NCI Laboratory of Molecular Biology
Oral History Project
Interview #1 with Dr. Ira H. Pastan
Conducted on September 24, 2008, by Jason Gart

JG: My name is Jason Gart, and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today is September 24, 2008, and we are at the offices of the National Institutes of Health in Bethesda, Maryland. Please state your name and also spell it.

IP: My name is Ira Pastan, and it is spelled P-A-S-T-A-N.

JG: I want to briefly mention the interview scope: Established in 1970, the Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, what we will refer to as LMB, currently has among its ten groups four members of the National Academy of Sciences. LMB has trained many other prominent scientists in its research and has contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history project to capture recollections of prominent scientists currently and formerly associated with the laboratory.

We are going to have two sessions. I thought today we can talk about your background, your move to Yale, your move to NIH and the development of the lab, and stop somewhere in 1990 when you switch your research emphasis to cancer. And then tomorrow we can pick up on that, and then continue through with your reflections on

doing science, the lifestyle of a scientist, your world view on training, and maybe some discussions of recent issues in science such as mapping of the human genome and big science today.

To begin, talk a little bit about where you were born and some of your interests as a child. I have read that you grew up in Winthrop, Massachusetts. Speak about your family background.

IP: I was born in Winthrop, Massachusetts, in 1931. My mother was born in Winthrop, Massachusetts. Her father, my grandfather, was an immigrant to the United States, had family in Chelsea, Massachusetts. The family story is that he was unemployed, had a friend who used to collect and sell junk in a horse and wagon, and one day he went out with his friend to Winthrop, decided he liked it there and decided he would move there and settle there. Whether that is true or not, I am not entirely sure. In any event, Frank Ceder, my mother's father, settled in Winthrop, had a fruit and vegetable small business, and my mother was born in Winthrop, married a man from Malden nearby, Jack Pastan, and I was born in 1931.

I went to local schools in Winthrop and to a local Hebrew school. I first went to the Shirley Street School, grammar school, and then I went to Winthrop Junior High School, and I then moved to Boston Latin School and graduated from Boston Latin School. I was always interested in science. In terms of choosing a career, it wasn't so clear then what

career choices one had, particularly for Jewish kids who knew there were prejudices in the world, and being a doctor, if you were interested in science, was a choice for many of us and that seemed to be what I wanted to do. So I went to college at Tufts College. Actually I spent one year at Middlebury College and transferred to Tufts College where I majored in biology. At Tufts College I remember one professor, Professor Roeder, who taught physiology. He really got me involved in thinking about science and loving science.

JG: Let's go back for a second. I have read that as a child you did some early experiments on worms.

IP: Yes. There is one event I do remember and that I tell people when food is discussed. Let me first say that my family has a strong interest in food and I have a son who is a chef here in Washington, DC, a very well known chef, owns two restaurants, Obelisk and 2Amys. So there is often talk about eating unusual things like insects. I recall that when I was a child I went in my backyard and saw a robin, I guess, or some bird eating worms and thought, well I might try that. I can't imagine exactly what was in my head.

JG: How old were you at this time?

IP: I can't remember. Maybe seven or ten, I am not sure. I remember tasting it and I remember it tasted very bitter and very gritty, I guess from the dirt it had eaten. I did not

swallow it, I spit it out, but the memory stays with me and I don't think I will choose to eat another worm. [Laughs]

JG: You mentioned that there was anti-Semitism in Massachusetts.

IP: I think it was not just Massachusetts. I think growing up in a—and there is of course still some anti-Semitism in the world, but much less in the U.S. than there used to be. But it was just a fact of life. It was well known that Jews had immigrated here to escape anti-Semitism, pogroms in Russia and other places, and there was anti-Semitism in grammar school. Winthrop, Massachusetts, had about 15,000 people, divided into three regions: a Jewish region where I lived, a Catholic region, and a Protestant region, each had about 5,000 people, and there was friction between the kids. I did not sense it in the teachers, but clearly among the kids. It was a fact of life and accepted then.

JG: You mentioned that it was common knowledge that firms such as General Electric and General Motors, that—

IP: Yes. There were very few if any Jews who could have a career, an upwardly mobile career, in those organizations at that time. And think about Henry Ford who was overtly anti-Semitic.

JG: Yes. Absolutely. What do you think you would have done if you did not take up medicine or biology?

IP: Actually I majored in English for one year in college because I enjoyed it, but I think I would have ended up in science. I find even now that I am seventy-seven and many of my friends have retired, I still have a passion for science. I read about science, I think about science, I think about experiments. It is hard to imagine me doing anything else.

JG: So you attend Tufts, and your undergraduate degree is in biology?

IP: Yes.

JG: I just want to go back for a second. So what brought on the major shift from English to biology? You mentioned Dr. Roeder.

IP: Although I thought I wanted to go to medical school, I was not really clear about my goals at that time. I came from a family that my father never went to high school. He probably had a learning defect. My mother finished high school but didn't go beyond that. Although I wanted to be a doctor, I was not being very realistic about focusing on it initially. Actually I didn't get focused until somewhere in the middle of my second year, when I met my now wife, Linda, who went to Radcliffe and who was an outstanding student. I decided if she could be an outstanding student, I might as well study hard and

be an outstanding student. So I focused on biology and really started to work hard, and I must say I have been working hard ever since and have not stopped. But I went from having a mixed record of B's to mostly A's or all A's.

JG: Speak about Dr. Roeder and his influence on you as a young student.

IP: He was the first scientist that I met who really did what I would recognize as experimental science. In addition to teaching physiology, which he taught very well, he had an interest in the nervous system of insects, particularly cockroaches. There were these stories about him walking down the hall—he had a closet full of cockroaches that he would use for his electrophysiology experiments and occasionally one would escape. He would see one running down the hall, grab it, look at it, and say male or female, and stick it back in the closet. [Laughs]

JG: You get your undergraduate degree in what year?

IP: Nineteen fifty-three, and I applied to medical school that year and was accepted at Tufts medical school, maybe one or two others, I don't remember, but Tufts was the obvious choice for me. It was in Boston, and my wife was still a senior at Radcliffe. We were married the day I graduated from college, and the first year she was a senior at Radcliffe.

When I was in medical school, I still had not decided I was going to do research, although I was interested in it. During my freshman year, I knew I wanted to work around or in a hospital, and I went to see my advisor, whose name was Bill [William P.] VanderLaan; he was an endocrinologist. At that time, advisors were not frequently consulted. It was rare that students went to see them. They were more paper advisors. And I said to him I'd like to work in a hospital maybe as an orderly or something just to see how hospitals work, because then medical students did not do clinical work in their early years as they do now. He said he would think about it, and when I went to see him in a few weeks he said I have a job in my lab, maybe you would like to come work with me. He said he had done work as a medical student at Harvard in a lab. So I went that summer, which would be the summer between my freshman and sophomore years, and worked on a lab project that he outlined for me. In retrospect it is clear that when he said to me, "Let me think about it," that he had to go look at my grades to see if I was worth supporting or not. [Laughs]

JG: At that point, when you first get into the Tufts medical school, how did you see your career progressing?

IP: I thought I would probably end up being a practicing physician. I didn't think I would do research. I found that I liked working in a lab and liked doing research, even that first summer, although there were a lot of problems with the experiments I was doing. Then VanderLaan left and went to the West Coast, and his boss, Ted Astwood, Edwin B.

