIH, and Public Health Service appointment, I had to get permission from the Berry plan to get out of this, and they gave it to me because they had too many doctors. Within a couple of years' time the Vietnam War heated up, and they were drafting people right out of their residency, Berry plan or no Berry plan. They needed general medical officers. So I missed by a

couple of years actually ending up in Vietnam instead of the NIH. I was actually toying whether to go to CDC or the NIH, because I was also intrigued with applying these technologies to epidemiological things, particularly in infectious disease, and an opportunity, because of the formation of the Child Health Institute, came along. It was an institute that, when I went to interview, was receptive to a lot of flexibility in the assignment. I didn't understand they didn't know what the hell they were doing, and this is why they were so flexible. And they weren't so cocked up, as it turned out later. They gave me, they offered me a position, I accepted it, and it wasn't clear what lab I was going to work in, but they said, "You could pick any lab you want." Next thing I know, after agreeing to that, two or three months later, maybe it was four months later, but well before I was supposed to arrive in Bethesda, sometime in the winter, '64-'65, I get a call from a guy at the Child Health Institute who's in charge of the Laboratory for Mental Retardation Studies. And he says, "Congratulations. You've been assigned to me." And I said, "With all due respect, there must be some horrible mistake." He said, "Why?" I said, "I have no interest in what you're doing." I mean, I told him that by that time I had been taking care of patients with acute leukemia, I was intrigued with the therapeutic advances that had occurred. Sidney Farber had introduced chemotherapy, changed the outlook for children with ALL, acute lymphocytic leukemia, from about three months' average survival after diagnosis to 18 months. That pales by comparison to today, where half of all the children with this disease are completely cured and the other half have very, very long remissions, and some of them indefinite but with problems. But it was a step; it was a major step, and it clearly was an advent of a new era in the approach to cancer. I was attracted to the biology of the problem, and also to the rare experience that I had had that a lot of people didn't, that in fact I thought made me able to help the

families. Many, many doctors, and particularly young doctors, would run away from patients with fatal diseases and their families and were unable to deal with it because of their own feelings about it, and it seemed to me that was precisely the time that a physician could do something very positively. Even if you couldn't do something about the disease process itself, if we didn't have that knowledge, there was a component of that compassionate care and helping somebody deal with this and understanding what their choices were and how to make those decisions that I could provide. And I think it was because two of our babies had died one of sudden infant death and the other in respiratory distress of prematurity. The first baby we had a very close emotional tie to, Sue and I, because the baby was home and very much a part of the family. The second baby was in the hospital and Sue had the emotional attachment to the baby; I didn't. And I think the death of that first baby in particular made me confront my own mortality at a much earlier age than I might have ever thought about it, and also to empathize with a parent who's about to lose or does lose a child. And I had also passed through a period, the only anxiety attack I've ever had in my life. Not long after that baby died, I'm sitting in a lecture in medical school. Lester Adelson, was the medical examiner or coroner--I don't remember which he was--of Cuyahoga County. And one of his major interests was sudden infant death syndrome. He turns out the lights, flashes up the first slide, and that's a baby, a little baby lying on a big autopsy table, and I'm sitting there in the dark, heart pounding, sweat pouring off, thinking, "He's going to show my baby, and I don't know how I'm going to be able to handle it." I decided that I can't get up and leave. If I get up and leave, I'm never coming back because I won't be able to separate these very powerful feelings from my professional responsibilities, and I'm going to have to sit it out. Fortunately, my child didn't come up on the screen and I was able to

control this before the lights came on. I was now composed again. And I really had done a lot of thinking and emotional work to deal with this. So I got interested in tumors and, as I said, I was interested in immunology, partly because of Janeway, partly because of Liebhausen [sp.] influence, partly because of these kids that I was working up, one of whom I think had a pure T-cell problem but never finally proved it. So I told this character that I didn't want to do that and he'd better get me in touch with whoever can make some change. So the guy who--I think it was Duane Alexander, who was still there, but I don't remember. Somebody was in charge who also didn't know much about what was going on. But I called him and said, "Look, there's been this mistake," and he said, "It does sound like..." Both of them agreed it sounded like there was a mistake. Well, the only lab they knew to send me to was the Rapp and Borsos lab because they had already sent Mike Frank there, and that seemed to have worked out all right. And Mike had been in the Child Health Institute, had come to you guys, and so they suggested I come look at this lab. What I did then was go to ask Lee what, whether I should go there and should I go to look at this lab. And I didn't know anything about the immediate preceding horrible fight that you and Lee had had, this public fight, intellectual dishonesty, all the rest of this stuff.

Borsos: You, meaning Borsos.

Colten: Yeah, right. I didn't know about this. But Lee said not a word about this. He said, "Go look at it. Come back and talk to me when you're back." I went there. I interviewed with Herb, who was as enigmatic as ever. I couldn't read him, but he seemed okay. And then I met you initially, you, Tibor, initially when you were in the lab, and you were flicking some tubes, and you said, "It's lysine, it's lysine, look at it, it's lysine." I didn't know what the hell you were talking about. But I did know that there was a kind of excitement in your approach to scientific discovery, that it was

