NCI Laboratory of Molecular Biology
Oral History Project
Interview #2 with Dr. Ira H. Pastan
Conducted on September 25, 2008, by Jason Gart

JG: My name is Jason Gart and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is September 25, 2008, and we are at the offices of the National Institutes of Health in Bethesda, Maryland. This is part two of an interview that we began yesterday. Please state your name and then also spell it.

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

JG: Thank you. I want to fill in a few things from yesterday and then I thought we would move on in our discussions from 1990 to the present—discussing your interests and also the interests of the laboratory. And then maybe halfway through we will switch from a chronological to a thematic format and talk about what it is like to practice science and big science, especially. I forgot to ask you yesterday, when did you first hear about Watson and Crick and the discovery of the double helix?

IP: I am trying to think about the year that the structure was published and I can't bring it to mind at the moment.

JG: It would have been April-May of 1953 in *Nature*—so you would have been in your early twenties.

IP: In 1953 I was a senior in college and I did not begin to do full-time research for another six years. I began to do endocrinology research, when I came to NIH in 1957, I studied hormone action and I actually did not think a lot about genes. I was mainly interested in how the enzymes within the cell work. As I mentioned to you yesterday, I began to study the pathways of glucose metabolism in the thyroid and to identify the enzymes that break down thyroglobulin in the thyroid to yield thyroid hormone. It was mostly characterizing enzymatic processes within the cell. I guess I would not have really started to think about DNA seriously until I started to do gene regulation studies. So I guess about 1967. Well, the first paper Bob Perlman and I published was 1968, so probably 1967. And then I began to read about genes, but not so much about the structure of DNA, but how genes were expressed and how they were regulated, and mutations that affected gene activity and things of that sort. The structure of DNA was in the background, accepted, and I did not think much about it.

JG: Yesterday we jumped around on some of your publications. In 1982 you wrote an article called "Journey to the center of the cell: Role of the receptosome," in *Science*, and it is a highly cited work. Talk about some of your important papers and important publications during the 1970s and 1980s.

IP: I think I mentioned to you already that I began to work with a colleague, Mark Willingham, studying how hormones and proteins bound to the cell surface, how they behaved on the cell surface, how they entered cells, and the pathway by which they

entered cells. Using new equipment we developed and a technique called video intensification microscopy, described in a paper in *Cell*, we began to look at molecules moving about in vesicles within the cell. And since we were working with receptors, and receptor mediated endocytosis, we said that this vesicle that we see inside the cell that is moving around and that contains hormones and other proteins, should be called a receptosome. It turned out that the receptosome was identical to a vesicle described by another scientist as an endosome. So the name endosome, was already in the literature. We had not realized the endosome was the same vesicle we were studying, because the person who described it was studying viral entry. To prove they were the same vesicle we did experiments that showed hormones and viruses entered the cell in the same vesicle. So receptosome and endosome are the same thing, and endosome won the day.

Here are a few of the observations we made. We measured the rates of internalization of different proteins through this vesicular pathway, how many different molecules could reside in the same vesicle, how many vesicles were formed per minute, diffusion rates of receptor-hormone complexes on the cell surface and the likelihood they would get into a vesicle and be internalized. A lot of this work was summarized in that article in *Science*, which is sort of a review article but was also a speculative article about the future.

JG: Was this your first article in *Science*?

IP: Probably not. I guess my first article in *Science* was a paper with Roth and Lefkowitz in which we described the binding of radiolabeled ACTH to the ACTH receptor. That probably is a pretty highly cited paper also.

JG: What does that mean? What did it mean for you professionally to have something in *Science* which is kind of like *The New York Times*. Both *Nature* and *Science* . . .

IP: It is because a lot of people will read your article published in *Science* or *Nature*. So people know what you are doing and it is also good for your career. But it is mainly because a lot of people read it and pay attention to it.

JG: And a lot of non-scientists as well.

IP: And a lot of non-scientists as well. Although at that time the number of non-scientists reading scientific magazines was fewer than now. Now if you look in *Science* and *Nature* the first ten or fifteen pages are mostly written by non-scientist reporters describing the importance of papers further back in the journal. I must say what is up front is much easier to read for me as well as for everyone [laughs] and scientists sort of confess, well, I have read the description in the beginning but I have not quite read the paper yet, and that is very common. Particularly now, it is written also I would say not only for non-scientists but for scientists in other fields who wouldn't get it. I would say

this kind of general description is more important for people in different fields who do not quite get it than the person in the field who would read it.

JG: The work that you were doing with Dr. Willingham—that occurred over a period of five or six years?

IP: Probably longer, probably twenty years because Mark came to NIH as a research associate to work with me and stayed on for most of his career. Mark is a very brilliant person. He graduated high school at age fifteen, he went to radio school for a year, he knew how to build machines, his father had a shop in the basement and Mark knew how to build things. He once went home and made a centrifuge head that we needed to do a special experiment using a lathe he had at home. And he was very technically oriented, interested in equipment and machines and how they could be used. He built our first instrument to identify and see and measure the fluorescence of hormones and proteins as they bound to cells and entered cells. He had those skills, and my skills were in receptors and molecular biology, so we made a pretty good team. We worked first on the basic science, but then we worked together also in the beginning of the immunotoxin project. He was in the Commissioned Corps, and when the retirement age came, and his kids were ready to go to college, and he needed money, he retired. He got a pension and took a university job so he could afford to send them off to college.

JG: Does he teach now?

IP: Yes and he also does research. He was in the Department of Pathology at the University of South Carolina. Later he moved to Wake Forest University School of Medicine at the Bowman Gray Campus. He told me a few months ago he is going to retire this year from Bowman Gray.