Astwood, a very famous scientist, allowed me to stay on working in the lab during the school year and also summers. So I got to know a group of people doing research in a very productive, serious way and I really liked doing that. But still I was not certain I was going to be a researcher, because it was just a life that I didn't know about. So I did research in medical school and I even published one paper. Then because Astwood was a very well-known scientist and my grades were very good, I was selected to be an intern at Yale, which was unusual for students coming from Tufts who usually went to Boston hospitals or clinically oriented hospitals.

JG: Before we get to Yale, let's backtrack for a second. Speak about Dr. Astwood and the significance of his research, and what it was like for you doing research at that time in your life as a young medical student. What were some of the tasks that you were assigned? And also speak about the slaughterhouse project.

IP: First of all, about Astwood. Astwood was a member of the National Academy of Sciences. He had won a lot of prizes, he was the editor of the journal, *Endocrinology*, and he had discovered antithyroid drugs for the treatment of hyperthyroidism—thiouracil and then propylthiouracil. He had also done a lot of work at characterizing and purifying peptide hormones, and one of my best friends, Gerry Aurbach, who was a year or two ahead of me and was a fellow in the lab, worked on parathyroid hormone isolation there. Gerry came to NIH the same year that I came and went on to isolate parathyroid hormone, determine its mechanism of action, and eventually had a very important career

in the area in bone metabolism. And there were other fellows in the lab doing interesting projects. But they were all ahead of me. I was a student, and in retrospect it was remarkable that Astwood allowed me to do my own experiments in the lab. I began working on a project of VanderLaan's trying to figure out in the thyroid when iodide negatively charged went into the thyroid cell, did a negatively charged ion come out or did a positively charged ion go in with it to maintain electrical balance, and if it did, what was it. I worked for more than a year on that project, and I had some evidence that it was potassium, but it was never published. To do those studies I needed to obtain thyroid glands from a slaughterhouse in Charleston. I would go there early in the morning to get the thyroids and then use them for my experiments.

JG: These were cow?

IP: Cow. Probably calf or cow thyroid. During that summer there was a strike and the slaughterhouse closed. I could not do my research, I did not know what to do. Astwood did not tell me what to do. I had been reading a lot about iodide and knew that there was an iodide transporter in the stomach similar to that in the thyroid. I had just learned in medical school about Meckel's diverticulum, a protrusion of the small intestine, that can bleed and cause pain like stomach ulcers. I thought maybe there is an area of the small intestine from which Meckel's diverticulum arises which like the stomach could transport iodide, and I thought I would go look for it and devise some experiments to find it. I did this all on my own. Astwood paid me a small salary and let me do these things. It turned

out that I got very good evidence that there was a small region of the small intestine that could transport iodide. I wrote it up for publication, but my result disagreed with some experiments done by a well-known thyroid person. The explanation turned out to be that I technically did my experiments a little differently. The well-known scientist, who was named Alberts, had done similar experiments but had not found this phenomenon, and it turned out that my experiments were more detailed than his. I divided the intestine in many small segments; he divided it into just a few large segments, so he missed this effect. When I submitted the paper for publication, it took a long time to get it reviewed, and when it came back, it was accepted. Many years later I met a scientist who was the reviewer of my paper, and he told me that he didn't believe that my findings were necessarily right because Alberts was such a well-known scientist, so he actually repeated the experiment and found that I was right. This would never happen today of course, but science was very different when I was a student. The fields were all small and all the people knew each other.

JG: So medical school ends, you get your degree, and then you are accepted into Yale.

IP: Yes.

JG: And at that point, you wrote "Without planning I had become an endocrinologist with a special interest in the thyroid gland."

IP: Well that was because of my work in Astwood's lab, which was an endocrine lab focused on thyroid.

JG: And there was no turning back?

IP: It would have been difficult to—I did not think a lot about it. Endocrinology was interesting for me. I did not say maybe I should do cardiology or maybe I should do something else. The field was just very interesting and seemed just a fine thing to do. Lots of questions to answer.

And I went to Yale. I applied partly to Yale, because the head of medicine was a guy named [John Punnett] Peters, and Peters had written this textbook with [Donald Dexter] Van Slyke, describing how to use chemical methods to analyze blood and help diagnose disease. This was a very new thing, and I was very interested in working with a scientist using this new laboratory approach to diagnose disease. Peters was also very well known for his liberal politics, and at that time McCarthyism was going on and Peters had stood up against it. So there were two things that attracted me to Peter's department. But shortly before I arrived, Peters died of a heart attack. When I went to Yale, the head of medicine was no longer Peters, it was Paul Beeson. He was an outstanding physician, but he did not have a major interest in endocrinology and metabolism. There were other people there who had worked with Peters. One was Phil Bondy, B-O-N-D-Y, and another was Frank Epstein, and so I began to interact somewhat with them. Bondy told

me that Dr. Peters had been treating patients with hyperthyroidism in a different way than Astwood. Whereas Astwood had developed propylthiouracel as a new drug, Peters was treating them with Lugol's solution, which has a very high concentration of sodium iodide. When given in large amounts it can inhibit thyroid function. He had been following patients to see how effective this treatment was and allowed me to look at Peters' notes and to put together a paper describing what Peters had done. So during my resident second year, I spent the little free time I had going over his notes and trying to contact patients and doing follow-ups to see how the patients had done.

JG: Would that have been untypical? Is that unusual today?

IP: That was atypical then, but I was very interested in thyroid disease and knew a lot about the field already.

JG: What was it like going through his papers?

IP: There were these small notebooks that he kept notes in when he saw patients, not big hospital charts, and very detailed writing about each patient every time he saw them. It was like knowing him.

JG: And what did you learn about him?

IP: That he was a very careful observer and kept very good notes. But it did not tell me more about him than that.

JG: You mentioned a minute ago McCarthyism and that you were impressed by Dr. Peters because of his stand against Joseph McCarthy. Speak about what Yale was like in what would have been, say, the late 1950s or mid-1950s.

IP: I was married and had one child and a second child was born in New Haven. The life of an intern and resident was work, work, work, go home, see your family, sleep. I did not have much time to think about politics at all. [Laughs]

JG: And your wife was very understanding about that type of lifestyle at that point?

IP: So life was very different then than it is now, and it just seemed that's the way life would be for a young doctor trying to get started. One was expected to work very hard. My wife had graduated Phi Beta Kappa from Radcliffe [College] and got a Master's degree in English from Brandeis. She would have gone to get a Ph.D. except she moved with me to New Haven and could not. Yale did not take women in the English department then. So it was difficult for her to adjust her career and raise children, but that was life then, which is different from life now.

JG: What is the profession like at that time? Where is biology going, say, in the late 1950s?

IP: The view of biology was totally different than it is today. For example, I guess I will talk more later on about when I began to do research at NIH in peptide hormones and receptors. Receptors were unknown for the peptide hormones. How peptide hormones work was not known; that the receptors for polypeptide hormones were located in the cell membrane was not known. Molecular biology was unknown. Gene cloning was unknown. So it is hard to imagine how different it was. It was very physiologically oriented with a bit of fundamental biochemistry and amino acid transporters and metabolism. The mechanism by which nucleic acids were made was unknown. Evidence that DNA was the material that encoded genetic information was just being developed by experiments in bacteria transforming cells with DNA. It was a completely different world.

JG: Do you think there was a closer alignment between basic science and clinical work?

IP: No, I don't think so. It was basic science and clinical work, and there was translational science. Astwood did protein hormone purification, which is basic science, but he also developed the drug to treat disease and then did the clinical trials himself, which was translational science. So both existed, but the size of the enterprise was very small. If you worked in a field, you knew everybody in the field.

JG: You are at Yale, you had been at Tufts, the center of the East Coast. What was going on on the West Coast at this time?