interest... I read some of the papers that you guys had published. They looked very serious and very; I wouldn't say that they fit the bill in terms of my interest in applying immunology to tumors, because by that time there was nothing essentially from the lab on that subject, although later on it became part of the lab. But it was a goal, and Herb outlined that, that you guys did want to do that, you were in the Cancer Institute, and you wanted to do something about that, and you were studying cell killing and therefore that sounded attractive. But it was mostly the excitement with science that you transmitted that convinced me it might be a good lab to come to. So I went back and talked to Lee about it, and he said, "Go there, and you will get extremely rigorous training. You will understand the science. You will be able to do science if you go there. And then when you leave from there, you will be a well-educated and well-trained scientist." So I said, "Okay," and I signed up, and you guys were free to take me. Little did I realize almost any schmegagy [sp.] could get in at that time because the lab was very new and it was just beginning and, you know, there were, there was a huge influx of people at the time, and it was a beginning of the lab, and also, it was lucky for me that that was so because I didn't have an extensive scientific background. I really got my scientific education in the lab, in your lab. So, that was that. I had a position. Child Health was going to sponsor me there. It was no skin off of your butt. You had an extra pair of potentially useful hands, and, if not, it didn't matter. Coming into that lab was a phenomenal experience. It was very, very disconcerting. I was a fantastic house officer. I was a resident who people called on both for content, for technique, for all kinds of things. I really was very competent at what I was doing and I felt comfortable and confident about it. I came into the lab and I had the anti-Midas touch. Everything I touched turned to shit. I couldn't get anything to work. Everything was, you know, I'd do a simple thing and it would

work, and then it would fall apart, and it was the usual stuff that happens to everyone when they first come into the lab and sometimes even happens, as I learned later on, even after you've been in a lab a long time. You can run into one of these dry periods. But the first time, you never know whether you'll emerge from it. If you've had success and you run into a dry period, there's a sense of having been there before. You know you've at least been successful, and if you've had more than one success, then you know that that wasn't just a flash in the pan, that the downtime is going to eventually clear up and you're either going to drop that subject because you can't solve the problem with whatever you know; you can't think about it or you don't have techniques to do it; or you'll never deal with it again. And possibly you'll come back to it later, but usually not. But there's a different thing when it's the first time, and I just was going nuts. I'd got onto something that Herb was interested in, after a little bit, though, which he was interested in looking at lysis of nucleated cells. And he thought that it would be nice to use conductivity as a measure, lysis at the residual cells, look at the salt content in the lysate, and therefore measure the lysis. It turned out I worked a lot on this, but it was a totally impractical method by comparison to the then-prevalent methods, both trypan blue and beginning radio-tracer type release methods, which both of you pooh-poohed as being horrible methods, and it turned out they were perfectly adequate for getting a lot of scientific things. They weren't precise, but I learned another principal there that you guys should have understood about that, too, and that is, you don't weigh a crowbar on an analytical balance. You didn't need an analytical balance for what needed to be done in nucleated cell lysis. But I think it was still the influence of Mayer [sp] that made her reluctant to accept any other method than *the* most precise method for getting a Y in the equation, 1-Y, meaning the fraction of cells remaining after lysis. So I was toiling away with this

problem and we were making little things that looked like David Wolf [sp.] or Wolper spiral conductivity cells, and then I had an idea based on doing hemocytometry and made the most sensitive conductivity cell that could be made, and it was so sensitive that the CO₂ in the air caused a change in conductivity. The conductivity would drift up as CO₂ would be dissolved in the deionized water. We had this method going very well and used it to do something that, in fact, if you look back at those old papers, there were some things that we discovered in the course of that that turned out to be very important facts later on but didn't appreciate because it was such a cumbersome technique and it was hard to do. The only useful thing to come out of that was a subsequent study that we did in which a direct comparison of the number of molecules required to lyse a nucleated cell and a red cell was done, and it was very clear from that, it was many more molecules of C1-fixing antibody that were required to lyse the nucleated cell, and that was a very nice paper--I forget the year we published that, but you can get it from the CV--in which that direct comparison then unfolded with a lot of work that you and Harry and a bunch of other guys did later on. Parenthetically, there was another bit of work when Alan Baker came and Bill Shipley, I think it was, where we were looking at DNA in nucleated cells lysed with complement. And I've looked back at that, too, because it's obvious it was the same thing as apoptosis of cells. The same kind of DNA cleavage was occurring in those cells that were lysed by complement as we see with all of these other things. So we were looking at that and didn't understand what we were seeing. But those techniques were used in that set of studies, too.

So, I finished that work, but in the course of it, one other very important thing happened. In the lab, at precisely 11:30, everyone went down to have lunch. Some guys later avoided that, like Hal Churchill, because he

couldn't stand being at lunch. He was attacked so often, it was--gave him indigestion, I guess, and so he often didn't eat there. But at that time I was going down to lunch, and I did for most of the time that I was there.

On one day, I had been having lots of trouble reproducing this method, and Herb said to me, "Okay, after lunch I'll sit down with you. I'll do the experiment with you," and this wasn't long after I'd come to the lab. And I was so uncomfortable from that. Was he doubting that I was telling him the truth that it was irreproducible because he was so invested in the method working? So we're talking about Herb wanting to do the experiment with me in the afternoon. So, one of the possibilities was that I just was so incompetent that I couldn't do it, or whatever. It was just such a departure from those days where I was competent and I was, you know, it was another example of the anti-Midas touch. So, instead of going down to lunch, I sat up and sulked. As it happened nobody else was there. Herb had gone down to lunch at 11:30 himself. You're supposed to go to lunch at 11:30 whether you're hungry or not. And I sat there sulking all this time, and I finally decided, "What the hell am I doing? I'd better go down and talk to Herb about, you know, what's bothering me. I'm going to have to work with this guy. I should not let this fester." I went down. He's sitting there alone, and I told him I'm sitting up there sulking and what was bothering me. He said, "Well, that's tough shit!" He said, "I have one job and one job only: to do good work, and lots of it here, and if you don't like that, you can go to Thule Air Force Base, you can get out of the Public Health Service. I'm going to do this because I've got to find out what's going on here, and if I don't find out, I can't find out just by asking you. We've gone through this for several weeks now and I've got to find out." I said, "Okay." So we went upstairs after lunch, and I had mixed feelings. Of course I wanted him to solve the problem there, because it was driving me crazy, too. It wasn't only driving him crazy.