JG: During the same period talk about some of the notable failed experiments and what happens when you consume, say, several months or a year and the hypothesis doesn't turn out to be what you had hoped to see.

IP: I can only think of one big failed experiment that I did and it was not in that period. The things I remember all worked one way or another. When I finished my training in [Earl] Stadtman's lab and came back to the clinical endocrinology branch, I was working on thyroid stimulating hormone and trying to figure out how it worked. But I was also greatly excited by the new things going on in molecular biology, and one of the things that happened was Marshall W. Nirenberg had developed a cell-free system which he used to solve the genetic code, where you programmed a protein synthesizing system with various kinds of synthetic RNAs, measured the production of small amounts of protein or incorporation of amino acids into protein. And I thought that this system could be used to make polypeptide hormones such as ACTH. So I decided I would isolate RNA from ACTH-producing tumors, add that RNA to the cell-free system that Nirenberg and others were working with, and show directly that RNA really encoded the

information to make a protein. This had not yet been shown. I spent a lot of time doing those experiments and they were unsuccessful. I probably spent a year or two doing it full time and I was pretty frustrated and disappointed. That was my first venture into molecular biology. I could tell you more of the details of why it did not work, but it was unsuccessful. People ended up being able to do it later on. They had a better system to work with and better RNA.

But that was my first failure and of course it affected me very strongly. I was very disappointed. I remember Jack Robbins, my boss then, saying to me, "Things are fine, Ira, but we can't give you a promotion because you haven't done a lot for the past year or two." It was true, and I thought very seriously about that, and since then I have not begun an experiment unless I was pretty sure it was likely to work. I have had postdocs tell me that they think I am totally fearless and will go into a new area that I never worked in and that is true. I will go into a new area. But I won't go until I have a pretty good idea exactly of what I want to do and how I am going to do it. And I think it is totally colored by that experience.

JG: So you prepare by looking at the scientific literature? Aren't you afraid that it will turn you away from projects or experiments that might be risky but lead to unexpected results. Or do you just play it through and you have a high probability?

IP: I would say when I went into that first project I did not know enough, but maybe there was not enough information to know, because it was the very beginning of this field. I now realize in retrospect that the concentration of RNA that I had was much too low to get it to work. That was one major problem. I had a very sensitive assay, but I probably did not have enough RNA with the right information to put into the system, and if I did, it would have worked. But I did not know it then, and I don't know why I didn't know it then, but I didn't know it. Maybe I had not learned to think quantitatively and now I do.

I will go into risky projects, I will go into areas people are not working in for whatever reason. But before I do it, I will have thought it through and read about it thoroughly and think about it obsessively before I begin. Here is sort of an example. One of the things we have done in the last couple years—me and a postdoc Yujian Zhang—is to work on a problem in synergy. We find that if we give immunotoxins and chemotherapy together to animals, we see a synergistic anti-tumor effect that we do not see when these two agents are incubated with cells in culture. Now this is an important finding, because it means when we treat patients with an immunotoxin we should use chemotherapy with it to get a much, much, much better effect. But we wanted to know the mechanism, and I spent about six months obsessing about what the mechanism could be. I can remember thinking about it when I woke up in the morning, I can remember thinking about it when I was driving in the car, and I remember thinking about and discussing it with my fellow, Yujian Zhang, who had a completely different idea of what was going on than I did. And one day, I put two and two together and said it is obvious what is going on. I just had not

thought about it the right way. And I said to him this is what is happening and we can test it directly, and I was right. But it took me six or eight months thinking about it. It was all there in my head but I had not put it together. And of course that is incredibly satisfying. It gets back to this aspect of science and puzzle solving. Science is a great big puzzle, and it is you against the unknown in biology, and that is what is exciting about it.

I think I may have told you this, or told someone the other day, that when I was young, my mother would stay up all night playing poker with her woman friends. And when I was young, I also used to play cards. I would play poker, I played pool, and I bowled, sometimes for money. But now I have no interest in gambling, because science has taken over. When I became a scientist, I felt like I was competing with nature instead of with my fellow humans. Science meets this inquisitive competitive instinct I have. [Laughs] I like to play tennis, but I do not care whether I win or lose. I like to hit the ball well, but winning does not interest me. But in science you have got to get it right and win or you have no career.

JG: But doesn't nature always win? [Laughs]

IP: We're whittling away. [Laughter]

JG: Going back again to yesterday. During this period, in the 1980s and then into the 1990s, who is your lab competing against internally and externally in the scientific community?

Were you waking up each day and saying I hope so-and-so at so-and-so doesn't . . . Is it that type of competitiveness?

IP: Well, there is certainly a lot of competition in science, and certainly I have been scooped once or twice in important areas, but generally I have tried to work in areas (at least in the beginning) where there is no one else in the field or very few people in the field. That is what happened in the beginning of peptide hormone action when we were looking at receptors. That is what happened when I began to work on cyclic AMP in *E. coli* and how it worked. We were the first people to really spend time studying cyclic AMP in *E. coli*—now there are hundreds or thousands of papers in the field. I tried not to get into an area where there is already a lot of smart people working, even though it is a very exciting area. I try to identify an area that has not been worked over and get started in it. So generally I do not find myself in a position of competing with a lot of people. Now when we began to work on the interaction of hormone and proteins with cells, I had several collaborators from various places who were very talented. We used a new technique called photobleaching with Elliott L. Elson and Watt W. Webb at Cornell to study receptor mobility. We looked at internalization when almost no one else was doing that kind of work at that time. People were looking at viral entry, but not at hormone and protein entry. There was one group in Texas, Brown and Goldstein, who were studying LDL metabolism and its relationship to atherosclerosis, and some of their work overlapped with ours. They showed that LDL went into cells by endocytosis and that they had mutant people who had a defect in internalization, so that was a clear clinical

application. But I think that was the only group that was doing similar work and only with a single protein and with a different focus.