IP: To my knowledge then, very little was going on on the West Coast. There was a great migration of scientists, I guess in the sixties and the seventies, to the West Coast, populating, expanding the medical schools. I was recruited on several occasions to join departments on the West Coast at Stanford and UCSF to join others who had gone before me. But I think the center of scientific research as I knew it then was on the East Coast. The annual meetings of various societies were frequently in Atlantic City where it was convenient for people on the East Coast but not the West Coast.

JG: Your internship, your residency, ends in 1959. What brings you to NIH?

IP: There was something called the Berry Plan. I do not know if you know what the Berry Plan was, but the Berry Plan was—the United States Army and Navy needed doctors, and they got doctors by drafting them. They continued to draft doctors even when they were not drafting people to go in the Army as foot soldiers because they did not have enough doctors. If you were a doctor and if you were pre-med and wanted to go to medical school uninterrupted by the draft, you joined the Berry Plan. You signed a contract that said they would allow you to finish medical school and do two years of medical training but then you would have to go in the Army or in the uniformed services for two years. At that time, the Public Health Service Uniformed Service Commissioned Corps became an

option, and you could go into the Commissioned Corps of the Public Health Service and be assigned to NIH. So a lot of the early people who came to NIH came as an alternative to going into the Army or the Navy, and I was one of those. It was very competitive, so the best students from the best universities, medical schools could come here if they wanted to and most did.

JG: As part of the Public Health Service reserve, what were your responsibilities?

IP: I was in the Commissioned Corps of the Public Health Service. I do not know whether I was in reserve or active duty, and my duty was to work in Bethesda in the clinical center. I was assigned to the Clinical Endocrinology Branch (CEB) of what then was the National Institute of Arthritis and Metabolic Diseases, which is now the National Institute of Diabetes, Digestive and Kidney Diseases, NIDDK. I looked after research patients who were on the ward and spent most of my time doing lab research. The chief at that time was J. Edward Rall [Ed Rall], who recently died. When I joined CEB, Ed said to talk to people in the group and decide with whom I would like to work. I did talk with people, and I also began to finish up some experiments I had started as a student in Astwood's lab trying to see if you could dissociate the thyroid into individual cells, and see if the cells would function. I continued to work on that project and actually published a paper on that project. But I also was interested in research being done by a guy named James Field who was studying how peptide hormones controlled glucose metabolism in

endocrine glands. So I decided to study if thyroid stimulating hormone stimulated glucose metabolism in thyroid glands. So Jim and I began to work together.

JG: You are coming from the Northeast and you come down to Bethesda. What is Bethesda like in 1959?

IP: Bethesda in 1959 was the South. There was segregation. There were segregated drinking fountains in Union Station, there were segregated movie theaters, and there was segregated housing. During those initial years here, my wife and I became active in trying to do something about this. There was a movie theater in Bethesda called the Baronet which was segregated, and many of us picketed the Baronet until they finally closed it rather than desegregate it. The Glen Echo Park, which is a national park, was segregated and that was picketed. Blacks could not get housing in Montgomery County. Also Jews could not get housing in some areas in Montgomery County. There was an organization called Montgomery County Fair Housing to which Linda and I belonged. Let me describe one of the things Linda did, that I cannot believe to this day. There was a black couple who wanted to move to Montgomery County. Linda would go look for houses that were for sale, identify a house, indicate to the owner that she might have an interest in buying it. Then she would show up with a black family who would then say they would like to buy this house. Legally, the people had to sell to them, even though the agent of the seller did not want to do this. But this was one of the ways that segregated housing in Montgomery County was mostly eliminated.

JG: You mentioned a second ago that you did not have time for politics, but now when you get to Bethesda, things are starting to change. You have more time?

IP: Yes. I still worked very hard, but I had more time for some other outside activities. And the people I worked with were all interested in the segregation issue. It was a very important national issue.

JG: Absolutely. So that is a little bit about what Bethesda was like. What was the NIH like?

IP: The NIH was an incredibly exciting place. It was full of young people, who had come here in various programs, and were interested in learning and doing science. We knew when we came here that we were chosen not just to look after patients, but to do some kind of science. So I was surrounded by many very brilliant people, many of whom are still my friends, in a very exciting environment. In the group I was in, you were told to identify an interesting problem and work on it, and if you did well, they would support you. So I worked for two years in the clinical endocrinology branch seeing mostly thyroid patients one day a week, taking care of a few patients on the ward, and mainly doing research in the lab on thyroid stimulating hormones. Our research went quite well and we had a lot of publications, but I realized I did not know enough biochemistry. So I had to decide if I wanted to stay in research, and if I did, what I could do to educate myself better in biochemistry.

JG: What were your limitations at that point? Why is biochemistry important for the work that you decided you wanted to do?

IP: Biochemical analysis of organs, bacteria, whatever, enables you to understand how they work. One had to know how to do experiments with enzymes, measuring enzymes, isolating enzymes, studying their properties, and I had no background in that. There was a night school at NIH, where they offered courses in biochemistry and immunology, and organic chemistry which I did participate in. But that was formal education, not hands-on education. So I looked around NIH to find someone with whom I could work and learn. There were several good options, but one of my NIH friends Roy Vagelos—Roy went on to be CEO of Merck and is a very famous scientist—was working in the laboratory of Earl Stadtman, a microbial biochemist. So I decided, based on Roy's advice, that this would be a good environment to work in. I applied to work in Earl's lab and was accepted and got a fellowship to support me. I would say that in Earl's lab I learned how to do science—how to ask the right question, how to design experiments, how to think about my results, and how to proceed in a very systematic step-by-step experimental way to a final solution rather than trying to hit a home run. The run was there as a goal, but the approach to get it done, the way I do science, is very systematic.

I was talking about this with a friend of mine recently, Lew [Louis M.] Staudt, who trained in David Baltimore's lab. He told me that David said you do science in small

increments carefully putting one foot after the other. So that is the kind of science I learned to do from Earl, a very organized step-by-step approach to solving one problem at a time, until you finally solved the whole problem.

JG: Give me an example—a layperson example.

IP: Oh dear. I'll answer that tomorrow. I will have to think about that.

JG: Very good. So for two years you are at the laboratory of cellular physiology.

IP: Yes.

JG: And what happens?

IP: Sometime during that time, Ed Rall offered me the possibility of moving back to the Clinical Endocrinology Branch in a full-time position, and I accepted and I moved back.

JG: Were you looking at any other positions?

IP: Had I been looking? No, I was not looking yet.

JG: At that point did you think that this is someplace that you would be interested and engaged to spend your career? Did you consider NIH as the place that you wanted to stay as your career progressed?

IP: The answer to that was yes. I guess my options would have been go back and do more medical training, perhaps go into private practice. My wife's father was a surgeon and I think he thought that was probably a sensible thing to do. Maybe I could have gone back to Tufts, but I did not really have many contacts at Tufts except Astwood. I guess I could have gone back to New Haven, finish up my medical training and perhaps do a fellowship and try to get on the staff. Or I could stay here. Here I was settled, I had friends, I liked the environment, they liked me. It just seemed fine. But I do have friends who went back to Harvard or Yale or other places where they had trained before coming to NIH.

JG: You mentioned your wife's father. How about your parents? How did they view the researcher lifestyle of a doctor versus, say, being a practitioner?

IP: My father was not very involved. My mother was happy having a son who was a doctor and was happy that I had success. She would have liked me to move back to Boston. But except for that, she was perfectly pleased with what I was doing. My wife and I had discussed moving back to Boston, maybe Cambridge since she enjoyed her college years so much in Cambridge. Later on there were several opportunities for me to take a job at

Harvard and move to Cambridge, but I was happy in my career here at NIH and hesitant to leave.