But if it was so easy to solve it, I would have felt bad not having solved it myself. And it was with very mixed feelings that we found out his was also irreproducible. He couldn't get replicates that agreed any better than I could. And there was something fundamentally wrong with the conductivity cell we were using, some aspect of the technique, and we had to go back to square one and fix it. So we finally solved all those problems, got it to work. I actually made a mistake the early part of that experiment that made me think that the number of cells we were looking at was tenfold smaller than we actually needed for the assay. Another reason why we should have abandoned this, it wasn't really a good method. But it just required too many cells and therefore was only good if you add a transplantable tumor, ascites form of a tumor or something else. We had zillions of cells. It wouldn't be useful for the ordinary studies that one wanted to do.

Borsos: What kind of nucleated cell did you use at that time?

Colten: EL4 cells and a number of mouse tumor cells that were in ascites, passaged in ascites form. They were convenient. You could get 10 to the, multiples of 10^8 , sometimes as many as 10^9 cells, and you could easily do all the experiments you wanted. So that was a convenient cell line. So we fiddled with it, finally got it to work, and published this paper in the JNCI as a brief communication for the method. It was a ridiculous first paper, actually, when you think about it, but I had another defining experience. Herb told me to write up a draft of it. I did. I came in, he took a look at it, he threw it in the wastepaper basket and said, "Okay, now let's start working on it," and then he wrote the paper, basically. I never quite did that with any of my people, but I was merciless, too, in the rewriting and got to be well known as the terror in Boston. But I think it paid off. The papers were better written after doing that, most of the time. There are a couple of exceptions, and I'll mention one classic one where a lab timer

was thrown across the room by you, smashed to smithereens as we were arguing, and I'm glad you thought of the guy's name, Jim Horton [sp.], because he was sitting there terrified that the two of us would [?] him. That was much later on. Anyway, what happened was things started to work. I got interested--I'd been reading some stuff, and I got interested in where complement was made. Not much was known, as it turned out. Certainly no modern studies had been done of the biosynthesis of complement. And I got very interested and by that time had been through the six months of, you know, agony of seeing things not work and understanding that you had to be able to follow the protocol exactly. It wasn't cooking, it was really much more precise attention to detail, and to know the difference when you could be sloppy, so to speak, when the precision of something was less important and when it was important, so that you actually, when it counted, you could actually be as precise as you had to be. And I also understood, partly from watching your style of working there, the value of the rough-and-dirty experiment, to know, before you've invested a huge amount in something, whether the general principle was correct, what's called proof of principle in the pharmaceutical industry now, but really is an important value. I mean, I saw Hal Churchill. Poor Hal Churchill seemed to be succeeding at the beginning when I was having all of those troubles, but he was succeeding and following an artifact. It was a fundamental problem. He didn't have the rough-and-dirty experiment to show that what he was following all the time was really a will-o-the-wisp, and he must have spent the first 10-11 months of that year on a project that was dead and should have been seen to be dead. And in a way, that was more Herb's style than yours. Herb, when he gave a project to somebody, didn't really have--he wasn't in the lab anymore. He didn't have a fingertip feel for whether it was going to work. He didn't have the preliminary data that said, "This is a doable

thing.” Something that I did when we first did cell-free biosynthesis, when I was in Boston, I came in on Saturdays and Sundays, and I did those experiments. I wasn’t able to get the concentrated time during the week to do them, but I did them, and that’s why, when I finally turned that over to a graduate student, I knew it was going to work. He improved the technique markedly, and he’s the one that identified pro-C4 and uncovered the single-chain synthesis products of many of the complement proteins that were then pro-synthetically cleaved to make multi-chain proteins. And he did beautiful work. But I knew his project was going to work because I did the same thing that you did with these guys. And Herb didn’t, and he was supervising--Hal and you were supervising my work primarily, although, as it turned out, Herb took credit for them as well. And just before I left, that became an issue, too. So things started to work. I began to study complement synthesis, for no good reason except it was seen as the first component. I started with C1. And I decided I wanted to try a technique that had been applied to the study of single-cell production of antibody to complement production, just turn it around. You sensitize cells in a reagent for lysine cells lacking a complement protein. And much later on, that did work, but I got sidetracked because you had done some studies before with Kenny Pillemer and you said, “Take a look at this, because I think that it made complement.” Well, it looked like it did make complement and, in fact, does make complement. Those studies, when I look back at them, were technically not optimal. They weren’t as good as they could have been, but for their time maybe they were okay. Guinea pig gut was opened up, washed, put in a water bath, with not optimal nutrients. I mean, these nutrients didn’t keep the cells in the best shape, so all the experiments were short term. But they were enough to demonstrate, both by activity and by incorporation of radio-labeled amino acid and by blocking with inhibitors of protein synthesis that a C1 product