If we go up to the immunotoxin field, there were many, many people fifteen years ago working different kinds of immunotoxins to try to get them to work. And in a sense we were all competing to get an immunotoxin that would work in people and be useful. Almost everyone else has left the field because their approach was not working and only our approach of using molecular biology, gene cloning, and protein design turns out to be successful. Hopefully we will get a drug approved next year or the year after by the FDA and maybe more after that. There are other people now working with different toxins doing very similar things to what we are doing and maybe those things will pan out also.

So mostly I have tried not to get into a competitive situation by avoiding fields where there are a lot of people already working. There were some projects that we were scooped on. We worked on EGF receptor cloning. None of the genes for any of the protein receptors had been cloned. They had been identified but not cloned. We worked on the EGF receptor and tried to get its sequence. There were at least two other labs doing it at the same time. Glenn Merlino worked with me on that project. We were beaten out by a few months by a group in England. I was scooped because the postdoc who was working on the project turned out not to be very good and we lost at least a year. Also we did not have the right equipment to do the sequencing of DNA. It was in the

early days of DNA sequencing, and our collaborator was not as good as the people at our competing lab.

JG: How about the lab itself? Does the LMB see itself in competition with other labs across the country?

IP: I do not think so. That would never have occurred to me. I think the competition is scientist to scientist on the same projects and clearly people feel competitive about that. You are going to talk to Sankar?

JG: Yes.

IP: So Sankar developed a model of gene regulation, called DNA looping, and Mark Ptashne at Harvard worked in the same area. That is a clear example of competition. Competition is only on a scientist-to-scientist basis, and it has not been frequent.

JG: So for you, as you mentioned before, the competition is against nature?

IP: I view it that way, yes. For me, that is what is interesting. I want to do something that other people are not doing. That is the fun. But some people enjoy being in a field where there is a lot of activity and competition, and they do not mind, or they tolerate, the competition just fine. But that gets to another point which probably deserves a little

discussion. Young scientists come to me sometimes and talk and say they can't imagine how to identify a problem to work on. I say to myself they should not be in science, because I feel I could be put down in a cardiology lab or a kidney lab or any kind of lab to work, and within a few months I think I could identify something interesting to do. One of the reasons I enjoy doing science is I can identify things to work on. But it is a problem for many people. I do not know why.

JG: Do you think this is generational? Some have talked about the bandwagon effect in science and how postdocs pick their topic. There is the belief that if you do not pick the right topic early enough it may impact your career and how it progresses?

IP: I think it is much more difficult to get money and positions now than it was when I started out. When I started out, the medical enterprise was growing and growing and growing, and there was a lot of support for people to do original things. Now it is much harder because the competition for funds and positions is pretty ferocious.

JG: Are there topics that young scientists should not go into—that would adversely impact their career?

IP: I spoke the other day about focus. I am not sure it is the area as much as the approach. They have to identify something that is really interesting and work on it and nothing else, no detours. A lot of people get detoured. Something does not work, so instead of

ignoring it, and say I am just not going to do that, they try to figure out why it doesn't work. That is a waste of time, and it can waste a lot of time. You can just say okay, it does not work, that is a technical thing not related to my main goal, I will do it some other way and I won't worry about why it is not working.

JG: Ah, and they want to know why it is not working?

IP: Yes, because it is the puzzle. They want to solve the puzzle, but it is not a very interesting puzzle. No one cares, not even their mother. [Laughs] So that is common in research where people run into a technical glitch, and instead of taking another approach which is more likely to work, they get hung up in trying to figure out why it isn't working and lose sight of the goal. I say to my fellows all the time that you have to keep your eye on the target and ask questions of them that are relevant to how you get there.

JG: And this gets back to the discussion on making sure you know where your experiment—

IP: You have to know where you are going and why you are doing it, yes.

JG: Let's switch gears. The lab in 1990 would have celebrated its twentieth anniversary. I guess it is now the twenty-fifth anniversary, correct?

IP: No, no. We are way beyond that. To 2002, thirty years. This year is not anything special except people like to get together, talk science, and see old friends. So we have these reunion meetings every few years. We did one I think on my seventieth birthday. That was the last one. That was number two, this is number three.

JG: Speak about what the lab was like in the 1970s and the method of doing science thirty years later. Try to compare and contrast—

IP: When we started in the seventies, the lab was created with this idea of combining people doing genetics and biochemistry to attack the problem of how genes worked. We worked together a lot, and if you look in the early papers, you will see my name and de Crombrugghe and Gottesman and Adhya all together. As people have gotten older, gotten more successful, they have moved into slightly different areas, because the world of molecular biology, gene regulation, gene activity, really expanded, and they each developed their own groups. So the interactions became less and less frequent as people became more and more senior and say successful. You should speak with Susan and Sankar about what they are doing.