JH: So you are back in CEB. How does your career progress and what are some of the things that you start to take interest in?

IP: I wanted to know how thyroid stimulating hormone worked to control thyroid function. All we knew then was that if we put thyroid stimulating hormone on slices of thyroid from a dog (or another source) glucose metabolism changed very quickly, but I wanted to know the steps in between. Sometime during that period, Jim Field left and went to Pittsburgh, so I did not have the opportunity of working with him anymore. I was on my own, and I did some experiments in which I added TSH to a preparation of disrupted thyroid cells to see if glucose metabolism was increased but I saw no effect so I could not use biochemical methods to study the problem. We never saw any stimulation. And then a guy named Earl Sutherland discovered a molecule called cyclic AMP. He showed it mediated the effect of epinephrine on oxygen metabolism in the liver. So I thought maybe in the thyroid, cyclic AMP might mediate the effect of TSH on glucose metabolism and/or thyroxine release and/or thyroglobulin synthesis. So I started to study these events. I found that TSH activated the enzyme, adenylyl cyclase, in the thyroid and that it raised cyclic AMP levels and that the addition of cyclic AMP reproduced many of the effects of TSH on thyroid cells. So we had pretty good evidence that TSH was working through cyclic AMP. But the question was how.

JG: And this is circa 1963-69?

IP: Yes.

JG: Are you still working—you have a bit of funding, you have your own lab at this point?

IP: When I came, I was given a module. A module is a 13 x 20 lab. I was given a technician, and later on, I was given a fellow to work with me, all supported intramurally by NIH.

JG: At this point, now the mid-sixties, late sixties, what is it like doing this type of science?

IP: Well, very few people in the world were studying peptide hormone action, no one else was doing it in the endocrine group at NIH. Sutherland's discovery of cyclic AMP stimulated people to think that cyclic AMP might be acting in the system they were working on. Some people at NIH then started to think about cyclic AMP as a second messenger. I previously mentioned my friend Gerry Aurbach who worked on parathyroid hormone, he was thinking that parathyroid hormone worked through cyclic AMP in the kidney and showed that it did, and I think there was a group in the heart institute working on cyclic AMP, and Marty Rodbell worked on cyclic AMP in fat,

thinking it was a second messenger in fat for catacholomines and peptide hormones. So there was beginning to be an interest in this area.

JG: At that point, how long did it take to build an experiment, to go through the process to get something published? What is it like at that time? Compare and contrast a little to what it is like today.

IP: I think of course the amount of data you needed was much less then, because less was known. Standards were different, but I do not think it was very different. It was not slower. It was about the same as it is today I think. Maybe from the time you submit the paper to when it appeared, maybe six months, I don't know, more or less.

It was about that time, perhaps 1965, that my friend and colleague Jesse Roth came to NIH. Jesse and I then began to work together to try and identify the first step in hormone action. Jesse had trained with Sol Berson. Berson was the discoverer of radioimmunoassay and used radioiodine to do the immunoassays to measure peptide hormones. Jesse trained in his lab, knew how to radioiodinate hormones, and came to NIH. He was primarily interested in insulin and how insulin worked, and I was also interested, so we began to work and discuss and plan experiments that might demonstrate what the earliest measurable step was in hormone action. And we decided that the first step must be binding. So we added hormone (TSH or insulin) to living cells in the cold, washed away the free hormone, and warmed up the cells to determine if the cells

responded. And they did. We next determined if we could remove or destroy the hormone and abolish the response and that also worked. We did this by treating the cells with antibodies or trypsin. My post-fellow, Enzo [Vincenzo] Macchia, and Jesse and I did these experiments and published them in the *Proceedings of the National Academy of Sciences* (PNAS). The paper was titled something like "Polypeptide Hormone Binding: The First Step in Hormone Action." As far as I know those experiments are the first evidence that there were saturable specific receptors on the cell surface that represented the first step in polypeptide hormone action.

JG: Talk about Dr. Roth. Where was he trained and how do you describe him as a researcher?

IP: Incredibly imaginative, articulate, brilliant person. We are still friends. He came here to head up the diabetes program. He eventually became scientific director of the diabetes institute (NIDDK). He then moved to Johns Hopkins and then moved to New York where he is now at Einstein. Jesse was trained as a Talmudic scholar and has what I call a Talmudic way of thinking. Several other scientists I know were trained that way, a very logical way of putting everything together. Often it is right, sometimes it is wrong, but it is always very logically constructed. Jesse is a very useful person to talk to and to discuss experiments with. So we collaborated actively on studying the early steps in hormone action, TSH, ACTH, and insulin at that time. In CEB we had a very strong thyroid group, endocrine group, but the major endocrine problem in the world then and

now is diabetes, and so the leadership wanted to build up a diabetes unit and Jesse was the person they brought in with hopes that he would do that, and he did.

JG: At this time, 1969, you become head of the molecular biology section.

IP: I moved to the cancer institute.

JG: And what brought that move about?

IP: So I was in the Clinical Endocrinology Branch of the National Institute of Arthritis and Metabolic Diseases (NIAMD). I was working on hormone action, but I also had started work in cyclic AMP in *E. coli*, and with Bob Perlman showed that cyclic AMP is a very, very important regulator of gene activity. It was a very big deal at that time and still is. I became very well known throughout the world because of that work, more than for my work on hormone action, and I would get visits from scientists from Japan and other countries because we had discovered a new mechanism in gene regulation. Up until that time, the only known mechanisms of gene regulation were only in *E. coli*, only bacteria, nothing was known about animal cells. The genetic studies by [Jacques] Monod and the biochemical studies by Wally Gilbert had shown that the *lac* repressor repressed gene activity and derepression occurs by lactose (or IPTG) binding to and removing the repressor. Everyone assumed that genes were constitutively on and regulation occurred by repression. But we showed it was more complicated. Many genes are inactive and

need to be activated to be expressed. We showed that the positive regulator was cyclic AMP and its target protein we called CRP (cyclic AMP Receptor Protein). We discovered a totally novel mechanism of gene regulation and received a lot of attention.

Okay. So there I was in the Clinical Endocrinology Branch working with Bob Perlman. We were the only ones in the group doing microbiology and genetics, no one else was doing that, probably very few people at NIH were doing it. I had then two modules, not much space for two very active research programs, and I was the junior member of the department and not likely to get more resources or space in the near future. And I was being recruited actively by many institutions—by Stanford, by Harvard, other places.

JG: Because of your work with Perlman?

IP: Mostly because of the work in bacteria. Now you should know that I play tennis regularly, three times a week in the morning, before work. At that time I played tennis every Wednesday with a guy named Mort Lipsett, who was an endocrinologist working in the cancer institute. I said to Mort one day, "I can't see you next week. I'm going to look at a job at Stanford. A NIH former colleague invited me out to look at a job as head of a department, but I'll be back the week after." So I went to Stanford and I looked at this job—Stanford's beautiful. Have you been there?

JG: Yes I have.