was being made there. That actually led to a lot of side issues. Asano [sp.], this complete dodo from the point of view of science, who came in along with the yellow parade crowd, did some experiments with assembly across species of C1 subcomponents, also showing that you only needed C1 and activated C1S. The C1R was no longer necessary. A lot of interesting experiments came out of the technical aspects of that first set of experiments. But that kind of launched me, and I then went on to do human gut, which was very important because my previous advisor--and I'm skipping way ahead in time, but it's an interesting aspect of it that says that the science is anything but all rational, that there's lots of emotional stuff involved in this. I had decided, when offered an opportunity in '67 to stay on, to stay on, and I told Lee that, and he refused to talk to me after that. It was--he was merciless. I would see him at meetings, walk right past me. I'd say hello, he'd say nothing. He was furious with me. It was okay to go to the enemy for training but not to stay with them. And he still harbored some bad feelings about the fights that had long antedated my coming to the lab.

Borsos: Verbal fights.

Colten: Verbal fights, yeah. But long antedated my coming to the lab and had to do with the whole system and a fight really between players that really didn't even include you and Lee, but there was loyalty to your respective mentors. And it reminded me later, when I read the history of the work in the Metchnikoff and the Ehrlich laboratory, when they were talking about the origin, the cellular origin of complement, Metchnikoff said it all came from macrophages, Ehrlich said it all came from the liver, and for 15 years their guys showed just what their bosses said was right. It turned out both of them were correct, and neither would look at the other one's data or look at it in a rational way because it got to be a fight rather than an intellectual exercise. That became clear to me from that really awful

experience at being shut out of the life of this guy, who was formerly a very important mentor. That was resolved. The thing that triggered my thinking about it, that was resolved following my presentation of the biosynthesis of human C1 by human gut at the complement workshop in Boston in 1968. And Lee wrote me a letter afterwards saying that. And I had the first paper on the program. That--we were up in the Library. About a hundred people attended the meeting total. And he wrote me a letter about how beautiful the work was and how proud he was of me and how he was glad that at some point in my life he had had some influence on getting me into this field. And from then on, we reestablished a very close relationship that continued till the time he died. In fact, I was at a small meeting that Fred Rosner and I had at the--I forget what club it was at. It doesn't matter. It was one of the nice old clubs in Boston--St. Botolph Club, it was, for Lepow when he was near to death. He had an indwelling catheter, which he was receiving medication for his tumor. He had lost enormous amounts of weight. We came there, people that had worked with him at one time in our lives, and presented some current science and had a nice dinner. Fred arranged this beautiful setting and the event, and Lee was magnificent there. He just talked about the future of what the meaning of this and what kind of experiments downstream. He didn't once--nobody talked about how awful he looked or how soon it was that he was going to die. It was a very, very powerful experience. Marti Lepow, his wife, was there. I can't remember who all was there, but, you know, Chester was there, Fred Rosen, I was there. And a number of people who were with him in those old days in the Pillemer lab, too, were there. And I had a chance at one of the mini symposia at FAES [?] following this dinner, the next spring, to give a short eulogy because I was chairing the session and somebody asked for me to make a comment about it. And I actually have a copy somewhere, stuff that I wrote, if you ever

want that. It was what I said. It was a--I mentioned that particular event because of the relationships that were revealed were very important. So, back to the lab there. Things went pretty well, and then--oh God, I forget the guy's name but we'll get it from the CV again, who did the first work on C2 synthesis, and there the macrophages made a hell of a lot of the C2. Later on, many studies thereafter, that methodology was exploited and I spent a good bit of my career first studying biosynthesis, then genetic defects, then the molecular biology of complement and then molecular genetics of complement as a result of those things that I learned in the lab. I referred earlier to this thing of Herb's and authorship, and there was a paper that you and I had worked on, Herb didn't even know about. I think this emerged--I think this paper was the one on temperature effect on C1 affinity for immunoglobulins by GM and IGG class, but I'll look up the paper. I think that's the paper that caused this problem. I had shown him, as the branch chief--it was after he was already branch chief--just as a matter of courtesy because I thought anything that came out of the branch should be seen by the branch chief, and he said it was a very nice paper, and it came out with only one correction, and that was he stuck his name on it. And I got pissed. You talked me out of making an issue because I was going to be leaving. Had I stayed, had I been contemplating staying at the NIH at that point, I would have made an issue out of it because I think there was a point there where this business of the two of you always publishing things together had some value for the two of you, but with other people coming into the lab, it was a major impediment in attracting people who were going to have long-term collaborative relationships with either one of you. You guys were diverging in your interests, and it's my view, not even in retrospect then, I thought, should have been separate, some things together, some things separate. In fact, the thing that made me decide to go to Boston ultimately was not only the excitement of what was