The immunotoxin work is a collaboration but with younger people. I collaborate with Dave FitzGerald, who is an expert on toxins. We have a lab meeting together every week and a journal club together every week, and we discuss problems in making immunotoxins and how toxins work. I have two clinical people who take, what we are

doing in the lab, and carry it into the clinic and do clinical trials, and we all meet together once a week—Bob Kreitman, Raffit Hassan. My approach has continued to be a team approach except the team is different. For a while I collaborated with Dr. Lee, who is an expert in protein structure and gave us advice on protein design. He worked with us, a lot a few years ago, less now because we do not have that kind of problem to work on anymore. Susan Gottesman works now on small RNAs, of which she is a world expert. Sankar works on details of gene regulation, of which he is a world expert. The way we used to work together in the gene regulation area, I still try to do in the immunotoxin area. The success of our program which has been to design and to make a new drug to treat cancer and to test it here has all only been possible because of all these interactions.

JG: What about some of the changes in technology over the last thirty years? There have been advances in techniques, computing power has changed, you can now call up data sets on the Internet. How has that changed since that video we saw?

IP: I guess your question is how much does that affect what I do day to day. I would say the major way it affects what I do is just being able to keep up with what is going on through the Internet and reading. I have e-mails with scientists around the world every day. Somebody just e-mailed me last night that they found in omental fat, the protein mesothelin we had discovered in cancers. He wants to know what mesothelin is doing and how he can study it and could we send him some antibodies. We had three e-mails in the last ten hours about the project and how he might approach it. That might have taken

six months and several phone calls. His English is good and he writes well—he is Italian. So that has changed a lot.

Since we had protein structures and Dr. Lee could help us design proteins, we were dependent upon new developments in protein structure and molecular modeling. That all happened about ten years ago. Most of the stuff we do now—although the reagents, the test tubes and all are smaller—is dependent on cloning methods that were developed twenty years ago although they are much easier now. We do not use nanotechnology, which a lot of people are into. I might if I were young and just starting out, but I think it is a competing technology to immunotoxins, and I do not see so far that it is better. So I am less dependent on proteomics or genomics or other things than other labs are at the moment. I probably won't ever use proteomics and I do not use genome-wide scanning and probably it won't affect what I am doing very much. Right now I know the project I want to work on and I have been working on it for almost twenty years and things are going very well. And so far new discoveries in genomics have not impacted us.

JG: Speak about the human genome project.

IP: The human genome project is fantastic in terms of understanding disease and understanding how cells work, but it has not yet led to many new therapies. It has the promise to, but it has not unlocked any secrets yet that enable people to make a drug. Human Genome Sciences has tried very hard to do this, so far without much success.

In the beginning the human genome project was very controversial. There were people like Bernie Davis, who was a professor at Harvard, who said he was afraid that all the money would go into big projects and there would be less money for basic research, and of course that theme exists today. Some want to put money in all sorts of big programs and into translational research and take it out of basic R01 [research] grants. That tension still goes on today. But fortunately, the budget expanded and the genome project turned out to be cheaper than they thought. Technology advanced rapidly so they could get sequences. Now we are all dependent, if we want to study disease or how genes work, on sequencing and knowing gene sequences. Recently there have been several publications of sequencing the genomes of glioblastomas, to see what abnormalities occur. Also colon cancer has lots and lots of mutations. It is hard to know what this means. I imagine eventually a new therapeutic target will pop up. But so far the major advances are in our understanding and not in therapeutics.

JG: In your work in immunotoxins, since the mid-1990s, what have been some of your projects and what is your current research?

IP: Currently the most successful program is making an immunotoxin targeting CD22, which is a protein expressed on B-cell leukemias and lymphomas. We made an immunotoxin called BL22 (for B-cell lymphoma, CD22). This was done in collaboration with Dave FitzGerald and Bob Kreitman. BL22 is very active in drug-resistant hairy cell leukemia,

for which there is no other treatment and the patients would die if not treated. BL22 produced about a fifty percent complete response rate in these patients. The median time to relapse was three years. So those patients got a complete remission, had no cancer detectable for three years. One patient is now at nine years and still in complete remission. So that was very successful. We tried BL22 in other B-cell malignancies in which the number of receptors was lower and got many fewer responses. Receptor number is very high in hairy cell leukemia, 40,000-50,000 sites per cell. But in other common B-cell leukemias, like chronic lymphocytic leukemia, the cells only have about 1,000 sites per cell, and because of this forty-fold difference, they are at least forty times harder to kill.

Using genetic engineering approaches we designed a more active immunotoxin and called it HA22, high-affinity anti-CD22. HA22 was made first at NCI. It is now being developed with us by AstraZeneca MedImmune and we have almost finished a Phase I trial in hairy cell leukemia. In hairy cell leukemia, it is just as active as the old drug, maybe more active. We hope it will be active in patients with CLL [chronic lymphocytic leukemia] and non-Hodgkin's lymphoma and kids with ALL [acute lymphoblastic leukemia]. We just started a trial with kids with ALL. We plan to start treating patients with non-Hodgkin's lymphoma and CLL next year, when there is more drug available. So that has been very successful. The current plan is that MedImmune AstraZeneca will carry out a trial to get FDA approval of HA22 for the treatment of hairy cell leukemia, while we, and they also, try and show it will be useful in these other malignancies.

HA22 is now several years old and we have already made something better than HA22. It looks like it is more active and would have fewer side effects in patients. I do not know if the new agent will ever get into the clinic, because we need a company to do it. Maybe eventually. Maybe if HA22 is really great it will never get in the clinic. The important thing is that we have been able to continue in the same direction using molecular biology to make immunotoxins better and better.

JG: Is it difficult to convince the pharmaceutical companies to buy into this? I guess this is classified as high risk research?