IP: Oh, it is beautiful. And it was a great job. It was head of a department and all that. They arranged for me to play tennis [laughs], and I came back. But my wife was from the East Coast and her parents were here, and it just seemed not possible to leave the East Coast. So I saw Mort and he said, "How was your trip?" and I told him all about it, "But Linda, my wife, said we just can't leave the East Coast; so I don't know what I'm going to do." And Mort said, "Well I'm head of the Clinical Endocrinology Branch in the cancer institute, and we have a lot of space and resources. I thought you were happy where you were in CEB, but if you're not, why don't you join my group and I'll give you six modules and two technicians and three fellows and an office, and whatever you want." So I thought it over for a bit, I hesitated because cancer then was not as it is today. Today we understand a lot about cancer and it is an exciting field, but we did not have oncogenes then. Cancer had no scientific basis, and endocrinology did. So it was moving into an unknown area and an unknown group. But I thought it over and decided I would move. So I moved my group to the tenth floor from the eighth floor in Building 10 with six modules and two technicians and expanded my research interests.

JG: Talk a little about the politics at NIH, that one laboratory can have so much funding and another does not.

IP: At that time I was unaware of differences in funding in different institutes. Now I know cancer has a lot of money, but I was unaware then. Again, I knew all the

endocrinologists, I knew Mort, I knew everybody, and Mort knew my boss and obviously went to talk to him when he offered me this position. So I just thought for some reason he had more space, and I would join his group, which I did.

JG: At that point the laboratory—was it called the laboratory of—

IP: I was not a lab chief yet. I headed the section of molecular biology within the endocrinology branch of the cancer institute.

JG: What were some of the other programs that they were doing? What were some of their interests?

IP: They were interested in steroid hormone action and androgen action and corticosteroid hormone action. I think Griff Ross was interested in prolactin and other hormones. They were interested in endocrinology and also endocrine cancers because it was the cancer institute.

JG: And you get called by Dr. Berlin. Is this leading up to . . . ?

IP: So I was perfectly happy there. But Mort decided that child health was the future. They had recently started the child health institute, and he thought endocrinology and child health and development was going to be the future. Also he was unhappy. He wanted to

have a high-level position in the National Cancer Institute (NCI). He wanted to be clinical director and he was not given that job. Then they offered him this job in the child health institute where they had lots of resources. Mort's idea was that we all would move there and child health would give us a little bit more than we had. He came and he said, "We're going to move to child health," and I said "Why?" he said, "We'll have a little more resources and we can do the same thing. It'll be fine," and I said "Fine." About that time, Cliff Barger, who was on our advisory board, was in the department of physiology at Harvard. He had arranged for me to come up and look at a position at Harvard in the physiology department, which I was considering but probably would not have taken. Nat Berlin, who was the scientific director, knew Mort was leaving, knew they would have a lot of resources, and decided that he would like to use those resources to set up a new laboratory of molecular biology with me as head of it. He asked me in to talk about it, and offered me the position because he had an available block of space and positions that were generated by Mort leaving.

JG: Why did you decide not to go to Harvard? You would have been closer to family and back to Boston.

IP: It is complicated. There were family reasons for going and family reasons for not going. It was the uncertainty of having to get grants and funding, where here I was extremely well supported and could do pretty much whatever I wanted to do. So for me it was just

easier. Everything seemed fine, I was happy here. There are people who have the Harvard mystique, I don't.

JG: Do you think that it would have been a more stimulating or less stimulating environment to do research?

IP: Oh, I think the research environment would have been very stimulating there. There was a lot of uncertainty about getting organized and getting a program going and getting grants and all. If I had had to do it, it would have been fine.

JG: You had been at NIH I guess about a decade at this point.

IP: This was 1969 or something?

JG: Yes.

IP: Yes. I came in 1959, so yes, ten years.

JG: At that point, do you decide that you are going to make the South your home?

IP: It was becoming less and less the South and more the North. [Laughs] I would say now it is indistinguishable from Boston. So it is changing pretty rapidly. Yes, at least for a

while. I did not think in "forever." I was thinking for a while, see how things went. So it was not open and shut, but I was pretty happy here. I don't know how old I was in, what year was this?

JG: 1969. So say you were thirty-nine going into forty?

IP: Yes, so I was about forty with a very successful career.

JG: Walk me through . . . Dr. Berlin calls and you decide to accept his offer?

IP: Yes.

JG: What is it like to now set up an entire new laboratory?

IP: Perlman was my closest colleague at that time, and I discussed with Bob joining me in this new enterprise. He was still in the arthritis institute after I had moved to cancer, but we still collaborated actively. So I discussed with him joining me in the new lab, and he thought about it. But when I did not accept the job at Harvard, they offered him the job and he went. But they did not give him tenure. This was a mistake. [Laughs] So after about ten years, he had to leave.

I decided I would like to have a lab that was doing molecular biology. Bob and I were collaborating with a geneticist named Max Gottesman, who was in the arthritis institute, giving us genetics advice, and I decided that the future was a combination of genetics and biochemistry, which of course turns out to be molecular biology. I asked Max if he would like to join me, and Max said yes. I also decided I wanted someone in the animal cell field who was doing something different than I was doing, and I thought virology in the animal world has always made great steps forward. I discussed joining me a guy I knew and had worked a little bit with called Bob [Robert M.] Friedman, who was a virologist, and he agreed to join me. So the original lab was going to be me and Max and Bob Friedman and the people who were working with me, junior people. Bob eventually decided not to join and stayed in the Department of Pathology and he eventually moved to the Uniformed Services Medical School at the Navy, so that didn't work out. But Max joined me and he set up a microbial genetics unit. There were also the people with me, some of whom were working in *E. coli* and some in animal cells. So there were really two groups, and I was involved in both.

JG: At that point, how much money do you think your lab had?

IP: I don't know. Nat [Nathaniel I.] Berlin said to me "what do you need?" and I sort of figured out each senior person needs a lab or two or whatever, I don't know. So we agreed on some amount of space, and he said fine. The space was on the B corridor on the fourth floor of Building 37 which was recently constructed. I was then in

Building 10. But Nat also said to me, "This is not going to be enough space for you. I'm sure you will come back, and we'll do something for you." I don't know exactly how I made the space calculations. The budget then was different from the way it is done now. You did not have a lab budget. The cancer institute had a budget, your boss had a budget, and within reason you spent money and he approved it and you functioned. It was much later, when individual labs were given yearly budgets, and even later when individual senior scientists were given their own budget. Today, each senior scientist has their own budget and they know exactly what it is for personnel and for resources. But then we did not. We were told if you order something, order it and if we have enough money we'll buy it. We usually did not run out of money. We thought much less about money than we do now.

JG: Talk about Dr. Gottesman and Dr. Friedman, about what type of scientists and what type of researchers they are?

IP: Max went to medical school. He was a medical student at Yale when I was an intern and resident and said he knew me, but I did not remember him. And then he worked with Fritz Lippman at the Rockefeller, and then came to NIH to get out of the draft. He was working with a geneticist called Michael Yarmolinsky. He was doing genetics studying the bacteriophage lambda. Bob Perlman and I were trying to isolate mutants in *E. coli* in the cyclic AMP pathway, and Max gave us a lot of advice on how to do it. So that is how we got to know each other and got to know his abilities and intellect.

JG: During the late 1960s, everything is going "molecular." Historians of science have noted that laboratories, academic courses, all take the "molecular" name. You decide to name the lab the "Laboratory of Molecular Biology." Is that done for a reason?

IP: Because as I said the combination of biochemistry and genetics is molecular biology. It is doing experiments with DNA and studying how DNA works and how genetic information is controlled and transmitted to the cell, and that is what molecular biology became. Now I will tell you a funny anecdote. I was on a committee, the American Society of Biological Chemists, with many other—I can remember a few people on it—whose task it was to decide whether they would like to change the name of the society or the journal, I can't remember which, to the American Society of Biochemistry and Molecular Biology, because there was not then and there still is not today in the United States a society for molecular biology. There is in Europe, but not here. We suggested this was a good idea, and we put it to a vote of the membership, and they turned it down. One of the arguments was molecular biology was not a field of science, it was a technique that people used to do biochemistry. [Laughs] So that was the view at that time. They did not understand that there are biological questions that cannot be answered by traditional biochemistry.