going on there with Charles Janeway and the chance to work with somebody who was a distant hero, but it was a conversation I had with Fred in Building 37, when he came to tell me that Janeway wanted me to look there, and I was close to deciding and Fred said, "Look, if you come, you'll be in the lab on my floor, but I want you to understand, what's mine is mine, what's yours is yours, and what's ours is ours." And he said it spontaneously. He didn't know I was right at that time having a big fuss with Herb over this. So that was an issue that I saw emerging as time went by in the lab. Other things about the environment: It was a very tough environment. One of the things that, just by nature, I'm getting dumped on if I think I'm wrong, "Okay," I'll say, "I'm wrong," but if I think I'm right, I'm going to fight back. Also, even if I think I'm wrong and I'm being attacked, not discussed, I'll fight back to get it. And that was fine. In that environment, I think that was appropriate. I think anyone who didn't do that was quite miserable, and there were many miserable people who came through the lab who couldn't tolerate the environment, which was for the most part, correct, but even when wrong, was equally vicious. There were most--it was, on balance, more right than wrong, but I don't think there was a ganging-up on people who, even if they had a point to make, got suppressed. And I think that hurt in terms of some of the diversity of input that could have been in the lab that otherwise was lacking. That's another example of how I think. Had you or Herb had some separate components, it might not have been quite the same because it wouldn't have been that kind of... It was a very bad time in the lab while I was still there, and that was when you were writing the book. I think the lab--Herb neglected the lab altogether during that period. He wasn't in that lab, he was somewhere else, and you spent most of your time with him writing the book, and it took longer than anyone imagined it should have. Although I think the product was good, I think it was not an

efficient process, and it also ended up really hurting the lab's reputation as the place for trainees. Up to that time, lots of people thought that it was a great place to be a postdoc. And some good people came after that. But I think it actually hurt the lab's reputation in--no pun intended--in places like Boston, somebody like Alan Baker [sp.], who went back for a while, and others who, places that could supply very high-quality trainees, and that many labs benefitted from at the NIH during a time when the shuttle between places like Washington University, like Hopkins--well, Hopkins not as much, but the Boston ones, because Hopkins thought it had everything. It was an arrogant place. But the Boston guys knew that you sent people to the NIH to get rigorous training, and they'd come back and be much better clinician scientists, or you sent them over to MIT later on when the MIT, when the Whitehead was established, that you sent people away. Hopkins didn't do that as much, but many of the great medical schools--Dallas Southwestern--got guys shuttling back and forth and built itself as a result. I think your lab started to get a reputation for not being a good place. I loved it because the environment was stimulating. I thought it was very productive for me, and I saw a lot of people around me productive. It was interesting. I got immersed in the killing of the cell more than the tumor itself, so the target was no longer important, and then none of it was important except where were all these interesting proteins being made. And so I--when the opportunity to go to [?] laboratory for a kind of sabbatical time and then come back came up, I really was attracted to that because that was now back to something more akin to the immunochemistry that you guys had started out with and would have rounded out a different viewpoint. And I was seriously thinking of going there. But it became clear to me, if I didn't finish my pediatric training; I was never going to have the flexibility of being in a clinical department if I ever wanted to. So it was a choice between those two, and I decided,

because I was offered the opportunity to continue working in the lab and be a resident and be, turns out, their only clinical immunology consultant, that I'd do that because I could kill a couple of birds with one stone. I went back and did that and learned another lesson. That was when Joel Spalter [sp.] was in the laboratory. He was doing a set of experiments which the preliminary kinetic data to establish this method, he made a fundamental mistake. I was not close enough to the lab to see it till I came back and saw what the problem was, and everything--all the data were not at endpoints, so we had to go back and redo all those experiments that had taken him six months to do. We were able to do it in two months because we knew what needed to be done, but nevertheless, it was obvious to me that you couldn't do really brand-new work while you were away. You could only do fill-in kind of stuff where you already knew what the overall picture was.

Borsos: At this point you already had the chance to have your, not your own postdoc, but you certainly were in charge of some postdoc work.

Colten: Yeah. I was in charge of Spalter and I was in charge of Baker.

Borsos: So you were...

Colten: But even there, even there, it was a tricky thing because there was a tradition in the lab that everyone--you and Herb were supposed to put your name on everything, and there was one paper that I published without you guys, but it became obvious that establishing an independent career in that laboratory would never happen. I was known by that time because I had carved out an area that I was interested in that hadn't been part of the lab before, but it was also clear that for me to follow my own career without getting bound up in the controversies, there was no way I was going to it if I stayed there. But I was still not thinking about leaving when Kimmy Ishazako [sp.] approached me. He was putting together a group. Chris Henning was going to be the cellular guy. He wanted a complement guy.

He and--Terry was going to continue doing complement, but she was already drifting away from that, and he certainly was not doing that. The downside was--there were several downsides. One, it was in Baltimore and Sue didn't want to go to, pretty scuzzy. It was not right at the medical school campus; it was at the Good Samaritan Hospital. The pediatrics chairman, Cook [sp.], didn't think immunology was a discipline that belonged in the pediatric department. He was building a great neurology, pediatric neurology group, but he didn't think immunology belonged there and Kimmy was in the Department of Medicine, and E. McGee Harvey [sp.] was willing to give me an appointment there, but I needed a peds appointment. There was lots of negotiation. And in the meantime, you and I met Fred Rosen for a cup of coffee, and you raised the question about whether I'd be interested in looking in Boston. As I said, this conversation convinced me to go look. I went up there, and it took me six hours to decide I was going there, no farting around. That's what was going on in Hopkins. I told Fred, who was driving me somewhere. "Fred, tell Dr. Janeway I'm coming. We'll work out the details later"--no negotiating. But Fred persuaded him to match the Hopkins offer in terms of salary and whatever startup, and I went. And I went in the fall of 1970. I think Lee was absolutely right. I learned something about science, I learned something about the passion for science as well as the actual conduct of science, and it was an invaluable experience. I think my science education was, in that setting, not broad enough. I think had I done a Ph.D., I would have had more breadth. But my focus allowed me to get work done at the same time, and so my education took a lot longer in science. I gradually did learn a lot of other things in science. But it took much longer than had I gone for formal study. And I might have done that at that time, when I was at NIH had the NIH offered a degree and the kind of coursework. It certainly had the