IP: The answer is yes. One major reason is that these are foreign proteins, so you can only get them for one treatment cycle to most patients, and drug companies can't make any money on that. Fortunately, the immunotoxins targeting B-cell malignancies are not very immunogenic in people, because you are treating people whose immune system does not work very well for two reasons. One is they have gotten a lot of chemotherapy that kills bone marrow and immune cells, and the second is the diseases arise in the bone marrow and cause bone marrow suppression. When we treat patients with chronic lymphocytic leukemia, we give many cycles ,because they do not make antibodies. In hairy cell leukemia antibodies do occur, but not very often. So that brings us to a solid tumor program. We have a solid tumor immunotoxin targeting a protein called mesothelin that Mark Willingham and I discovered many years ago. Mesothelin is present in

mesothelioma, ovarian cancer, many lung cancers, most pancreatic cancers, many stomach cancers, and it is good a target for immunotoxin therapy, because it is not expressed on many normal cells, so you will not kill people by targeting it. We have an immunotoxin against it (SS1P) that has completed Phase 1 trials and is now in Phase II trials combined with chemotherapy.

Another large part of our program is to figure out how to make nonimmunogenic immunotoxins by engineering the toxin so that the B-cell epitopes (the regions on the protein that are immunogenic because they are foreign to humans) are changed so they are not immunogenic. This is called deimmunization. We have made a lot of progress in this direction recently. We do not have a nonimmunogenic immunotoxin yet, but we have been able to show that we can make a less immunogenic immunotoxin. We hope eventually to go on with this and make the immunotoxin less and less immunogenic so we will be able to give patients three or four or five treatment cycles before antibodies appear. That is a major part of what I am doing at the moment.

JG: Do you go and visit with patients who come in for treatment?

IP: Yes. We have a collaboration with Alan Wayne, who is the clinical director of the pediatric oncology program at NCI and treats children's cancer. He tested BL22 in children and found it was safe, but only had low activity even when we kept raising the dose. We never reach the maximum dose in kids, but when the new agent (HA22) came

along, which we know is tenfold more active, we stopped the BL22 trial and have switched to this new drug. We hope when we get to the same dose level it will be ten times as active in these children and maybe be useful. So do I go see patients? Yes. Monday mornings at 11:30, we have rounds. Bob Kreitman, Raffit Hassan, Alan Wayne, and I meet in Building 10 where the patients are. We discuss all the patients who are being treated, who are being recruited, and then go see the patients in the hospital.

JG: I can imagine that that is very rewarding?

IP: It is very rewarding, when the patients have had a good response. For hairy cell leukemia, it is very rewarding. For solid tumors, our responses have been minor, and so less rewarding, but we are going on.

JG: Let's switch gears again. How has the laboratory changed over time—you've spoken a little about this. How do you make sure that people interact and know what is going on inside the lab and then also outside in the broader scientific community? What is it like to manage a lab with the diversity of researchers?

IP: Each of the individual senior scientists goes off to meetings, works in their own field, has their own budget. I go to meetings, I get asked to speak at meetings, I encourage my postdocs to go to meetings, give posters and talks at meetings and so on. Every scientist does, some more than others. I now tend to get invited to meetings which are related to

immunotherapy, antibody-based therapies and protein, antibody engineering. Last year a new society was formed called The Antibody Society, which is devoted to antibody-based therapies mostly. It has taken all those years to get a separate society just interested in that area.

My group meets once a week for something we call data club. It lasts a couple of hours on Tuesday afternoon. We also have a weekly journal club, which is focused on papers related to the kind of research we are doing. We do not choose the latest exciting work. We learn about that in the many seminars given every day at NIH. We do papers that are related to what we are working on, worrying about, and thinking about. I either tell the postdoc to do a specific paper or ask them to show me what they are going to present and why they chose it so that we end up with good papers. We do not want a relevant paper that is lousy. And then on Friday at 12:15, the whole department meets. Each week a senior person is responsible for either presenting work from their lab or having one of their postdocs or someone from their lab present, or inviting an outside speaker who would be of interest to most people in the lab.

So that has worked pretty well. But now our problem is that we have a basic science group and we have a clinical science group, and over the years they are getting further and further apart as we get more into clinical trials. Susan Gottesman and I discuss what to do about that, and there is no easy solution. You have to be really an omnivore. So that is a problem for us, and I do not know how we are going to solve that. For me, I

used to do basic science, I go to them all, I like them all, it is fine with me. But some of the people just like one or the other and do not like to do both, so we have to solve that.

JG: What about collaboration and lab etiquette? The image of the lonely scientist working at the bench—is that still true?

IP: I think there are very few scientists who work by themselves. Here, most of the senior people do not do much bench work, because they have a bunch of postdocs to look after. Some do, or have fewer postdocs. So you spend your time talking to postdocs and students and figuring out what they have done and how they could best go ahead in their research. That takes a lot of time and thinking. We are also on committees. For example, I am chairman of the tenure committee and on a few other committees.

I do have collaborations with other people in the lab, and also other people at NIH, who are doing similar work. We do complementary things on the same project. We spent some years looking for new genes and new proteins as therapeutic targets for immunotoxins. We discovered a few interesting proteins that are useful as vaccine targets but not antibody targets, because the proteins are inside the cell and not on the surface. So we collaborate with two groups that are developing vaccine therapies, Jay A. Berzofsky and Jeff Schlom. I collaborate with a group at Duke who does immunotoxin therapy in brain cancer, Darrell Bigner. We have done clinical trials with him. Yes,

there is certainly collaboration. I think most people collaborate with people both here at NIH and at other institutions.

JG: One of the other changes that we have seen in the last thirty or forty years has been there are now more women in science. Your thoughts on that?