JG: Is this just semantics or a generational debate?

IP: Yes, it was a generational debate. People did not see what molecular biology could do. Now of course they do, but they did not then. But I was fascinated . . . we did not talk yet about my relationship with Perlman and going into *E. coli* and molecular biology. That is what affected me in my thinking. I was working on peptide hormone action with Roth, which was going extremely well, and I had begun to work with Perlman on gene regulation in *E. coli*, which I thought was going even better. But cyclic AMP in *E. coli* got me into the new world of molecular biology, where one could do experiments with genes and figure out how genes worked. That seemed such an incredibly interesting and challenging thing to do and I wanted to do it.

JG: How so?

IP: It is closer to the heart of how cells work. One would like to know, ultimately, what is the nature of the life process. That is a question that none of us can approach even still today. We don't understand how to approach it. But one of the important components of understanding the life process is how information is transmitted from DNA to the cell, and there was a way of studying that. It was very attractive to be able to work and study that process.

JG: In the 1970s when you move to Building 37, what are the aspirations for you and also for the new Laboratory of Molecular Biology?

IP: It began earlier. That is what I was trying to say. It began earlier and then when I thought that one could use a combination of genetics and biochemistry to figure out how cells worked, something you could not do with genetics alone because genetics makes hypotheses, but it requires biochemistry to test them. And you can't do it by biochemistry alone, because you need mutants to set up the hypothesis. But if you put the two together, you can actually ask and understand, get answers to such questions. So the whole idea was to have a laboratory which would be an environment where people had strengths in both areas and could work together to address those problems. Initially we studied bacteria, because working with genes in animal cells was much more difficult, but soon thereafter we began to work in animal cells.

JG: Who else do you recruit?

IP: I recruited Max, and Max recruited Sankar Adhya, who was in India. I don't exactly remember how he knew him. And Max recruited Mark Shulman who might have been at MIT, and Don Court, and Susan Gottesman came as a postdoc. Susan was here, because her husband, Michael, was an M.D. assigned to NIH to work with Marty Gellert, a biochemist and molecular biologist in what was then the other laboratory of molecular biology in NIAMD. So Michael came as a physician, and Susan had a Ph.D. in microbiology at Harvard working with John Beckwith, one of the best geneticists in the world. She came here on a fellowship and she joined Max's group. Same last name, no relationship. There might have been other people in Max's group. I would have to look

at a picture from that time. I don't remember. But anyway, that was the core group. Max and his folks were on one end of the hall, and I with my group was on the other end of the hall. Max was interested in bacteriophage genetics, and I was interested in how the *lac* operon and the *gal* operon was controlled by cyclic B. I was working with Benoit de Crombrugghe, one of my postdocs, and soon thereafter was joined by [Shigetada] Nakanishi. And also I had several people who started to work on cancer cells and cyclic AMP and figuring out if it controlled the behavior of the cancer cells.

JG: You are recruiting people that have expertise in both biochemistry and genetics?

IP: I would say either/or. Very few people had expertise in both. I had expertise in biochemistry and was trying to learn genetics. Max had expertise in genetics and knew a little biochemistry.

JG: Were you also looking for diversity of research styles?

IP: Well, it was a pretty small group. I could not have much diversity. No, I think we had to focus. I would say we were interested more in focus than in diversity. I am still a very focused researcher. I tell my research group all the time, figure out what the question is and ask it and keep thinking about it all the time. So we were interested in focus. We had several people working in genetics, several doing biochemistry, several in the

bacteriophage virus area, and several people working on animal cells. We were not looking for a lot of diversity, just biochemistry or genetics.

JG: In the early seventies, what was the lifestyle of the lab? How did you work together and collaborate as a group? You were all the same age in a sense.

IP: I was a little older, but yes, right. But I had recruited everyone. We met regularly and worked very closely together. We had a small library on 4B where we had our seminars, where we had a lot of the books, where we had journals, where people went to talk. One room, that was it. We also published together. So, we worked together and we published together. Now everyone has a big group of their own. This has happened for two reasons at least. One is we are much older, have our own independent careers, and the system encourages people to work independently and get independent recognition. If we were starting a new department today, you would find people who would mainly work on their own. You might collaborate as part of it, collaboration is encouraged, but individual identity is now very important. For some reason then it was not a big deal, at least for me, but I do not think it was for them either. You would have to ask them.

JG: Is that something now lost in the sciences?

IP: Yes. For me, the fun of being together and working together with people at your own level. Now I mostly work with junior people, and they do not have a broad view of

science. So there are certain things we discuss, but there are other things they just have not thought about.

JG: Well, it is a different world view in a sense.

IP: Yes, it is a different view. So it was extremely—however, I would say of all my interactions with people, collaborations, the one that was the most enjoyable for me was the one with Bob Perlman. I have somewhere a video of one of our old reunions where Bob gave a little talk—I'll find it for you so you can hear what he said. But he basically said that—his wife, Carol, and my wife, Linda, must have thought we were like school kids. We would talk on the phone every evening about our research, like school kids call each other in the evening because we were so excited and interested by it. That was when we were showing that cyclic AMP actually did control gene expression, which was a totally radical idea at that time. It was very exciting, and also we had a point of view about life that was very similar; so it was very exciting and interesting.

JG: Were you together socially as well—were there barbecues and did you get together for other group events?

IP: Yes, we did. Less so now, although we still have a yearly picnic and a yearly holiday party, and we have some formal social interactions, weddings, bar mitzvahs. But then we

were much more oriented to being together and having dinner or doing something like that.

JG: What was your style of management at that period in the seventies?

IP: I would say I was pretty inexperienced compared to now. I did not think about it much.

JG: Right. And it is not something that you would have been trained to do.

IP: I was not trained to do it, and it all happened very quickly. I was about forty and I had this large group of very talented people to work with, but also I was the boss. I did my best to satisfy everyone and initially everyone stayed. Eventually Max went back to New York; I think he always wanted to go back to Columbia. He was from New York; he wanted to go back there. Sankar has stayed. Susan was a postdoc and returned to Boston. We brought her back and her husband came back with her. He stayed in LMB for about twenty years and left to be head of another lab in NCI. Several of our other people would have stayed, except they were recruited to be heads of other labs at NIH. So they are around NIH, but not in LMB. I think it has gone pretty well. People now have a lot more space and resources than we did then. In looking back, people were pretty happy, were productive with much less space than we have now. I am not sure other groups had more space, I just don't know. I was brought up in a culture where people did not have much lab space, and I did not think a lot about supplying it to people

or asking for it for our people then. I clearly had more than others. You would have to ask others how they sensed it worked. We did have one or two problems with people who came and did not fit in and left, but mostly things worked well.

JG: Talk about some of the younger people that join and then leave. You have postdocs now, you have fellows, and things of that sort.

IP: When I moved from NIAMD to NCI, Benoit de Crombrugghe came with me, and he worked on *E. coli* and gene regulation. Then when I got interested in cyclic AMP and cancer, we had found that cyclic AMP regulated the adhesion of cells, and when cells bind to substrates, they do so through collagen and fibronectin. So Benoit and I began to study collagen and its role in cell adhesion and cell interactions. Eventually Benoit got very interested in that area and expanded to have his own section within the laboratory. Then after many years, he decided he would take a job in Texas as head of genetics at M.D. Anderson. You could ask him why he left. Did he want more resources? Did he want more recognition? Did he want more money? We never discussed it. He did not come to me and say look, I have this job offer at M.D. Anderson, but I would stay if I could have this or that. We never discussed it. He just was recruited by them and went. So he is the first of the people who worked with me. You probably know Hal [Harold E.] Varmus worked with me before I was a lab chief. He just stayed at NIH two years and then left.