talent to give it. And I think it was a mistake for the NIH not to do that at that time. It would have been a very valuable resource at a time when the competition from extramural institutions would have been much less, particularly for M.D.s who wanted to get a Ph.D. degree. It wasn't the union card so much as the breadth of scientific education. And I alluded to this fight we were fighting about whether they'll organize a table with more vertical than horizontal, and you and I got when we were writing up this paper with Jim Gordon [sp.], and the three of us were sitting in this crowded office. We were in the Auburn Building then. We had that horrible man, that technician that convinced me that long-term, I would never stay at the NIH. We always had plenty of money, but once an incompetent got in, it was almost impossible to dislodge them, and this man was such an idiot. He needed to be removed, but I was convinced, after investigating later on, what it would take to remove him, that we'd spend six, eight months of paperwork and still the conclusion might be that he would stay, so I told him first to just sit there, and then later I told him, "Don't even bother coming in," because he was really a space-occupying... He was terrible. But we were sitting in that room and we started arguing about this, and you picked up--you, Tibor--picked up one of those gray timers, threw it against the concrete block, it smashed to smithereens. You yelled at me. You said, "Well, if you don't like this, you can get the hell out," and I said, "Okay, I'm going." And Jim Gordon [sp.] thought we were going to turn on him. He thought we would kill him. And we should. He was such an idiot. But, anyway, we finally resolved this serious question about whether the table ought to be organized horizontally or vertically in order to show the ident... We weren't arguing about the data, just how to display it. I guess you can argue that violently about trivia. If it's really important, you have to have another way to resolve it. So, you asked about the general environment and

the interactivity with other groups. My earliest recollection, when John Fahey and Bill Terry [sp.] and all those guys were connected with the lab before it became a branch, and we were still in Building 10, there was almost an aggressive defensiveness on the part of the Rabson-Borsos lab, so that, you know, jokes about the chain gang and all the rest of that, they were doing decent chemistry on immunoglobulins. You didn't like that they were dealing with myeloma proteins. Those weren't antibodies. It turned out they were antibodies. We just didn't know what the specificity was of those. And I think the Rabson-Borsos laboratory was somewhat isolated from the mainstream of immunology at NIH because of that kind of aggressive defensiveness, a mocking of some things that were outside of the strict, old-time immunochemistry that, in fact, were improved upon later. They weren't fully formed at the time, and the criticisms were correct, but I think the criticisms were done in a way that cut off discussion, didn't promote it. I think the NIH also lacked formal mechanisms, then, for training in and for education in areas apart from the ones that were required by law. For example, I took the radiation safety course because you had to. It was a good thing. I mean, that's how I got certified so I could handle radioactive stuff. Even later, wherever I went, that always stood me in good stead. But there were things--there was the emerging stuff in molecular biology. In fact, the code was being worked out in Marshall Nirenberg's lab at that time at the NIH, and there were no offerings. There were--later on, there were clubs formed and interest groups that got together, but very little of that was going on, and it was a pity. It was also a pity that the other academic institutions in the city had the same attitude. They didn't want to have anything to do with all this talent at the NIH. I tried to get those people to invite folks from the NIH who were doing interesting work to at least come and give seminars, but they were intimidated by it. They didn't want visiting professors from

NIH at these places, by and large, because they were big fish in very little ponds, and I think the academic institutions in the Washington, D.C. area suffered as a result of that. There was spectacular science going on in a lot of places, but there was, because of the richness of equipment, you didn't have to see these people, and often parallel investigations of identical things were going on side by side, banks of centrifuges sitting there in Building 10, unused most of the time because each person was able to purchase equipment but couldn't hire people or get rid of incompetent people. So they substituted for it by equipment, not always labor-saving equipment. In other words, that might have been okay if robotics was stimulated by it, but it wasn't that. You'd just buy whatever gadgets were around when you saw you had some money left in your budget at the end of the year. Otherwise your budget would be cut, the usual sort of ridiculous budgeting of government. I think of all government agencies, it probably was the least offensive in terms of the bureaucracy, but it still had plenty of it, and there were things that were inhibitory of that. I don't regret being there during that time. I think it was, on balance, a terrific experience. But, as I say, I think the environment could have been more conducive to the cross-fertilization of ideas. And I found that even though Harvard has a reputation for similar kind of, you know, silos, separate silos and isolation and conflict, I found much more interaction there than the NIH, and even more so at Wash. U. when I got there. And I don't think it's simply a reflection of my status at the time, although that does influence it, because I saw other people at junior levels interacting in those environments in a way that showed a very different progression. It may have been a different time, but I think it also was a product of the system. For example, at Harvard, it was big and there were lots of opportunities to just go to your own bunker and do your work and forget about the other guy, every now and then lob a missile at him. At Washington University,

it was a smaller place, much more necessary to do some things cooperatively because you couldn't afford to duplicate things the way you could at Harvard and even, to a greater extent, at the NIH. So sometimes too much of a good thing can inhibit the kinds of productivity that come from people from different fields asking "naive" questions. You know, they come at it without all the assumptions and you actually sometimes end up collaborating. I began some collaborations in Boston because I ran out of a reagent that a guy on another floor had been using, and so I went and borrowed it. We started talking about what we were doing with it. It happened to be cyclophosphamide [unclear]. We ended up doing a collaborative study. A nice JCI paper came out of that, and a lot of productive talk about our respective works. I think I understood immediately that pro-C4 was pro-C4 when it didn't make sense that it didn't dissociate under reducing conditions because this guy was working on insulin and he was looking at hyper pro-insulin anemia, and although I knew about pro-insulin, it was the only pro protein that had been recognized when we first did these experiments. Just having it talked about on a regular basis made me think about, right away, how I didn't have to dig it out from another place. So NIH could have benefitted from that. I think the fact that we moved a lot--the lab moved from place to place--wasn't really optimal for us, and, frankly, I think when we finally ended up in the NCI building, in 37, it was not as good for us as when we were in Building 10. We were much closer to those guys. It may have been better for you, but for the rest of us it was more isolated.