IP: Right. Well, I have made an effort to recruit women. The first was Susan Gottesman. I do not know if you know this, but Michael Gottesman, who is deputy director of research at NIH and is very well known, is Susan's husband. When I recruited Susan I had to find a job for Michael. So he came and we became friends and collaborators. Fortunately we had many interests in common.

Susan said "I need a job for Michael." I went to Al Rabson, my boss, and said "I want to bring Susan down for this opening we have, and she has a husband, Michael, who I believe is also a terrific scientist. Will you give him a job?" and Al said yes. Basically that is how it happened. It could not happen now. We might still do the same thing, but through all sorts of complicated processes.

The next two women we recruited are Sue Wickner and Jane Cheng. We were looking for very good people and we had openings. Being a woman was part of the reason for recruiting them, because there were other good people around, but these women were very good. So yes there was an effort to recruit women. We had a fourth woman, Sue

Garges, who left the lab. So at one time we had four women senior investigators, but now we have three, and two are National Academy members. We cannot do it exactly that way today. You cannot say that woman is great and we should hire her. You need to identify a field of interest, get permission to recruit, etc. If it was up to me I would hire excellent women independent of their field of research as long as it was relevant to cancer.

I also recruited two black scientists. One of whom is Ken Olden. He ultimately became director of the National Institute of Environmental Health Sciences (NIEHS). He is now retired from that job. Another is Alfred Johnson. Both people wrote to me and came to visit and I said, "Gee, they are as good as anybody else I have. Yes, we should have them."

JG: Do you think that goes back to your experiences—

IP: I believe in equality and integration. I don't know where that came from.

JG: In the broader scientific community there has not been the same emphasis in many cases. Has this changed over the years?

IP: I am on a committee of Dr. Zerhouni's to try and make life better for women here at NIH. There are a lot of statistics on how women are doing, and it varies of course a lot field by

field. In physics it is hard for women; in biology much easier and microbiology much easier.

JG: Is it generational again?

IP: Yes, I think it is a generational thing. There were clearly men, who for some reason or another, just were not going to hire women. I do not know why. Were they more comfortable with men? Maybe. Did they really have lower regard for women? No way I could tell you. I have no idea. But I think it was very generational and I think it is mostly gone. Now people are trying to figure out how to keep women and how to make life possible for them here knowing they need to just put more time in with their family than men do.

So, I will tell you a story. My son, Stephen, is a nephrologist. He went to Amherst College, Harvard Medical School, and trained at Beth Israel Hospital where he ended up being chief resident of medicine. He has a very outstanding record. When he was starting off at Harvard, he married a woman who was an art historian, and her first job offer was in Indiana. So Stephen left Harvard and went to Indiana so his wife could get a job. Then her next job offer was as a professor was at Emory, so he left Indiana and went to Emory so his wife could get a job. And that is why he went, period. So that is the difference in the world.

JG: The role of publications in science. I have your curriculum vitae, you have 1,143 publications, something around there I guess?

IP: Yes. A lot.

JG: You are also one of the top fifty most cited researchers.

IP: Obviously you have to publish—publish or perish. But you have postdocs and you have an obligation to get publications for them so they can get jobs. I am sure I would publish less, if I did not have the responsibility of getting my postdocs publications so they could get jobs. I can't wait for each postdoc to hit a homerun to get a publication. They are of good quality, but some are better than others.

JG: So, in the convention of the science, you add your name and publish it with them?

IP: I add my name because I directed the project and told them what to do. There is the ethics of when do you put your name in a paper. NIH has very clear guidelines about that.

JG: Right. Each lab has—

IP: No. Not each lab. NIH has published guidelines indicating when you should be a co-author or not. Did you conceive of the research? Did you do the research? Did you contribute valuable ideas to the research? Did you contribute an essential reagent to the research? There may be another. But they are all clearly spelled out, and those are the rules we follow.

JG: Well, my line of questioning was going—how are you able to balance the work of doing the science but then also find time to write up the findings? Do you have a method?

IP: Well, I used to be an English major so I can write. [Laughs] Actually it would be much easier to write papers myself than write them with postdocs, because you have many postdocs who do not write well. There are foreign postdocs who simply cannot write proper English. I let them do one or two drafts and then try to correct them. I have been doing science a long time also and I now know how to write a paper. I have thought about the data totally before I write the paper usually, so the writing is pretty formulaic. The introduction is why you did it and what the background is and nothing else. And the same with the results. Each section needs an introductory sentence and should end with a conclusion of some sort. And the discussion should discuss the important results and not restate them. So it is not that hard to write a paper, if you have all the data arranged. It is hard to get the data together, but we get the data together in data club as we do the work. The best writer I ever had was Harold [Varmus]. He had been the editor of the Amherst

College paper and he was an English major, so he could turn out a good manuscript in a weekend. [Laughs]

JG: I have seen in the library books titled "Writing Well for Scientists."

IP: I have tried to hire somebody to help my postdocs write but it failed. I have given them Strunk and White.

JG: Yes. *The Elements of Style* by Strunk and White.

IP: I have given them that.

JG: In graduate school I remember my advisor saying that if you do not understand what you are explaining then you cannot write it well. Is there a bit of that as well?

IP: Yes, there is. In our data club where each person presents every week, or every other week, we have handouts of what people have done. I ask them on their handout to put a goal, an approach, their findings, and their conclusion. I say look, make believe you are speaking to a high school student. I tell them that I have never come away from a lecture, where someone said that lecture was too simple. Never. And that is how you should be. You should be simple and clear, and that is a very hard thing to teach people. They want to be complicated. They just for some reason think that what they know everyone else

knows so they do not need to explain it. It is something I struggle with and work on constantly with trainees. These piles of papers are all the handouts from my meetings from the last two years or so. I try to teach them how to think about a project, use that to write a paper. Why did you do the experiment? What did you find? And what does it mean?