JG: He goes on to win a Nobel Prize. What was he like as a young researcher?

IP: Harold came in 1968 as a clinical associate. When my research started to go well, my boss said you could have one of the new clinical associates to work with you. I interviewed several of them and one was Harold. He went to Amherst, he was editor of the school newspaper, then he got a Master's degree in English at Harvard, and then he decided he wanted to do medicine so he went to medical school. Then he came to interview with me. He had not done any research, but he was obviously very smart. Let me tell you an interesting story, and it is in his Nobel Prize lecture I think. I had to choose between Harold and several other very talented people, like Bob Lefkowitz, and I chose Harold. In most respects they were indistinguishable, brilliant students, etc. The reason I chose Harold was that my wife, Linda, was an English major and a writer, and Harold had an interest in English and writing. So I thought Harold would be an interesting person for Linda to talk with at parties, dinners, etc. So I chose Harold over everyone else because of his background in literature.

JG: [Laughs] Fascinating.

IP: When I interviewed him he thought he was going to work on thyroid stimulating hormone, TSH, because he was interested in endocrinology. By the time he arrived, I was working on cyclic AMP gene regulation. I told him on the phone before he arrived that we're going to work on cyclic AMP gene regulation in bacteria. He was surprised,

but he said okay. So that is what he did when he arrived. He learned to do things like DNA-RNA hybridization to measure RNA levels, and most of the techniques of molecular biology that he used to work on the SRC oncogene for which he eventually got the Nobel Prize. I have a movie, which is a very bad 8 mm movie I will show you later, and one frame from the movie is Harold standing in the lab pipetting. This is my lab on the eighth floor (8N246) of Building 10. Here is a picture of Bob Perlman in the lab. Here is a picture of me. But anyway, there was Harold pipetting, learning to do hybridizations to measure the effect of cyclic AMP on *lac* messenger RNA half-life. We published several papers together. But he was interested in cancer, and he left after two years to work in labs that were doing cancer research, and worked with Mike Bishop.

JG: In the mid-1970s there is the recombinant DNA controversy. How does that impact your laboratory, or does it?

IP: It did impact on our laboratory, because in order to do a cloning experiment, you needed to follow special isolation procedures. So NCI had to build, in Building 37, a lab where one could do recombinant DNA work under these very tight restrictions. In order to do cloning and put DNA into bacteria and grow the bacteria, you had to be in this special room. There was one room in NCI and we all shared it. You could not get in it all the time, you needed to make a reservation. We were competing with people at universities who had better access to such rooms. So that did slow us down. Still we were the first to isolate a cDNA for fibronectin and for one type of collagen although another lab at

Harvard did it about the same time. So this enabled us to study those genes. But to do that cloning under those conditions was very restrictive, and we probably lost a year, maybe two years.

JG: And this is 1974 or 1975?

IP: Yes. So cloning under such restrictive conditions made research very difficult. Around that time I went to a meeting in Cape Cod on how to do experiments to show the public that it was safe to work with recombinant DNA. The meeting was in the Cape Codder Hotel in East Falmouth, Massachusetts. Many of the participants were against cloning and were not bench scientists. There were people from the Center for Science in the Public Interest talking about how dangerous it was and how we were going to destroy the world. And there were people like my colleague, Max Gottesman, who said, "Mix me up half a glass of any recombinant bacteria containing any gene and I will drink it." [Laughter]

IP: So those were the two extremes. I am not sure I would have drunk it, but Max was convinced it was safe to drink it. We had not cloned that many genes and they were mostly bacterial genes. Yes, so it was very restrictive.

JG: This kind of interaction between science and the public—is this something that starts to emerge in tandem with molecular biology?

IP: Oh, it emerged because of cloning, because of the fear of putting genes in *E. coli* that might spread throughout the world and cause bad things to happen. That was the fear. And of course we were only starting with little pieces of genes, but eventually they feared that this would happen. So the activists made it very difficult to do these experiments, and the scientists took it seriously and tried to design experiments to show that it was not a concern, which was done.

JG: Did you face more difficulty because of your new lab, because you were at NIH, because of your research agenda?

IP: The only difficulty we faced was that working in a government institution like NIH and getting permission to go ahead and build such a lab was very complicated and slower. Don't ask me why. Don't ask me why not in a university. It was just bureaucratic stuff.

JG: Walk me through to 1990 when you decide to change focus? In 1982 you are asked to join the National Academy of Sciences. How did that impact your career?

IP: Getting elected to the National Academy of Sciences (NAS) is a big deal for all scientists in the United States. They elect sixty new members a year from all the scientific disciplines—chemistry, physics, mathematics, biochemistry, and medical sciences. Not many.

JG: At that point there were only 1,100 people ever elected to it.

IP: It was a very small number. Getting elected was and is a big deal.

JG: How did you find out?

IP: They call you. Everyone knows the day they meet and vote. It is a very elaborate process. Do you want to know about how it works? I know a lot about it because I was involved in the process. Basically, there are the major disciplines and each major discipline is a class. Medical sciences is Class 4 and has sections in different aspects of medical science like immunology or genetics or cancer. Each section gets to nominate a group of people, and there is a vetting process, and it goes up and up and up and committees meet. Within each section, maybe one or two people get elected every year from each of the sections. When you are elected, the head of the section, which has nominated you, calls you up and says you have been elected, congratulations basically. And all the people you know who are members also call you and friends call you up. It is the ultimate recognition of scientific achievement in the country, I guess in the world. To get elected you must have made discoveries that are important and made you well-known. In addition, you need NAS members to support your candidacy. There were people who supported my candidacy, and I know one of them is a scientist who came to work in my lab for one year as a visitor named Gordon Harris. I remember one time in

conversation with Gordon, who was a member of the National Academy of Sciences, saying, "You're not a member? My God." So I assume that based on that conversation, he helped promote my candidacy, although we have never discussed it. But having seen what has happened since, it is very likely that that happened.

JG: What did the laboratory do in honor of your election?

IP: We have a party in the lab, drink champagne, invite other members of the National Academy at NIH. We may have pictures of that party. And then my colleague David FitzGerald put together this recognition document hanging here on the wall that says "In celebration" and he got everyone in the lab to sign it. And then there are official activities at the annual meeting the year after you are elected when you are inducted.

JG: Move me through the 1980s to 1990 when you decide to change the focus of your research.

IP: I stopped working on bacteria because I thought that questions I wanted to work on, "how cyclic AMP worked," were mostly answered. We can talk in detail about that later. The one thing that we missed was getting the crystal structure of the protein that cyclic AMP binds to (CRP) which in turn binds to DNA, and I missed that. I actually made a lot of protein, collaborated with a crystallographer here at NIH, and his group was unable to get crystals. But a group at Yale, Tom [Thomas A.] Steitz, also worked on the project, and

they were able to get crystals. His trick was he added cyclic AMP to the protein and that stabilized it and enabled it to crystallize it, and we didn't. So that I missed. So I stopped working in the *E. coli* area and decided I would work on mammalian cells. I was working on several aspects of animal cells. One was to study how hormones and other protein molecules interacted with the cell and were internalized by the cell. I did a lot of that work with Mark Willingham who initially came to work with me as a research associate and then stayed on for many years. He and I did a lot of work on developing methods to study the interaction of peptide hormones with the cell surface, such as their mobility, the rates of internalization, where they went in the cell, all sorts of things like that, some of which Mark built the equipment to do. Several postdocs worked on the project such as Fred Maxfield, who is now Chair of the Department of Biochemistry at Cornell, John Hanover, who is here at NIH, Jim [James H.] Keene, who is in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University, Dick [C. Richard] Schlegel, Chairman of Pathology at Georgetown, and Bob [Robert] Dickson, head of oncology at the Georgetown Lombardi Comprehensive Cancer Center. Bob just recently passed.