Borsos: Do you think that the fragmentation in so many of our buildings was counterproductive in NIH?

Colten: Well, there was no way to put them all in one building. But I would say that the counterproductive was that the organization could have been better by putting groups that had either similar technical or similar conceptual

interests in one building instead of going institute by institute, because there were people in the Dental Institute who, and in the Cancer Institute and then AI who were doing things that really ought to have been more proximate than they were. The fact of the matter--had we been interacting with more cancer people, it would have been a good thing too, but basically they were going off... It was as if we weren't there. So you had to find your own connections, and we all did, but I look at that time and I think I should have done more, and I think the reason I didn't do more is those chance encounters with people in a faculty lounge sharing a ridge and borrowing a ridge and sharing a machine. You know if you're signing up for use of a centrifuge in a place where there are multi users, you're there and you're seeing somebody else, not somebody from your own lab there. You're seeing other people. When you have, you know, room for all of 25 ultra centrifuges and somebody comes in and they're only...., yeah, maybe you'll bump into someone, but you don't have to linger there. You do your own stuff and you're out. You don't stop to talk about what's going on. So it's chance things.

The seminar series. I think there wasn't nearly as much going on in the way of seminars that I was aware of any way that, as in every other place I've ever worked. And I think that was a mistake, too. How many times did people come to a seminar for an outside speaker unless it was one of these big NIH-wide things, which did occur. But for speakers that came through our lab or somebody else's lab, it was just pretty uncommon to go across barriers to hear, unless it was a very famous person, and, you know, a lot of the not-so-famous had something to say too.

Borsos: Are you saying that the NIH is so large and so many scientists in so many different institutes that this is uncommon [?]

Colten: No, no. The size... I mean, the size only fit that you couldn't take

advantage of all of them. But what I'm saying is that there was a compartmentalization along pretty arbitrary lines that made it so. There was a richness of equipment that made it unnecessary to share equipment. Everyone in the extramural environment has to share equipment, even when you've got HHMI people, which has a lot more money than others.

Borsos:

What HHMI?

Colten:

Howard Hughes investigators, Howard Hughes Medical Institute investigators. They have much more money. But in a place like WashU., you know, if they've got equipment, they can synthesize peptides, and you need peptides, you talk to them about what you're doing, and eventually you get, you talk enough, some of those guys, you're going to interact with and even collaborate with. NIH didn't require that because it was rich in the equipment and poor in the personnel. And I think that was a horrible thing. That really is inhibiting. NIH was and still is to some extent a place where riskier science should be done, and it's not my impression that that's uniformly the case or even the majority of the case in the intramural programs. There's much more oversight and necessity for annual reports and stuff. But it is still not as competitive an environment at, even in the best places, within the intramural program as it is in the extramural program. I think for everybody, there is an added kicker when you're up against competition. It's in part why systems that provide an entitlement without periodic test of whether it's still fulfilling its function are gradually run downhill because they end up accumulating a lot of people who are willing to coast--not that everyone is coasting. There are a lot of people that are motivated enough for a variety of reasons--curiosity, pride. Whatever is motivating them, it doesn't need that external stimulus. But I found, for example, every time I wrote a grant, as onerous as it was, I had to refocus my thinking. There were some things--I got insights about things that were staring me in the face before but I didn't have to come to

grips with till I had to justify, till I had to compete against other people for that money. And at that time, that wasn't part of the NIH model, and I think it wasn't good for it because the intramural program, instead of using that freedom as a place to really take flyers, when you look at the productivity of NIH overall--I'm not talking about that lab, but NIH overall--you can't point to the intramural program as being disproportionately more on the leading edge than the extramural sources, even taking into account that there are many, there's much more money spent, many more people outside than inside. I just don't think that it was an environment that got the best out of everyone and got rid of people who just weren't cutting it anymore. It hung on to lots of folks who were asleep--not just technicians, but senior scientists too.

Borsos: Would you give a short description of your career after you left the NIH.

Colten: Yes. So I went to Boston. Janeway said to me that he wanted me to do allergy, and I said, "Dr. Janeway, I don't know anything about allergy." He said, "That's perfect." He said, "I want you to come here, teach yourself allergy, set up your laboratory. If we like you and you like us, you'll be chief of allergy," and that's what happened. It's an interesting thing. When I first came there, I had a very tough month setting up the lab. I went to slice cells with antibody and complement. And Fred Rosen gave me temporary quarters in his lab in the basement at Children's Hospital till the Enders Building was finished and my lab would be available. That was a wonderful lab. The only person with an office there was Fred's secretary. Fred had a round table which actually still exists. I've now given it to my daughter, but it existed in our house for many years, had a new top made for it and all of this. That was his office, this round table in the middle of the laboratory, at which he would meet with people in the lab, and I got a little half of a bench and access to the tissue-culture lab and all the equipment, and that was my temporary space. So I