JG: The poster sessions at meetings seem to be something new in the last ten or fifteen years. I was in the lobby in the visitors center and there are numerous posters everywhere. Was that the case in the 1970s?

IP: There were many, many fewer people doing science and at meetings the large majority got a chance to talk for ten minutes, but now it is not possible for everyone to talk. So the only way to communicate is to have big poster sessions, and you can pick and choose among the posters that you like and look at them and talk to the people. I think it happened because of the expansion of science. There are a lot of things people are doing that need presentation, so people look through the list of posters and go to the posters they are interested in.

JG: Let's talk about how NIH funding has changed over time. Talk about funding pressures.

IP: I have only worked here in the intramural program. The way funding was done when I began my research was that the laboratory got one budget and people did research and

used that budget. We lived within it. But we did not assign budgets to people. In the beginning of my career at NIH I worked in clinical endocrinology. Unless I wanted to buy something very, very expensive, all was fine. But once I remember going to my boss, Jack Robbins, saying I need to buy a lot of radioactive amino acids to do this experiment (that ultimately did not work). [Laughs] He said okay. But then we underwent a major change about fifteen or twenty years ago. A concern arose about some lab chiefs having too much power over money and people. To counteract that a new system was established in which each senior investigator had their own budget. So now in this department, each senior investigator gets a budget which is based on the number of people that work with them. And the number of people that work with them is determined by review committees and promotions over time. So when you begin you have a few people. If you do better, you get more and more people, more space, and money. If you do not do well, you lose resources. But each person gets exactly the same budget per person. And then for big equipment, once a year, we get together and decide what we need and ask for money to purchase it for the whole lab.

JG: What about at a broader level? Have you seen the cycle of funding go up and down with presidential administrations?

IP: Yes, it has certainly gone up and down. It has been much tighter the last eight years. We have had flat budgets basically or even diminishing budgets because of inflation. So we have been more and more and more careful, bargaining better with companies, switching

to methods that are less expensive. One year we had to give up one of our research positions so that the money we would have paid that postdoc could be used for supplies and services. In the past few years many people in the cancer institute, intramural program, left or retired. We have had a huge cutback in personnel. I do not know how many, but it is a big number. We could not recruit for about ten or fifteen years, but now we can and have one new recruit already and we are about to get a second recruit. The leadership now, the scientific director and the director, are both very supportive of the intramural program. Bob Wiltrout's the scientific director. Very nice person, very good judgment. Also the current director is quite supportive of the intramural program. The bottom line is that we are living within our means but rearranging.

JG: Speak about your responsibilities to younger scientists—to the postdocs and fellows. What role have they played over the last, say, thirty years in the lab. Some of them, I guess, like Harold went on to do great things?

IP: A number of them have done very well, not as well as Harold, but many are chairs of departments and very, very well known. So far only one other besides Harold, [Shigetada] Nakanishi, is a member of the National Academy of Sciences.

JG: Do you keep in touch with them?

IP: Yes, I keep in touch with many of them and visit them when I travel or they come here. One of the reasons we have a reunion every five years or so is for people to keep in touch.

JG: I was thinking about a different question. How much did they contribute to the ideas and how much did they contribute to carrying out the work successfully, technically?

IP: Certainly the latter is true. You have to have a very skillful postdoc, and you have to have one with good scientific judgment because it is easy for them to go astray and doing other kinds of things. I try to keep on top of what they are doing. Sometimes they enjoy it; sometimes they do not. But I tell them just tell me everything you are doing, even those things that did not work. It is probably more important for me to know what you tried and did not work as what you tried that did work. I was trying to think of major advances that we made where a postdoc had conceptualized something that I had not thought about, which significantly changed the way we were doing our thinking. I would say it is not frequent. One example is the work of Vijay Chaudhary who designed and made the first recombinant immunotoxin.

JG: What about the need to help them understand the scientific method and the scrutinization of errors and of data and all that?

IP: We all have to be totally open about data, and that is why I say you have to bring the things that did not work as well as what did, because we have to know what is going on. Why are you doing it? What is your goal? What did you find? That is for me the major part of teaching every week. I try and make them think that way and do it that way and share the information with their fellows, so that all the fellows know what they are doing so the fellows can discuss what they have done in an open way. Also, I sometimes will ask them a question to which I know the answer so everyone will understand what the issues are. One is always worried about error and about dishonesty. I think any scientist who has worked with many people always worries about that. There are crooks in every field and some are in science. So one has to be very careful. If there is anything you think does not make a lot of sense you might ask someone else to repeat it. I also have had people who were not very productive, their work was not very good, whatever. Everyone has a share of those and you just live with it and they leave. So yes I am very careful about seeing as much primary data as I can to prevent fraud.

JG: I assume a scientist has to be very skeptical on one hand, but at the same time, very creative. How do you help them understand this balance?

IP: Skeptical: I say to my postdocs all the time that you have to be really careful. Here is my mantra. I tell them that I only believe what you say and what I say, and I am not so sure about what you say. They have to be skeptical. They can't just get swallowed up in something right away. So that is very important, and the balance is really hard because sometimes you will hear something you think is totally crazy and it is right. [Laughs] We have all been through that. On the other hand, you have to be skeptical, so there is some balance to that. Absolutely. But I am not sure that relates to creativity necessarily. Creativity to me has mostly come from working in a new area, but it can also be a new insight to an old problem.