One day we got a new postdoc named David FitzGerald who wanted to work with us because he was working on a toxin, and he wanted to know how the toxin got into cells. That toxin is Pseudomonas exotoxin A. So we started to study Pseudomonas toxin and how it got into cells and how it killed cells. Now at that time, there was an interest in treating cancer by attaching toxins to antibodies and using them to kill cells called

immunotoxins. There were many people working with different antibodies and different toxins and different technologies, but no one on Pseudomonas toxin. So we decided we would use our expertise in cell biology and eventually in molecular biology to make immunotoxins to target cancer cells, all based on the fact that David chose to come to work with us to study how toxins enter cells. And I said "ah," this is great. I can use my medical background, and my receptor background, and my skills in molecular biology and genetics to attack the problem of "can you develop new agents to kill cancer cells." But it was a big field then. A lot of other people were in it, but they were all using chemistry. They would hook a toxin onto an antibody chemically, and slowly by slowly they all got out of the field. What they made did not work when they got to the clinic. But we thought we could make agents that would work when we got to the clinic and we have.

I was also working in one other project at that time, and that was also because I was interested in doing something about cancer. I had begun to work with Michael Gottesman on cyclic AMP mutants in CHO cells. He was doing the genetics and I was doing the biochemistry. So in around 1990 we decided to work together using his genetic skills and my biochemistry skills to attack the problem of drug resistance in cancer. Actually, before getting started, Michael and I spent some months making rounds once a week with clinical people to try to identify a clinical problem we could work on. This problem of why anti-cancer drugs work on some cancers but not others is an important problem that we thought we would try to address genetically and biochemically. So we

began to collaborate on drug resistance when I also was working on immunotoxins. Michael and I worked together quite successfully for a long time in this area, but when the immunotoxin project really got into the clinic, I did not have time to do both, so I had to give one up, and so I gave up the drug resistance project with Michael and he has worked on that alone for the last ten years or so.

JG: You have written that you could not do the immunotoxins research anywhere else because of its high risk nature.

IP: Well, you need funding, and it is very hard to get funding for such projects because it is not basic science, and there just is not funding around. Drug companies won't fund it, because they want something that is going to work soon. They do not have patience for long-range things. They will buy up things after they are working. And biotech companies might develop it for a while, but they will run out of funds. So I have been very lucky that my bosses have supported me. We have these things called site visits. Every four years there is a committee coming in and they review your work, and they give advice to your boss about whether your work is good or bad, and whether your resources should be expanded or cut or kept the same and so on.

JG: This has been since the lab started in the seventies?

IP: Yes. They have always existed but they are more formal now. I can remember a site visit some years ago when I switched to immunotoxins and began to work on them, and the reviewer said to my boss, Al Rabson, in his report: "A, it's too expensive, and B, it will never work." My boss took it under advisement but said keep going. But if I were a junior scientist, that would have been the kiss of death. It was only because I had succeeded in other areas that Al said keep going. One of my recent site visits they said to me: "Ah, you've got it working in leukemia. That's great, but it'll never work in solid tumors." So that is my current challenge. Solid tumors are harder to treat with chemotherapy for various reasons, and that goes for immunotherapy, too.

JG: As we end this morning name the best project that came out of the 1970-1990 period.

IP: The best project is clear to me. It was showing that cyclic AMP regulated gene action in bacteria and figuring out exactly how it did it. That was to me scientifically the most beautiful project. We understand the switch, we understand how the switch is controlled, and we understand how the switch works. For me it is the most exciting, rewarding, and satisfying project I have done.

JG: Let's walk through how it works.

IP: Okay. There is something called the glucose effect that Jacques Monod worked on. If you have *E. coli* growing on lactose and you add glucose, the bacteria stops using the

lactose, stops making the enzymes needed to metabolize the lactose and uses the glucose. And everyone said "how could that be?" "What is the switch? " Now we knew from the work of Sutherland that *E. coli* has cyclic AMP and when you add glucose the cyclic AMP levels plummet. So we hypothesized that cyclic AMP is required for *lac* operon expression and when cyclic AMP levels fall, *lac* operon expression is abolished. Glucose lowers cAMP levels by causing cyclic AMP to come out of the cell into the medium. So, if cells are growing on lactose cyclic AMP levels are high. You add glucose, and they fall. There are many other genes that are controlled in this manner. People had all sorts of ideas about metabolites of glucose that might be the switch. But they were wrong and glucose was lowering cyclic AMP levels. To prove the role of cyclic AMP we made mutants of *E. coli* that did not make cyclic AMP. They did not make ß-galactosidase until you added cyclic AMP. We also made mutants that had cyclic AMP that could not activate *lac* operon expression. We found the mutant was missing a protein that bound cyclic AMP. We showed that the cyclic AMP and this protein we call CRP (cyclic AMP receptor protein), was required to activate the *lac* operon. The biology was simple and beautiful. Then I went to Cold Spring Harbor and talked about our work. Monod was there and was very complimentary. To me it was amazing. He was the most famous geneticist in the world. I would say figuring that out in almost all of the details was very exciting and satisfying. We got a real clear answer to a very important problem.

This year my grandson, Daniel, went to visit Washington University with my son, Stephen. Stephen is a nephrologist in Atlanta, Daniel is a senior in high school, and

Stephen took him to visit a biochemistry class at Washington University. They were talking about how cyclic AMP regulates gene expression. They did not mention my name and Stephen said to Daniel, "Your grandfather discovered this."

JG: Getting back to the names on the wall, like J. Robert Oppenheimer. Was there an "aha" moment in the discovery when you knew that you had actually solved the problem?

IP: I do think there was a real "aha" moment on that project. But I can't remember the day. I would have to sit down with Bob and talk about it. Maybe there was more than one. But I do remember an "aha" moment on the hormone action project with Jesse Roth. I would say getting evidence that there was a saturable receptor binding site on animal cells from peptide hormones was an "aha" moment.

There are other very satisfying moments. The first time we gave an immunotoxin to a patient and got a response. I remember Bob [Robert J.] Kreitman treating a patient with an immunotoxin and calling me up the day after he gave it to a patient with leukemia saying, "the leukemic count is falling, it's falling, it's half down twenty-four hours after we gave it." Now it is routine in patients with hairy cell leukemia to see a fall in leukemic counts. Within a couple days the counts can go from high to zero. So we are now used to it, but in the beginning, we were excited.

JG: I assume that can be an amazing thing.

IP: Yes. Yes, particularly when someone has told you it will never work and it is too expensive. There were the safety issues, too. Toxins have a connotation of being dangerous. Unfortunately someone gave these drugs the name immunotoxins, which is a terrible name, because it is a scary name, but it is what they are called. So there is always that thing in the back of someone's mind they are going to inject me with an immunotoxin and it is going to be bad. We need another name, but that will never happen.

JG: Shall we pick it up tomorrow?

IP: All right. We can pick it up tomorrow.

JG: Thank you very much.

IP: You are very welcome.

[End of interview]