started by trying to set up the basic reagents, red cells and a complement source and all of this. I couldn't lyse red cells. Nothing was working. So I went up to--at that time Irma Jeely [sp.] was at [?] before they moved to combine Brigham and Women's Hospital. I went up to her laboratory and everything worked there. So I did the usual exchange of buffers and this and that, and it didn't work. And it turned out that the water in Rosen's lab killed the complement, so that was a month of setting up the lab. But, actually, things got really rolling nicely in that lab, and I got first studies on human fetal biosynthesis and complement, some nice work, which was possible then until the State of Massachusetts and then the federal government said it was illegal to study fetal tissues. But by that time, things were launched. And just about the time I was leaving at a meeting Mike Frank reported the C4 deficient and we decided to work on that. Janeway's prediction about them liking me and me liking them, I would be chief of allergy, came true. I was named chief of allergy and subsequently promoted to associate professor and then finally to full professor. At that time, only 5 percent of the people at the Children's Hospital had tenure, and I fully expected not to be one of them because most very, very talented people came and went from there without getting tenure, and to me it was a little bit of a surprise that I got it, but it was very nice, and I was very successful at running the allergy division. I established it. So, I established for the first time there a scientifically based allergy division, attracted some extremely talented people, first as fellows and then on the staff, and it was a program that was building. Harry Shwachman then retired, and he had been one of very few people to describe cystic fibrosis in all of its clinical details. We began to look for a successor, and Janeway again decided, "Well, Colten did all right with the allergy. Let's give him this one," and so I took that over, and that was kind of okay because it fit in the sense that that was a chronic inflammatory disease of the lung, and I was

already identifying myself as somebody who as interested in inflammation and in the proteins and ultimately the genes that were regulated in the course of an inflammatory response. Funny story. When I did get tenure, it turns out, at Harvard, in order to be tenured, you need, like at Oxford or at Cambridge, to have a degree from that university, and I did not have a degree from Harvard, so I actually hold an honorary master's degree from Harvard because of that. And one of the few faculty meetings I went to, Derek Bok, who was the president of the university, presented it, my diploma to me in the fall. And he said, "We comb the country and even the world for talented people at the undergraduate level, but we sometimes miss a few. We do the same in our graduate schools and even in our post-graduate studies. Occasionally we miss a few. But we always correct our mistakes." And so he presented this honorary degree to me. That was a terrific run of 16 years that I was in Boston. I worked at the *New England Journal*. I worked at the JCI as an associate editor. In each case, I learned a lot from that. My clinical programs were booming. I trained a lot of good people who came through the lab and who did terrific work themselves. The lab, in the days when quarters grew and we alternated cloning the complement genes, it was a lively, friendly competition because his lab was interested in the structure of these and I was interested in expression. In fact, I was one of two people invited to present for Porter when he was retiring, and it was a magnificent meeting. It was at a time I was considering a job in St. Louis, and Herman Eisen was there and we had coffee one day, and Herman had been at Washington University as a chairman before he went to MIT, and he advised me strongly, as did many other people, to go to Wash. U. I had been looking at chairmanships before that, ironically also at Hopkins, decided I wasn't going to go to Hopkins because they were so certain everything was perfect in the department, and I saw, although there were good things, lots of problems

to solve, figured don't take a job where everyone thinks it's all perfect because you'll never get a chance to fix any of the real problems. So I decided to go to Wash. U. Tragically, incidentally, right after that meeting, Porter was on his way to take a holiday long overdue and was hit head-on by a car and killed instantly. So, what would have been still a very productive career beyond that was cut short. And that Porter lab suffered a great deal for five years after that happened, before they each, the guys who did reestablish, got on track and did as good work as was going on before. Lots of people came from overseas, many from the States. All told, I think some 60 or more people did postdocs or their Ph.D.'s in my lab, and a lot of them now are in very prominent places, so I feel very good about that part of my career. I spent 10 years as chair, almost 10 years as chair, at Wash.U., and that department grew scientifically, grew clinically, and became one of the major players, is now, by all accounts, number five or six in the country. It was nowhere near ranked, even, when I took it over. It was a great school, but the Pediatric Department improved markedly during that time. And under my successor, a guy I recruited--I recruited about, over the 10-year period, some 80 people to the, between 80 and 85 people to the department, which was originally 65 full-time people, when I left, about 100 full-time people in the department, and it was a wonderful run. I came to Northwestern as dean with the express purpose of bringing a second-tier institution into the top tier. I was assured by the leadership that they wanted that to happen, and I believe they're sincere about that, but found, within a year, that the cultural gap was going to be the impediment to that happening. There are some talented people here, but the dominant culture is more of a school that aspires to be tops in its region at best or in the metropolitan area at worst, but that isn't yet prepared to go as far as is necessary in order to be a top-tier institution nationally and, as a result, decided to resign from this.

I believe the resignation was correct. The choice in coming here rather than to the University of Washington obviously, in retrospect, was not correct, but who knows. Maybe there would have been a different set of problems there that could have been equally frustrating. I don't think so but will never know. What comes next, I don't know. All in all, I think I got appropriate recognition for what I did do both in terms of being offered responsible positions and a few little various honorary things, and I can't complain about it. So, that's what I did, and I think so far, so good.

Borsos:

Thank you, Dr. Colten, for this wonderful description of your career at NIH and also other places, and this concludes my interview with Dr. Colten in Chicago, which took place at his house in the afternoon of October 4th, 1999. Thank you.

End of Interview