JG: Describe some of the successes of those that you have mentored or worked closely with?

IP: I worked closely with Bob Perlman, we were collaborators, and Bob went on to a career in hormones and receptors. I worked with Jesse Roth collaboratively. Jesse's a giant in the field of receptors. Harold Varmus was my postdoc. You know him. I also at the same time mentored Bob Lefkowitz who was Jesse's fellow, but he worked in my lab because Jesse was busy with other things. So Bob and Jesse and I published some key papers together. Lefkowitz won the Shaw Prize last year and is a very famous receptor biologist. Benoit de Crombrugghe then joined me at that time, and Benoit worked here on collagen. He is an expert on bone and collagen development, soft tissue development.

I was going to mention Nakanishi, and Tadashi Yamamoto who discovered several oncogenes. He was here recently for three months as a visiting professor. I think he is in a meeting in Spain at the moment, but we have continued to keep in contact over the year. And Fred Maxfield and Jacques Pouyssegur and Ken Yamada and John Hanover and Dick Schlegel, who was a co-discoverer of the vaccine for cervical cancer treatment with Douglas Lowy, with whom I collaborated early on, but did not train.

JG: Who are some of the scientists that you have looked up to over your career? The people that you have come in contact with that have really influenced you?

IP: Who did I look up to? That is an interesting question. When I was a young scientist, I would go to the meetings of organizations like the American Society of Biological Chemists to hear the famous people talk, and I would sit down front. Even if it was not my field, I just wanted to hear their approach to science, whoever it was then. So Ef [Efraim] Racker, I remember. There were other people, I can't remember now. People working on mitochondrial oxidative phosphorylation was a hot field when I was a young scientist. [Earl W.] Sutherland certainly had a big effect on my life when he discovered cyclic AMP. I was teaching a course here on hormone action and we invited him to give a seminar. It was his first visit to NIH and I got to know him a little bit. [Jacques] Monod certainly for his work in gene regulation. Wally Gilbert for his work on the *lac* repressor and its regulation of genes. Stanley Cohen who discovered the EGF receptor and that it was a phosphoprotein. I trained with Earl Stadtman here at NIH. He did

amazing biochemistry on understanding glutamine synthetase regulation. If his work had not been in *E. coli*, he would have won a Nobel Prize. What happened is the Nobel Prize awards in biochemistry switched from bacteria to animal cells. So Earl did this great regulation stuff but it was at a time when people became more interested in animal cells.

JG: As we finish up today, describe the state of science today. Is it healthy?

IP: Yes, it is healthy. It is incredibly exciting. First of all, we have very few new treatments for cancer. We have all this information, but we do not—so the possibility of having them exists. Maybe the pharmaceutical industry will develop it. We understand a lot about cancer but not enough about cancer. We do not really understand how human cancers arise at the genetic level, whether it is kidney cancer or colon cancer or ovarian cancer or whatever. So there is a lot we do not know and there is a possibility of finding out. And this is the big question about the life process and what it is all about and what evolution is all about. I think it is still very exciting.

JG: How does the profession continue to attract young people into the sciences?

IP: That is a very, very difficult thing. Maybe with the collapse of Wall Street, bright young people will stop going to Wall Street, because I believe there is a huge pool of people who can do anything, like Harold. He could be an English professor or a scientist. I am sure he could make money, but got attracted into science, into cancer. And I am sure

there are a lot of people like that that just do not get attracted to cancer, because with the nature of our economy and our country, they get into other high-paying things. But if they were forced to be scientists, they might be great scientists. So we need a way to attract them and pay them and make the career path for them, a reasonable career path so they do not have to worry, worry, worry. Still we get some wonderfully talented people to go in and they are willing to put up with a huge amount of difficulty in order to do it. It is not so easy, but they still do it. If they were in the Army and the boss said you have to do science, they would do it, but they do not go into it because they want a different life. So we have to train them and have good teaching, but we also have to identify career paths. Right now we have one recruitment open in LMB in microbial genetics and we will soon see how many young people we get applying for that position. I hope we get a lot of very talented people. I do not know what the pool is. Our society has decided other things are more important and we are not going to put money into biological sciences.

JG: Tell me about the sweater that appears in the LMB photographs?

IP: Linda and I went to Seattle to a meeting on cyclic AMP and phosphorylation. We then went to Victoria, and Linda and I both bought sweaters made by local Indians. We take a picture once a year, so some years I wear my sweater, and often I wear a corduroy jacket.

JG: I have seen that.

IP: I still have that sweater. I will probably wear it this year. If we take the picture on a cold day, I will wear the sweater. [Laughs]

JG: I noticed it because someone told me when UPS or FedEx people come by, they look at the photos on the wall, and these are photos over thirty years, and that the sweater appears in say 1974, then makes a reappearance.

IP: Yes, if we take the picture in August, I am not going to wear it. If October and I remember, I will wear it. [Laughs]

JG: The last question. If you have one piece of advice, one lesson learned over your career that you would want to pass on to a future scientist or researcher operating ten or twenty years in the future, what would that be?

IP: I would say do something that you like doing and enjoy doing every single day, because that is the most important thing. If you like doing science, do science. But you really have to like doing experiments and like being in the lab and like being around scientists. It has to really occupy a lot of your thoughts to do it. Otherwise I would not do it. Find something that you really like doing, and hopefully you can make a living at it, too.

JG: Thank you very much.

IP: Okay. Thank you very much.

[End of interview]